SimFluVE USER MANUAL

This user manual pertains to SimFluVE

SimFluVE

SimFluVE is a stochastic agent-based simulation program, written in C++, for the transmission of influenza in a stratified population. SimFluVE performs a set of simulations with fixed values of the input parameters. Each simulation corresponds to a single outbreak.

SimFluVE can be operated using a command line interface as well as a graphical user interface. The following sections describe the ways in which inputs can be provided and outputs can be received from the program.

Model Description

This is a stochastic agent-based simulation program for the transmission of influenza in a stratified population. The program performs a set of simulations with fixed values of parameters. Each simulation corresponds to a single outbreak.

Population

The population is made up of different strata that have different characteristics.

Influenza transmission

The program calculates the daily probability that each person will be infected. These calculations depend on the transmission probabilities, number and distribution of contacts, and the prevalence of infection in the different strata. The details of the calculations can be found in the Appendix.

Initial infection

A given input number of people are chosen randomly to be infected and infectious on the first day of the outbreak.

Vaccination

The program is geared towards evaluation of the preventive effectiveness of a vaccine. Only the month of vaccination is known, and a person who receives the vaccine during a given month becomes effectively vaccinated on the first day of the following month. We define a binary variable V, with V=1 for a vaccinated person and V=0 for an unvaccinated. The value of V may change from 0 to 1 during the influenza season. The protection afforded by the vaccine depends on the vaccine efficacy parameter. There are two models for vaccination built in, leaky vaccine and all-or-none vaccine.

Leaky Vaccine

Under the leaky vaccine model, the vaccine provides partial protection against infection, i.e., once a person gets vaccinated, the per-contact transmission probability to that person is multiplied by a factor of (1-efficacy).

All-or-none Vaccine

Under the all-or-none vaccine model, the vaccine provides complete protection to a fraction of individuals who were vaccinated. The remaining vaccinated individuals do not benefit from the vaccine. Thus, once a person gets an all-or-none vaccine, that person is either completely protected from infection or not protected at all. The probability of being completely protected is defined as the vaccine efficacy.

ARI

Acute Respiratory Infection

FARI

ARI resulting from influenza infection (i.e., symptomatic influenza)

NFARI

ARI resulting from non-influenza pathogens. On each day, every person may develop a new episode of NFARI. However, a new NFARI episode cannot start when the person already has an NFARI or is infected with influenza. If a person with an NFARI develops influenza symptoms then the NFARI is terminated.

Covariates

The covariates X and U modify input parameters via multipliers that are specified in the input file. These multipliers may depend on a person's stratum, but do not change over time. Multipliers must be non-negative numbers.

X

X indicates the health status of the person. Only values of 1 and 0 are allowed, , where X=1 denotes a 'healthy' person and X=0 denotes a 'frail' person.
Health status may affect:

- Probabilities of being vaccinated
- Transmission probabilities and the probability of FARI
- Vaccine efficacy
- Probabilities of NFARI
- Probabilities of seeking care for ARIs

U

U indicates the person's health awareness. Only values of 1 and 0 are allowed for this parameter, where U=1 denotes high health awareness and U=0 denotes low health awareness.
This parameter may affect:

- Probabilities of being vaccinated
- Probabilities of seeking care for an ARI

Visit to clinic

A person with FARI or NFARI may decide to visit a clinic to seek medical care. The decision to seek medical care is made on the first day of an episode of FARI or NFARI. The probability of a visit may depend on V, X and U.

Inputs

SimFluVE takes a set of input parameters provided in a comma separated value (csv)-formatted file as input. This parameters file must be called Simflu6_input.csv and should have the following order of parameters. While operating SimFluVE in graphical mode, these input parameters could be provided using the input tables provided on the interface.

Title (alphanumeric)

Title of the set of simulations

Number of simulations

Number of simulations with the given input parameters

Seed

Seed for random number generation; must be a positive integer

All-or-none vaccine (Leaky vaccine if 'no')

SimFluVE is capable of simulating two kinds of vaccination scenarios. Use value ‘yes’ for all-or-none vaccine type, ‘no’ for leaky vaccine type (refer to the Model Description section for the definition of the two models for vaccine protection)

Output files

Followed by a list of twelve output files to choose from. Refer to the section Output Files.

Add timestamp to output file names

When set to ‘yes’, a time stamp is added to the names of output files.

Year of beginning of season

Year of the first month of influenza season; currently each simulation only simulates one season.

Month of beginning of season
Month number (from 1 through 12) of the starting month of the season

Number of months in the season
Length of the season in months

Number of strata
Number of strata in the population

Sizes of strata
Population sizes of each stratum; total population is the sum of sizes of all strata

Probability of X=1
Probability of a person having 'healthy' health status (X=1)

Probability of U=1 given X=1
Probability of a person having high health awareness (U=1) given that person is healthy (X=1)

Probability of U=1 given X=0
Probability of a person having high health awareness (U=1) given that person is frail (X=0)

Multipliers
We define a 'standard person' as an unvaccinated person with X=1 and U=1. Multipliers are used to modify parameters for a non-standard person.

Vaccination incremental coverage for X=1, U=1 (matrix - rows for months, columns for strata)
A matrix with number of rows equal to number of months plus one and number of columns equal to number of strata. Entries of the matrix are the percentages of additional persons, out of the initial stratum size, that receive the vaccine during that month. For example, the entry in the 1st row of the 2nd column corresponds to the percentage of individuals in the second stratum vaccinated prior to the season. Each person can only be vaccinated once. A person becomes 'vaccinated' on the first day of the month following the month of vaccination.

Vaccination incremental coverage multiplier for X=0
Multiplier to vaccination incremental coverage when X=0

Vaccination incremental coverage multiplier for U=0
Multiplier to vaccination incremental coverage when U=0

Initial number of infected persons
Total number of infected individuals before the season starts. These infected persons are randomly assigned across the whole population.

Number of contacts per day for each person
Total number of daily contacts made by a person from a given stratum.

Distribution of contacts - K by K matrix (rho)
A square matrix with size equal to the number of strata; this matrix gives the distribution of contacts across different strata. The entry in row i, column j is the proportion of contacts made by a person from stratum i with persons from stratum j. The sum of the entries in each row must be 1.

Length of latent period (days)
Number of days of latency of influenza for each stratum

Length of infectious period (days)
Number of days of staying infectious for each stratum

Probability of illness given infection
Probability of influenza symptoms for an infected person for each stratum

Relative infectiousness if not ill
This gives the relative infectiousness of an asymptomatic infectious person in each stratum. The transmission probability in a contact with an asymptomatic infectious person is reduced by this factor, compared to a contact with a symptomatic infectious person.

Transmission probabilities to unprotected for X=1 (matrix - rows for months, columns for strata)
A matrix with rows equal to the number of months and columns equal to the number of strata. This matrix gives the per-contact probability of influenza

transmission for unvaccinated individuals or persons who received the vaccine but remain unprotected in all-or-none model for a given month and stratum.

Transmission probabilities multipliers for X=0 in unvaccinated or unprotected

Multipliers to transmission probabilities in unvaccinated or unprotected persons given X=0

Vaccine efficacy for X=1 (matrix - rows for months, columns for strata)

Efficacy of vaccine for each strata and month for X=1

Vaccine efficacy multipliers for X=0

Multipliers to vaccine efficacy given X=0

Length of NFARI episode (days)

Length of non-influenza ARI episode in days

Daily probabilities of onset of NFARI for X=1 in unvaccinated or unprotected person

Daily probabilities of onset of NFARI for X=1 in unvaccinated or unprotected persons

NFARI probabilities multipliers for vaccinated or protected persons

NFARI probabilities multipliers for vaccinated or protected persons

NFARI probabilities multipliers for X=0

NFARI probabilities multipliers for X=0

Probability of visit for a case of FARI:

For unvaccinated or unprotected with X=1 and U=1

Probability of visiting a clinic to seek care for a case of FARI for an unvaccinated or unprotected person with X=1 and U=1

Multiplier for vaccinated

Multiplier to the probability of visiting a clinic for a case of FARI for a vaccinated person

Multiplier for X=0

Multiplier to the probability of visiting a clinic for a case of FARI for a person with X=0

Multiplier for U=0

Multiplier to the probability of visiting a clinic for a case of FARI for a person with U=0

Probability of visit for a case of NFARI:

For unvaccinated or unprotected with X=1 and U=1

Probability of visiting a clinic for a case of NFARI for an unvaccinated or unprotected person with X=1 and U=1

Multiplier for vaccinated

Multiplier to the probability of visiting a clinic for a case of NFARI for a vaccinated person

Multiplier for X=0

Multiplier to the probability of visiting a clinic for a case of NFARI for a person with X=0

Multiplier for U=0

Multiplier to the probability of visiting a clinic for a case of NFARI for a person with U=0

Sample Parameters File

Title (alphanumeric)	Case 10H Leaky	
Number of simulations	100	
Seed	1943	
All-or-none vaccine (Leaky vaccine if 'no')	no	
Output files ('yes' or 'no' for each)		
Input and calculated parameters	yes	
Vaccination *	no	
Detailed *	no	
Contacts *	no	
Prevalence *	no	

Incidence-daily each simulation	no	
Incidence-monthly each simulation	no	
Incidence-season each simulation	no	
Incidence-daily overall	no	
Incidence-monthly overall	yes	
Incidence-season overall	yes	
Outcomes file	no	
Add timestamp to output file names	yes	
Year of beginning of study	2010	
Month of beginning of study	10	
Number of months in the study	3	
Number of strata	2	
Sizes of strata	600	400
Probability of X=1	0.8	0.4
Probability of U=1 given X=1	0.7	0.5
Probability of U=1 given X=0	0.6	0.3
Vaccination incremental coverage for X=1, U=1 (matrix - rows for months, columns for strata) **		
0	0.5	0.4
1	0.2	0.1
2	0.1	0.05
3	0	0
Vaccination incremental coverage multiplier for X=0	0.9	0.8
Vaccination incremental coverage multiplier for U=0	0.7	0.6
Initial number of infected persons	10	
Number of contacts per day for each person	10	15
Distribution of contacts - K by K matrix (rho)		
1	0.7	0.3
2	0.4	0.6
Length of latent period (days)	2	2
Length of infectious period (days)	4	4
Probability of illness given infection	0.67	0.67
Relative infectiousness if not ill	0.4	0.4
Transmission probabilities to unprotected for X=1 (matrix - rows for months, columns for strata)		
1	0.025	0.03
2	0.025	0.03
3	0.05	0.1

Transmission probabilities multipliers for X=0 in unvaccinated or unprotected	1.5	2
Vaccine efficacy for X=1 (matrix - rows for months, columns for strata) ***		
1	0.6	0.6
2	0.6	0.6
3	0.6	0.6
Vaccine efficacy multipliers for X=0	0.7	0.7
Length of NFARI episode (days)	5	8
Daily probabilities of onset of NFARI for X=1 in unvaccinated or unprotected persons		
1	0.02	0.03
2	0.04	0.06
3	0.05	0.07
NFARI probabilities multipliers for vaccinated or protected persons	0.7	0.8
NFARI probabilities multipliers for X=0	1.5	1.8
Probability of visit for a case of FARI:		
For unvaccinated or unprotected with X=1 and U=1	0.6	0.4
Multiplier for vaccinated	0.7	0.5
Multiplier for X=0	1.3	1.6
Multiplier for U=0	0.8	0.6
Probability of visit for a case of NFARI:		
For unvaccinated or unprotected with X=1 and U=1	0.5	0.3
Multiplier for vaccinated	0.7	0.4
Multiplier for X=0	1.3	1.6
Multiplier for U=0	0.8	0.6
Comments:		
* For debugging purposes		
** Fractions based on initial stratum size		
*** Based on ratio of transmission probabilities		
X: Health status; Healthy: 1, Frail: 0		
U: Health awareness; High: 1, Low: 0		
FARI: Influenza Acute Respiratory Illness		
NFARI: Non-Influenza Acute Respiratory Illness		

Output Files

Along with the output on the console, SimFluVE produces twelve comma-separated (csv) output files. To select an output file, type 'yes' (without quotes) as a parameter in the input file in the line pertaining to that output file.

The following gives the description of each output file.

Inputs and Calculated Parameters

This file contains the input parameters provided in the parameters file along with the parameters that are calculated using those inputs.

Vaccination (for debugging)

This file keeps track of the vaccinations performed during simulations.

S: Simulation number
M: Month number
Month: Month of the year
Year: Year
K: Stratum
X: Health status
U: Propensity to seek medical care
Number of Newly Vaccinated: Number of newly vaccinated for given S, M, and K
Newly Vaccinated: IDs of newly vaccinated persons for a given S, M, and K

Detailed (for debugging)

This file captures the detailed state of events inside the simulations

S: Simulation number
D: Day of simulation, running over the entire season
Day: Day of the month
Month: Month of the year
Year: Year
I: ID of person
Stratum: Stratum
X: Health status
U: Health awareness
InitInf: Indicator of whether a person is initially infected before the simulation season starts (1=yes, 0=no)
Vac: Vaccination status of the person on the day of observation; person's vaccination status changes from 0 to 1 on the first day of the month following the month when the vaccine was received
Protected: Protection from vaccination; 0/1 for all-or-none vaccine; 999 for leaky vaccine
State: State of the person; 0=susceptible, 1=exposed, 2=infectious without symptoms, 3=infectious with symptoms, 4=recovered

DayInf: Infection day of the person, values range from 1 to the number of days in the infectious period
DNFARI: Non-influenza ARI (NFARI) day of the person, values range from 1 to the number of days in NFARI
Visit: Clinic visit; 0/1

Contact Report (for debugging)
This file gives the infection probability and occurrence of new infection of each susceptible person due to contacts with infectious individuals

S: Simulation number
D: Day of simulation
I: ID of person
Stratum: Stratum of person
X: Health status
U: Health awareness
Vac: Vaccination status
Protected: Protection from vaccination; 0/1 for all-or-none vaccine; 999 for leaky vaccine
P(INF): Probability of getting infected, given person's stratum (K) and vaccination status (V)
RANDOM: Random number generated
NewInf: Becomes infected (0 = No, 1 = Yes)

Prevalence (for debugging)
This file gives the prevalence of infectious persons for each day and stratum

S: Simulation number
D: Day of simulation
Day: Day of the month
Month: Month
Year: Year
Stratum: Stratum
Prevalence (S2): Prevalence of infectious persons without illness
Prevalence (S3): Prevalence of infectious persons with illness
P (INF| UNPROTECTED;X=0): Per-contact infection probability for unprotected (all-or-none vaccine) person with X=0
P (INF| UNPROTECTED;X=1): Per-contact infection probability for unprotected (all-or-none vaccine) person with X=1
P (INF|V=0;X=0): Per-contact infection probability for unvaccinated (leaky vaccine) person with X=0
P (INF|V=0;X=1): Per-contact infection probability for unvaccinated (leaky vaccine) person with X=1
P (INF|V=1;X=0): Per-contact infection probability for vaccinated (leaky vaccine) person with X=0
P (INF|V=1;X=1): Per-contact infection probability for vaccinated (leaky vaccine) person with X=1

Incidence-daily-each sim

This file gives incidence numbers for each day of each simulation

S: Simulation number
D: Day on simulation
Day: Day of month
Month: Month
Year: Year
Stratum: Stratum
V: Vaccination Status
N: Number of persons in given Stratum with Vaccination status V
Inc2: Number of persons infectious without illness
Rate2: Incidence rate of persons infectious without illness
Inc3: Number of persons infectious with illness
Rate3: Incidence rate of persons infectious with illness
IncT: Total number of infectious persons
RateT: Total incidence rate of infectious persons
IncNFARI: Total number of persons with non-influenza ARI
RateNFARI: Total incidence rate of non-influenza ARI

Incidence-monthly-each sim

This file gives incidence numbers for each month of each simulation

S: Simulation number
Month: Month
Year: Year
Stratum: Stratum
V: Vaccination Status
N: Number of persons in given Stratum with Vaccination status V
Inc2: Number of persons infectious without illness
Rate2: Incidence rate of persons infectious without illness
Inc3: Number of persons infectious with illness
Rate3: Incidence rate of persons infectious with illness
IncT: Total number of infectious persons
RateT: Total incidence rate of infectious persons
IncNFARI: Total number of persons with non-influenza ARI
RateNFARI: Total incidence rate of non-influenza ARI

Incidence-season-each sim

This file gives incidence numbers for the whole season for each simulation

S: Simulation number
Stratum: Stratum
V: Vaccination Status
N: Number of persons in given Stratum with Vaccination status V
Inc2: Number of persons infectious without illness

Rate2: Incidence rate of persons infectious without illness
Inc3: Number of persons infectious with illness
Rate3: Incidence rate of persons infectious with illness
IncT: Total number of infectious persons
RateT: Total incidence rate of infectious persons
IncNFARI: Total number of persons with non-influenza ARI
RateNFARI: Total incidence rate of non-influenza ARI

Incidence-daily-overall

This file gives incidence numbers for each day averaged across all simulations

D: Day on simulation
Day: Day of month
Month: Month
Year: Year
Stratum: Stratum
V: Vaccination Status
N: Number of persons in given Stratum with Vaccination status V
Inc2: Number of persons infectious without illness
Rate2: Incidence rate of persons infectious without illness
Inc3: Number of persons infectious with illness
Rate3: Incidence rate of persons infectious with illness
IncT: Total number of infectious persons
RateT: Total incidence rate of infectious persons
IncNFARI: Total number of persons with non-influenza ARI
RateNFARI: Total incidence rate of non-influenza ARI

Incidence-monthly-overall

This file gives incidence numbers for each month averaged across all simulations

Month: Month
Year: Year
Stratum: Stratum
V: Vaccination Status
N: Number of persons in given Stratum with Vaccination status V
Inc2: Number of persons infectious without illness
Rate2: Incidence rate of persons infectious without illness
Inc3: Number of persons infectious with illness
Rate3: Incidence rate of persons infectious with illness
IncT: Total number of infectious persons
RateT: Total incidence rate of infectious persons
IncNFARI: Total number of persons with non-influenza ARI
RateNFARI: Total incidence rate of non-influenza ARI

Incidence-season-overall

This file gives incidence numbers for the whole season averaged across all simulations

Stratum: Stratum
V: Vaccination Status
N: Number of persons in given Stratum with Vaccination status V
Inc2: Number of persons infectious without illness
Rate2: Incidence rate of persons infectious without illness
Inc3: Number of persons infectious with illness
Rate3: Incidence rate of persons infectious with illness
IncT: Total number of infectious persons
RateT: Total incidence rate of infectious persons
IncNFARI: Total number of persons with non-influenza ARI
RateNFARI: Total incidence rate of non-influenza ARI

Outcomes-File

This file gives information about onset of influenza infections and non-influenza ARIs. In each simulation, there is a main record for each person, followed by records pertaining to 'events' (if any) that the person has experienced throughout the season. There are three types of events:

1. Influenza without symptoms
2. Influenza with symptom (FARI)
3. Non-influenza ARI (NFARI)

The events are recorded by onset date. A person who did not experience any event will only have the main record.

Sim: Simulation number
Person: ID of the person
STR: Stratum of the person
X: Health status
U: Health awareness
INITINF: 1 if person is initially infected (before the simulated season starts)
DEFVAC: First day of the month following the month the vaccine was received; 999 if not vaccinated
Protected: Protection from vaccination; 0/1 for all-or-none vaccine; 999 for leaky vaccine
EventCounter: Sequential number of event
Type: 1 for influenza infection without symptoms; 2 for infection with symptoms; 3 for non-influenza ARI
OnsetDay: Start day of event
VacStatus: Vaccination status on the onset day
Visit: Clinic visit for this event

How to Compile

The source code of the program is accompanied with a make file that can be used to compile the source using GCC C++ compiler. To compile the source code on a machine with GCC compiler installed run the make command from terminal (Unix flavored operating systems). Cygwin or MinGW can be used to compile the code on a Windows machine. Compiling the code will generate an executable file named SimFluVE on Unix flavored OS or SimFlu.exe on Windows machines.

How to Run

Using command line interface

SimFluVE requires an input parameters file. By default, SimFluVE looks for a file named as Simflu6_input.csv in the same folder where SimFluVE executable is placed. This default option can be overridden by providing the path and name of the input parameters file as a command line argument.
To run from command prompt, change the directory to the one containing the SimFluVE executable and run command:

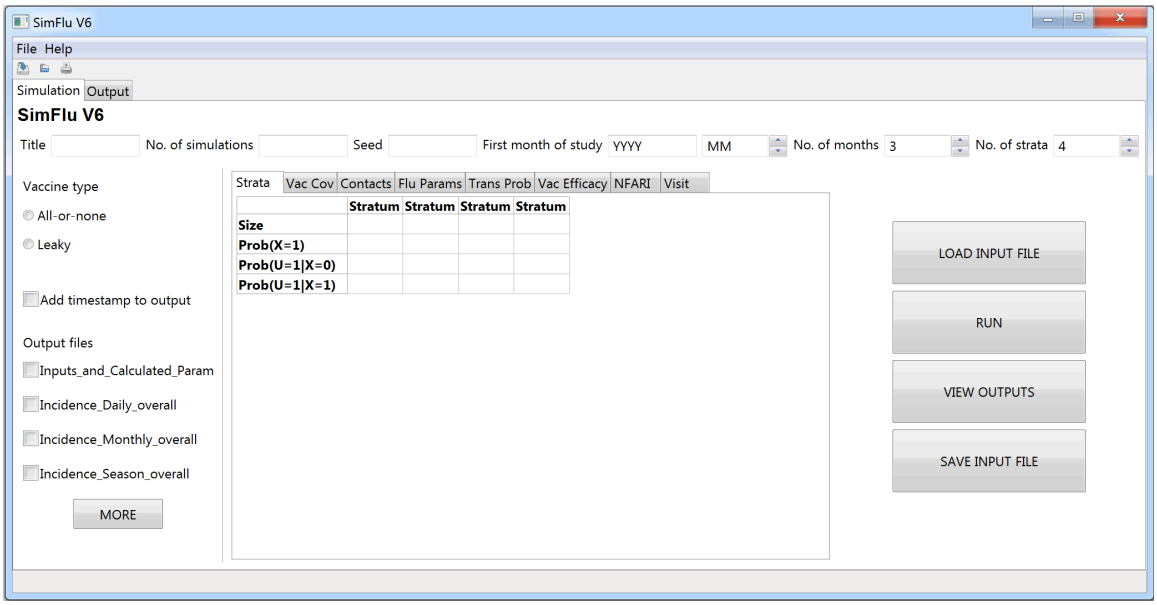
> ./SimFlu
or
> ./SimFlu <input_filename>

The program can also be executed (with default input parameters file) by simply double-clicking the executable file.

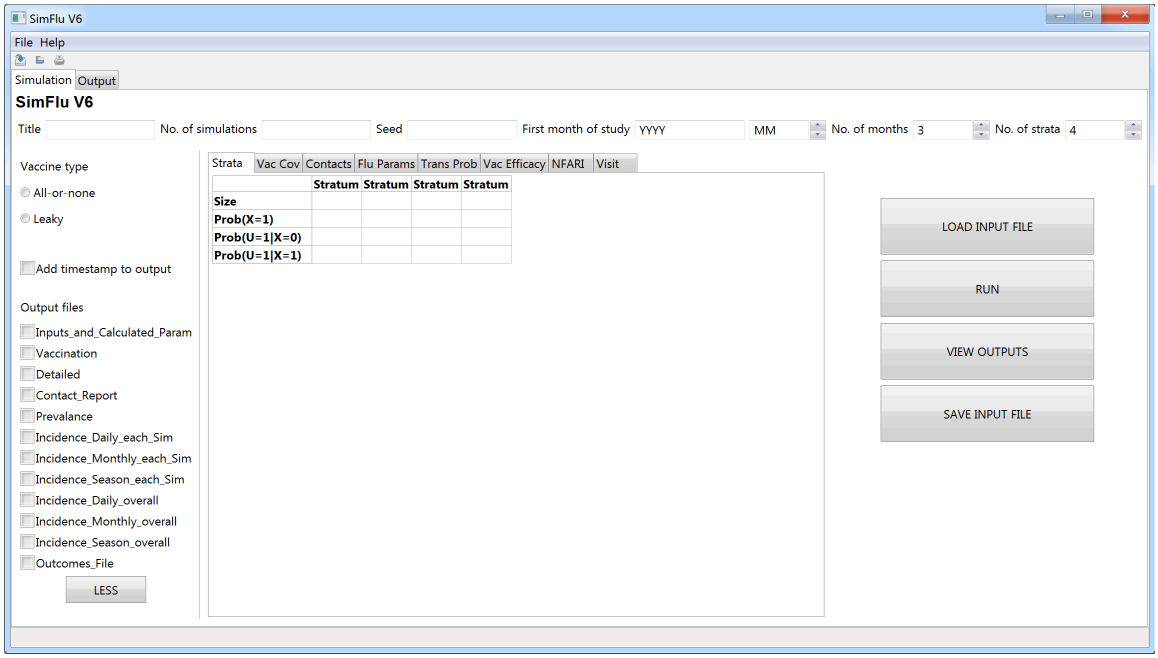
Using graphical interface

SimFluVE's graphical user interface lets users provide inputs, run simulations and save outputs in a friendly manner. Following screenshots will walk you through the process of using this interface for running simulations.

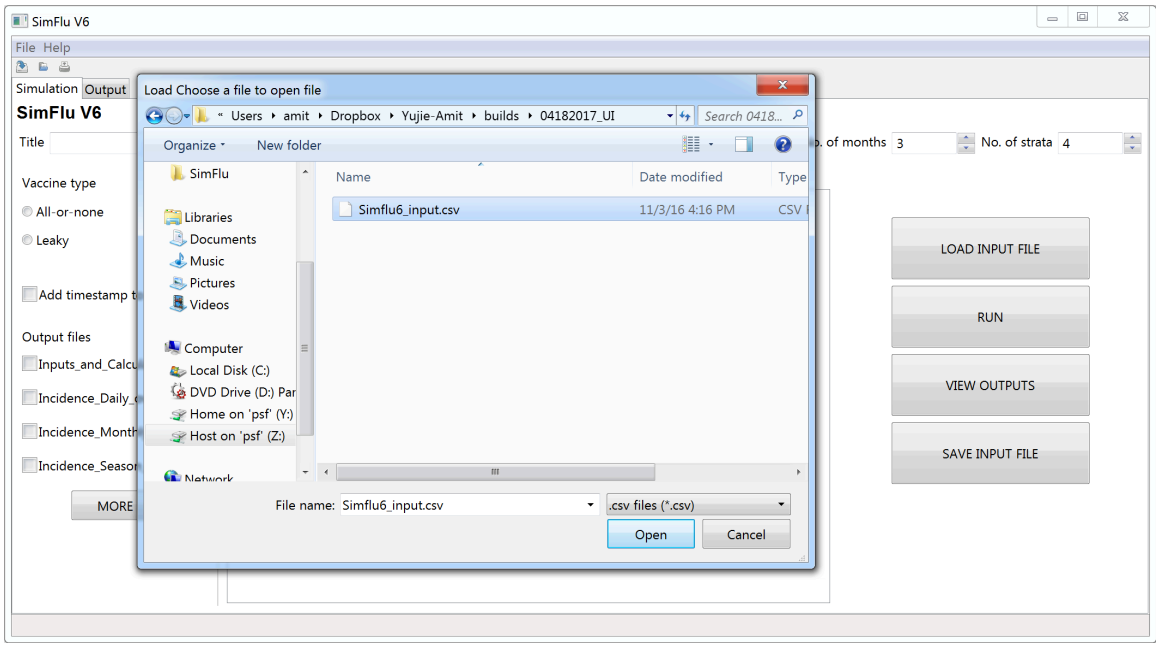
The following screenshot shows the default view of SimFluVE. The panel is split between two tabs. The simulation tab contains all the inputs and controls. Once the simulation run is complete, the Output tab populates the desired outputs.



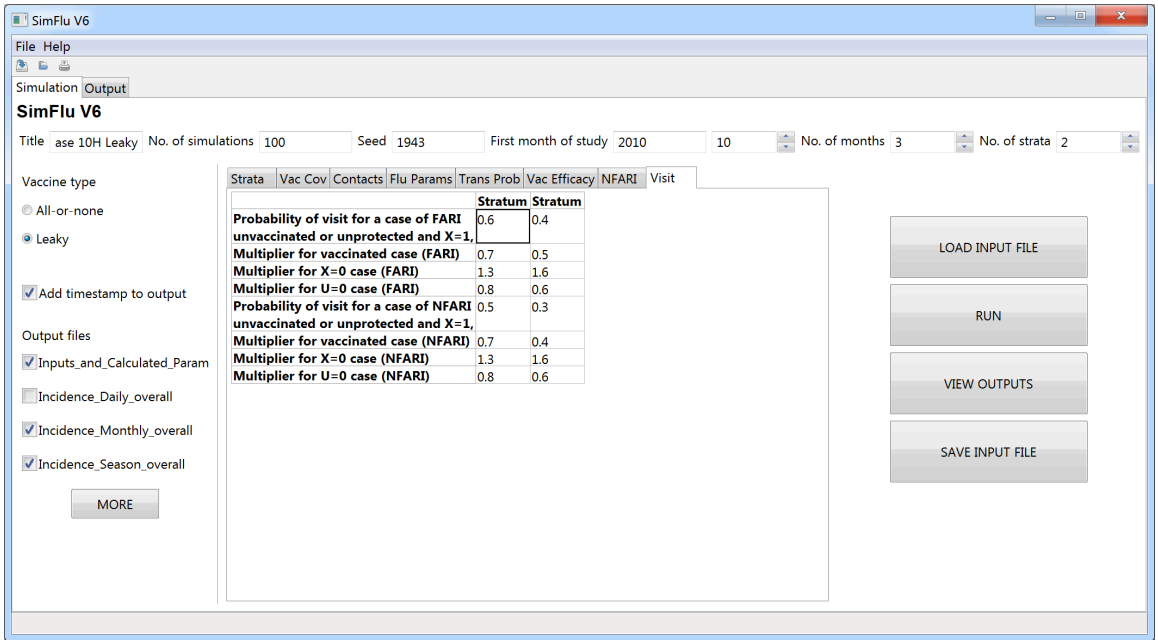
The top row of the Simulation tab provides spaces to input title, number of simulations, random seed, first month and year of study, length of study and number of strata. The left column lets users choose between all-or-none and leaky vaccine type and pick the output files to be generated. By default, it shows only the 'input and calculated parameters' and incidence related output files. Users can see the complete list of output files by pressing 'More' button (as shown in the next screenshot). The center box gives users the ability to provide the rest of the input parameters in a tabular way. These input parameters are split across different tabs that correspond to strata, vaccination coverage, contacts, flu parameters, transmission probabilities, vaccine efficacy, non-influenza ARI, and clinic visits related parameters.



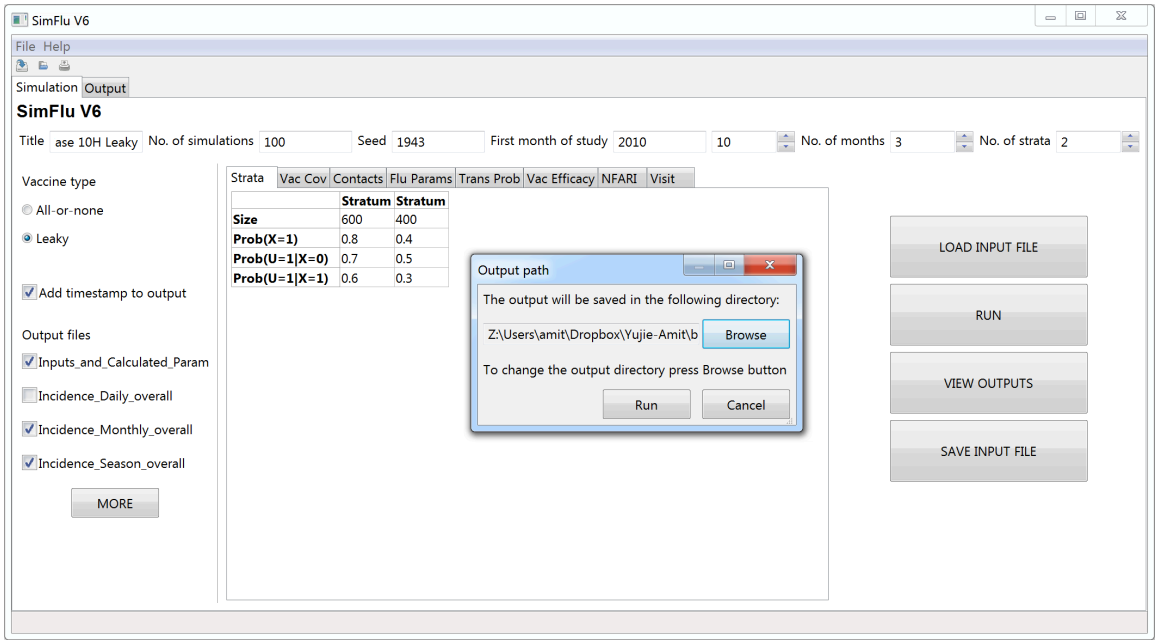
Users can directly import a .csv file using 'LOAD INPUT FILE' button placed in the right column. This csv file needs to be formatted as per the specifications provided in Inputs section.



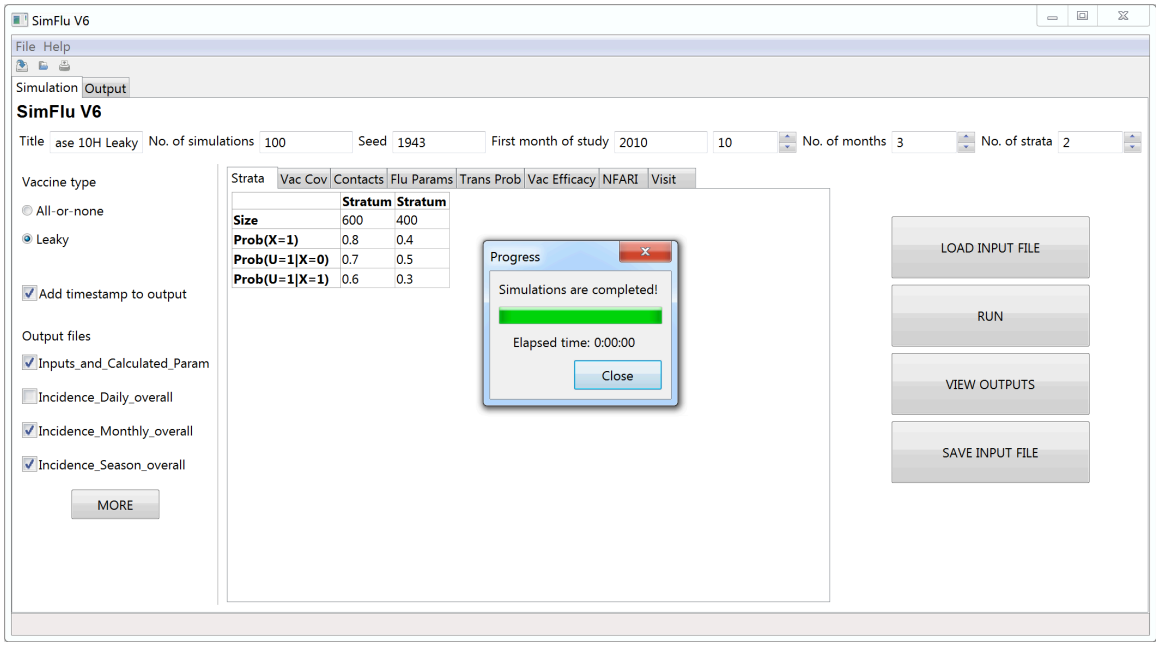
The following screenshot shows how the interface looks after reading in the input parameters file. Users can edit any parameter after loading the file if they choose to.



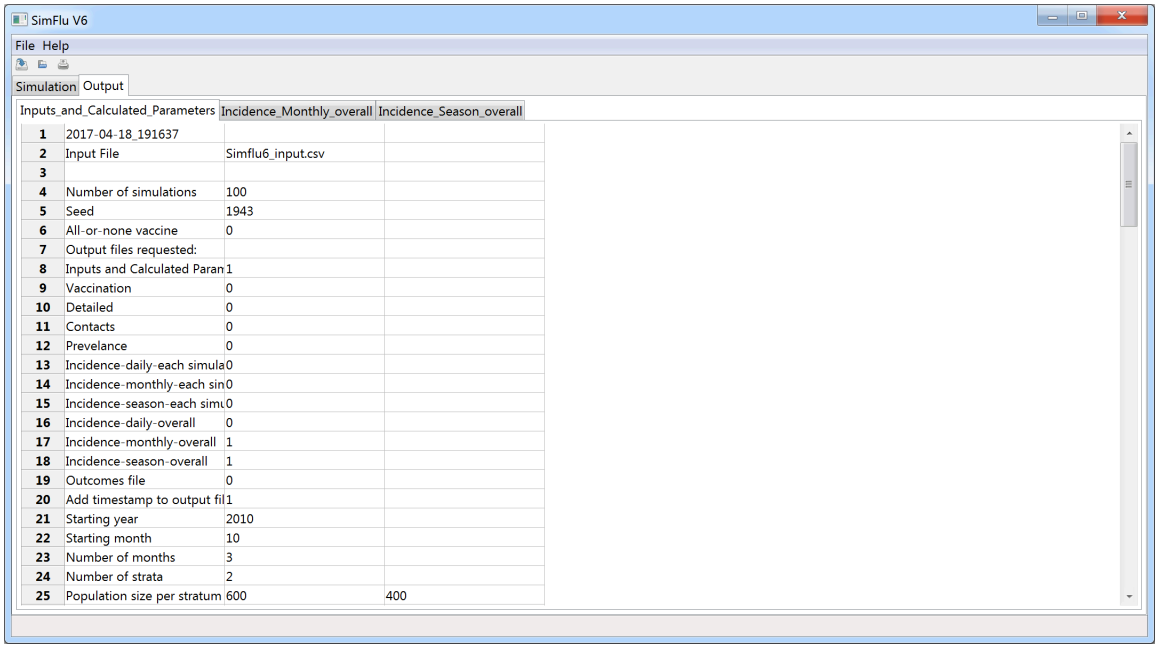
Before running the simulation, a directory can be specified for output files generated by the simulation. By default the simulator uses the same folder where the input parameter file is located as the source directory for the output files.

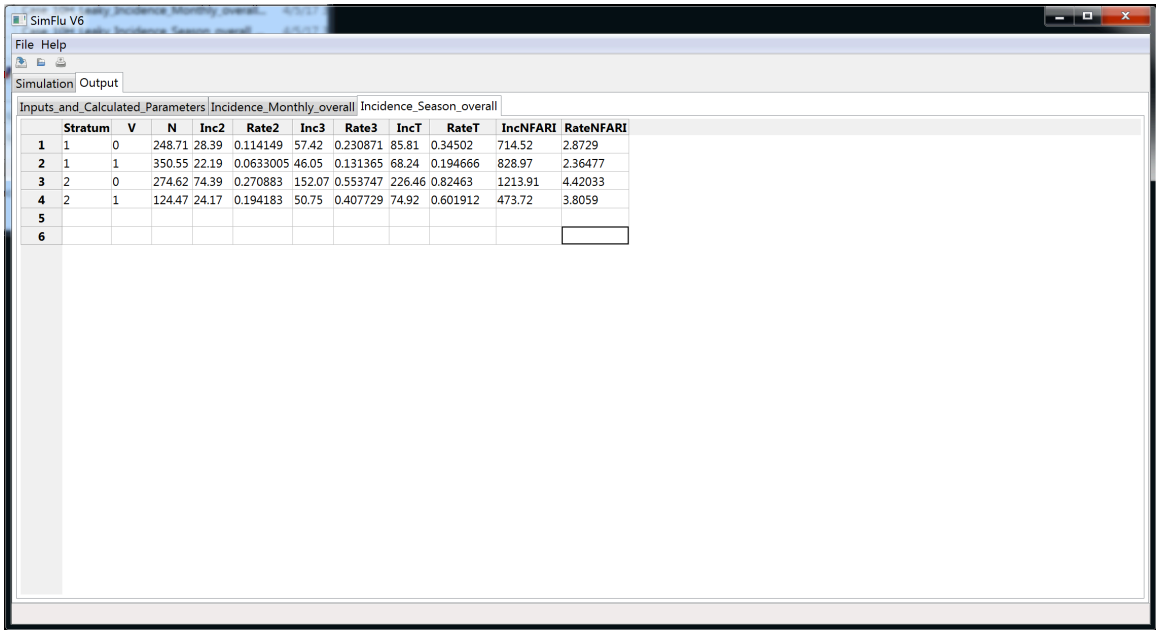


After this, we are all set to run. A set of simulations can now be fired using ‘RUN’ button. Once the run button is pressed, a progress bar will appear to show the progress of execution.



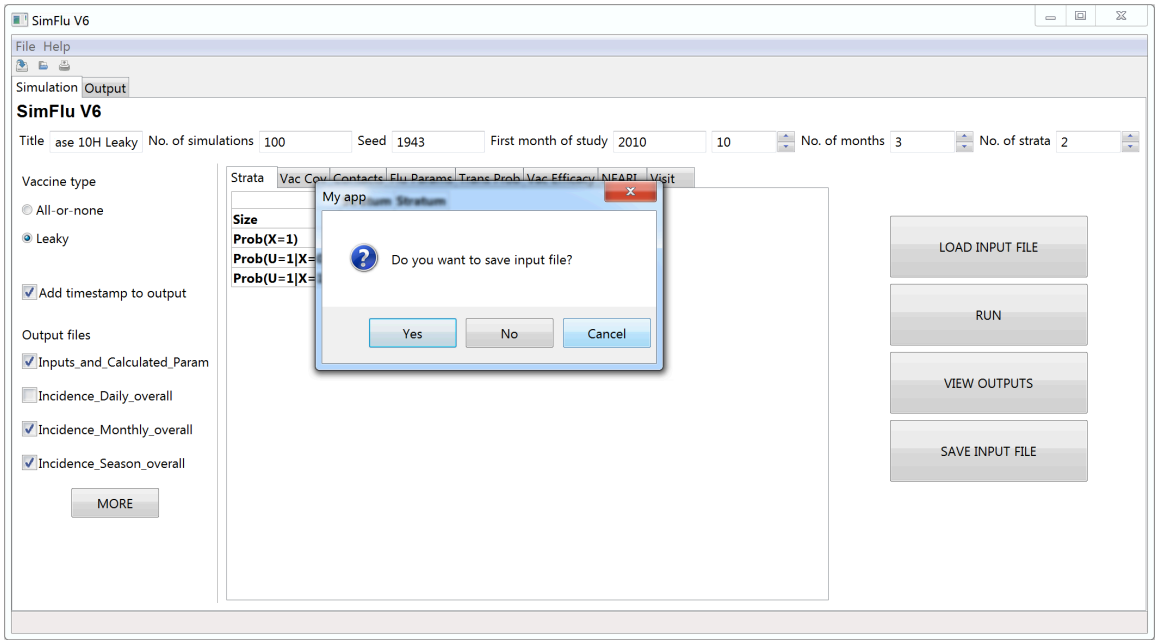
Once all the simulations are completed, users can check the selected outputs using the Output tab or by using the output files saved in the .csv format in the specified folder.





	Stratum	V	N	Inc2	Rate2	Inc3	Rate3	IncT	RateT	IncNFARI	RateNFARI
1	1	0	248.71	28.39	0.114149	57.42	0.230871	85.81	0.34502	714.52	2.8729
2	1	1	350.55	22.19	0.0633005	46.05	0.131365	68.24	0.194666	828.97	2.36477
3	2	0	274.62	74.39	0.270883	152.07	0.553747	226.46	0.82463	1213.91	4.42033
4	2	1	124.47	24.17	0.194183	50.75	0.407729	74.92	0.601912	473.72	3.8059
5											
6											

SimFluVE lets you save the set of parameters in an input file that can be loaded again for future simulations.



Appendix

Calculation of the probability that a person becomes infected on a given day

Consider a susceptible person A from stratum k and vaccination status v. On a given day, this person makes a contact with each of C_k individuals. Consider one of these contacts, and denote the contacted person by B.

First, calculate the probability P1 that person A becomes infected from person B when B is in stratum l $(l = 1,\ldots,K)$ and in infection/illness state h, where $h = 0$ for susceptible, $h = 1$ for latent, $h = 2$ for infectious but not ill, $h = 3$ for infectious and ill, $h = 4$ for recovered:

$$P1(k,v \mid l,h) = \pi(k,v) \cdot \lambda(l,h),$$

where $\pi(k,v)$ is the per-contact transmission probability and $\lambda(l,h)$ is the relative infectiousness of person B, defined as $\lambda = 0$ for $h = 0,1,4$, $\lambda = 1$ for $h = 3$, and $\lambda =$ a preset input parameter (the relative infectiousness of a person who is infectious but not ill) for $h = 2$.

Second, calculate the probability P2 that person A becomes infected from person B if we only know that person B is in stratum l :

$$P2(k,v \mid l) = \sum_h P1(k,v \mid l,h) \cdot \mathrm{Prev}(h \mid l),$$

where $\mathrm{Prev}(h \mid l)$ is the prevalence (proportion) of persons from stratum l who are in state h on that day.

Third, calculate the probability P3 that person A becomes infected from B if we do not have any information on B. The probability that B is in stratum l is $\rho(l \mid k) = \rho_{kl}$, (person A's contact distribution), therefore

$$P3(k,v) = \sum_l P2(k,v \mid l) \cdot \rho(l \mid k).$$

P3 is the probability that person A becomes infected in a single contact. The probability that s/he becomes infected on that day, i.e. s/he becomes infected in at least one of the C_k (independent) contacts is:

$$\mathrm{Pinf}(k,v) = 1 - [1 - P3(k,v)]^{C_k}.$$