A Universal Model of Epidemic: Optimizing Interventions

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Abstract The outbreaks of infectious diseases caused by natural factors or bioterrorism acts are, unfortunately, quite real threats for the overall population. Planning of an efficient response to an outbreak of an infectious disease requires coordinated efforts of various services aimed to most efficiently utilize the limited resources. This paper describes a model that optimizes utilization of resources when preparing to counter the bioterrorism threats or responding to epidemics caused by epidemiologically dangerous or socially significant pathogens. The model computes the volume of limited resources as well as the particular control activities (isolation, ring vaccination, or mass vaccination) necessary to minimize the optimization criterion, comprising the total number of infected persons, number of lethal cases, and several other characteristics. The model is available remotely via WEB-interface at http://vector-epimod.ru.

Keywords Epidemy, Mathematical model, Limited resources, Optimizing Interventions

1. Introduction

Mathematical models have long been used when developing the strategies for control of infectious outbreaks (see, for example, [1]). Since it is impossible to perform epidemiological experiments in human populations, they have to confine ourselves to field studies, and mathematical modeling actually remains the only tool for studying the effects of particular factors on the dynamics of epidemics.

Numerous works have dealt with selection of the optimal strategies for responses to epidemics [2–8], including vaccination (mass, ring, or risk group vaccination), quarantine, isolation, and treatment. However, the “cost” of interventions, as a rule, is not estimated except for rare cases (for example, [9]). This suggests a need in optimizing the response activities taking into account the losses caused by epidemics and the cost for intervention. The cost for intervention may include the expenditures for maintaining certain resource stocks independently of whether an epidemic will take place or not, in particular, stocks of vaccines, preventive drugs, or therapeutics; specially equipped facilities for isolating infected cases and contacts; qualified medical and paramedical staff; systems for controlling emergency situations; and so on. The cost of interventions is also determined by the expenditures for the intervention activities per se, that is, in particular, search for and isolation of infected persons and cost of the used drugs and other tools necessary for abortion of an epidemic.

Principles for optimization of the anti-epidemic activities aimed to control outbreaks of some infections (mainly, caused by special pathogens) and some obtained results are discussed.

2. Materials and Methods

The State Research Center of Virology and Biotechnology Vector is developing a universal model for predicting scenarios of development of epidemics (outbreaks) of special and socially significant diseases [10, 11]. It is assumed that this model is able to describe the dynamics of any epidemics of an acute infectious disease caused by infection from a certain external source or via random contacts as the main transmission routes independently of sex, age, and other sociodemographic population cohorts.

A universal nature of this model consists in that all the computations utilize the same equations, the same code, and the same interface for all infections. The infections differ from one another only in the set of editable parameters. Currently, the model is adapted to ten infections, mainly caused by special pathogens. The model provides a wide range of tools for studying local outbreaks and epidemics. User may interactively change all model parameters and thereby estimate the effects of particular pathogen characteristics, specific feature of localities or regions, resource availability, as well as the beginning and intensity of anti-epidemic activities on the prediction of epidemic dynamics. Moreover, an expert user may specify some other infection of interest, absent in the list of diseases already used for simulation.

The model considers several stages characteristic of each disease, differing in their symptoms, probability of correct diagnosing, and level of infectivity of the patients.

When computing the dynamics of an epidemic (outbreak),
three levels of anti-epidemic activities (AEA1-3), mainly
determining the rate of detection and isolation (observation)
of infected persons, their contacts, and suspects, may be
specified [10]. In addition to these three modes, it is
possible to specify quarantine, mass vaccination, and/or
vaccination of risk groups (contacts and suspects) for some
infections.

For some infections, one of the countermeasures in the
case of an epidemic (outbreak) is preventive therapy with
some drugs, such as immunomodulators, antibiotics, and so
on. The model does not consider such intervention in a
direct manner. However, it is possible to imitate this type of
intervention. An emergency mass vaccination and
vaccination of risk groups alter several characteristics, such
as the sensitivity to disease, severity of the disease course in
infected persons, and infectivity of patients. Prevention
therapy gives approximately the same effect.

All these countermeasures are implemented if the
responding resources are available; these resources
comprise qualified medical and paramedical staff; facilities
for isolation/observation of patients, contacts, and suspects;
and stocks of preventive drugs and therapeutics. When
resources are depleted, the levels of the corresponding AEA
detection, isolation, vaccination, treatments, etc.) may be
decreased to a complete cessation. The “default”
computation variant implies that implementation of the last
“strict” AEA level cancels any resource limitations. This
option is also user-changeable.

Initially, the model is deterministic and is mainly
intended for describing mass epidemics. However, it
provides the possibility to simulate an accidental infection
and, thus, to obtain a certain range of outcomes in the case
of many realizations of this random process.

The model is available remotely via WEB-interface at
http://vector-epimod.ru. The user can specify any set of
values of 89 parameters used in calculating dynamics of
epidemics and assessment of losses from epidemics, as well
as 81 factors that define values of the optimization criterion.

2.1. Optimizing Interventions

One of the options provided for by the model is
optimization of interventions. Indeed, it is possible to
manually select the values for factors that control an
epidemic by analyzing the computed epidemic dynamics.
However, the model allows for obtaining the values of
factors that minimize a certain criterion after their initial
values and permissible ranges are specified.

User may interactively specify the initial values and
admissible ranges for each optimization factor, for example:
- rate of asymptomatic contacts, suspects and patients
  in infectious stage daily isolated with AEA1–3;
- bed capacity in provisional hospitals and in
  quarantine departments for contacts as well as for
  patients in infectious stage;
- number of vaccination stations and/or points for
distribution of prophylactic drugs;
- reserve of drugs and/or vaccines and other.

For more details, see Tables 1 and 2.

It is assumed that maintenance of a certain level of
preparedness to a biological threat as well as
implementation of interventions requires certain
expenditures, material and/or human. Correspondingly, user
also specifies the “cost” for each unit factor; thus, the total
expenditures for maintenance or use of specified factor
values are also taken into account in the optimization
criterion. In addition, user may specify a characteristic that
canceling optimization of a factor. These data form the first
constituent of the criterion.

The second constituent of the criterion is the total losses
curred by epidemic, which depends on several
characteristics of the epidemics such as total number of
infected persons, lethal cases, quarantine days etc (for more
details, see Tables 3 and 4). And the user-specified weights
of these characteristics:

\[ F = \sum v_i f_i + \sum L_j \delta f_j \]

where \( v_i \) is the value of the i-th optimization factor; \( f_i \) unit
cost for this factor; \( L_j \), the characteristic determining results
of epidemic, which contributes to the losses caused by the
epidemic correspondingly to its weight, \( \delta f_j \).

Genetic algorithm [12, 13] is used for optimization. Its
program implementation is as follows:

(1) An initial population of “genotypes” is constructed,
where each genotype is the vector of values of all the
optimized factors. When constructing a genotype, the initial
values of each of the parameters are taken and subject to a
“mutation” with a certain probability, that is, to a random
change in the value having a Gaussian distribution with
mathematical expectation equal to the initial value. If the
new value in this case falls beyond the permissible limits,
the corresponding value at the boundary is assigned to it.
The population size is 100 genotypes.

(2) “Fitness” of each genotype is estimated, that is, the
epidemic dynamics is calculated for the given set of factors
and the value of optimization criterion is determined using
the above equation.

(3) The genotypes are re-ordered according to the fitness
so that the genotypes with a smaller value of the criterion
have smaller ranking numbers in the population.

(4) The genotype with the minimal ranking number, that
is, the genotype with the best fit, is taken to randomly select
a “partner” for it from those not yet involved in generation
of the progeny. Depending on the total fitness for the pair
and mean fitness of the population, the number of progenies
of this pair is determined. When determining the genotypes
of the progenies, a random “recombination” may take place,
when part of the “genes” (values of factors) is taken from
one parent and the remaining “genes”, from the other. A
part of the genes of the progenies is also subject to
mutations.

(5) The genotype next in fitness and its random partner
are selected, both from the genotypes not yet involved in
forming the progeny.
(6) The pairs are formed and the offspring is produced until the number of progenies reaches the specified population size. Thus, the genotypes displaying a higher fitness on the average give larger number of progenies.

(7) Then the fitness of the new-generation genotypes is estimated, new pairs are formed, and new progenies are produced. The process is continued until the number of generations is depleted or until the difference between the minimal and maximal fitnesses in generation becomes less than 1%.

(8) The genotype with the fitness maximal over all generations forms a new initial population without involvement of the remaining genotypes, and this cycle is repeated up to five times.

(9) The set of factors that give the minimal value of optimization criterion is regarded as “optimal” and used to compute the epidemic dynamics.

<table>
<thead>
<tr>
<th>Factors of optimization</th>
<th>Default values, limits of permissible values</th>
<th>Costs of factors</th>
<th>Values after optimization</th>
</tr>
</thead>
</table>
| Rate of asymptomatic contacts/suspects daily isolated with AEA2 (%), DolIz2 | 40 (0-50) | 10 | 50 | 5
| Rate of asymptomatic contacts/suspects daily isolated with AEA3 (%), DolIz3 | 60 (20-70) | 10 | 70 | 6
| Rate of patients in infectious stage daily isolated with AEA1–3 (%); i, immune | Iz_P1 | 20 (0–50) | 10 | 50 | 2
| Iz_P2 | 40 (0–70) | 10 | 70 | 3
| Iz_P3 | 60 (0–90) | 10 | 90 | 4
| Iz_P1 | 10 (0–20) | 10 | 0–20 | 5
| Iz_P2 | 20 (0–40) | 10 | 0–40 | 6
| Iz_P3 | 40 (0–70) | 10 | 80 | 7
| Minimal rate of symptomatic patients daily isolated with AEA1–3 (%), Iz_0 | 10 (0–10) | 10 | 0–10 | 8
| Maximal daily rate of having prophylaxis in risk groups (%), %, RiskVac | 20 (0–30) | 5 | 0–7 | 9
| Number of medics/paramedics involved in AEA, NoMedPer | 2000 (100–10000) | 100 | 478–3177 | 10
| Number of teams searching for and isolating infected cases and contacts, NoMedSt | 100 (10–500) | 200 | 48–215 | 11
| Number of patients/contacts detected by one team per day, NoContSup | 20 (5–100) | 50 | 15–37 | 12
| Number of points for distribution of prophylactic drugs, NoVacpoin | 500 (0–500) | 200 | 0–195 | 13
| Number of persons treated at one point per day, NoVacPer | 500 (0–500) | 50 | 7–500 | 14
| Reserve course doses of prophylactic drugs, NoVacSup | 100000 (0–10000000) | 2 | 0–96633 | 15
| Reserve of drugs in hospitals (for one treatment course), DrugDoses, 3 | 100000 (1000–100000) | 3 | 1000–93381 | 16
| Bed capacity for strict isolation, NoRemPl, 100 | 300 (100–1000) | 100 | 647–780 | 17
| Bed capacity in provisional hospitals, NoSupPl, 50 | 2000 (100–10000) | 50 | 100–1130 | 18
| Bed capacity in quarantine departments for contacts, NoContPl, 70 | 1000 (100–10000) | 70 | 2653–3635 | 19
| Values of optimization criterion | 2427681331 | 412478590–414255942 | 20

1 The third column in Table lists the minimal and maximal values for optimization factors obtained after five iterations of the procedure.

2 The limit permissible values are boldfaced.
### Table 2. Results of optimization of anti-epidemic activities for smallpox

<table>
<thead>
<tr>
<th>Factors of optimization</th>
<th>Default values, limits of permissible values</th>
<th>Costs of the factors</th>
<th>Values after optimization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rate of asymptomatic contacts/suspects daily isolated with AEA2 (%), $D_{olIz2}$</td>
<td>20 (0-50)</td>
<td>10</td>
<td>0 - 3</td>
</tr>
<tr>
<td>Rate of asymptomatic contacts/suspects daily isolated with AEA3 (%), $D_{olIz3}$</td>
<td>50 (0-70)</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>Rate of patients in infectious stage daily isolated with AEA1–3 (%), $i$ - immune</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Iz_P1</td>
<td>20 (0-50)</td>
<td>10</td>
<td>50</td>
</tr>
<tr>
<td>Iz_P2</td>
<td>40 (0-70)</td>
<td>10</td>
<td>0 - 70</td>
</tr>
<tr>
<td>Iz_P3</td>
<td>60 (0-90)</td>
<td>10</td>
<td>90</td>
</tr>
<tr>
<td>Iz_Pi1</td>
<td>10 (0-40)</td>
<td>10</td>
<td>0 - 7</td>
</tr>
<tr>
<td>Iz_Pi2</td>
<td>20 (0-70)</td>
<td>10</td>
<td>1 - 16</td>
</tr>
<tr>
<td>Iz_Pi3</td>
<td>40 (0-80)</td>
<td>10</td>
<td>80</td>
</tr>
<tr>
<td>Rate of patients in final stage (severe case), daily isolated with AEA1–3 (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Iz_Ih1</td>
<td>40 (0-60)</td>
<td>10</td>
<td>60</td>
</tr>
<tr>
<td>Iz_Ih2</td>
<td>60 (0-80)</td>
<td>10</td>
<td>0 - 80</td>
</tr>
<tr>
<td>Iz_Ih3</td>
<td>80 (0-90)</td>
<td>10</td>
<td>0 - 53</td>
</tr>
<tr>
<td>Rate of patients in final stage (mild case), daily isolated with AEA1–3 (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Iz_Il1</td>
<td>20 (0-50)</td>
<td>10</td>
<td>48 - 50</td>
</tr>
<tr>
<td>Iz_Il2</td>
<td>40 (0-60)</td>
<td>10</td>
<td>35 - 60</td>
</tr>
<tr>
<td>Iz_Il3</td>
<td>60 (0-80)</td>
<td>10</td>
<td>0 - 80</td>
</tr>
<tr>
<td>Minimal rate of symptomatic patients daily isolated with AEA1–3 (%), $I_0$</td>
<td>10 (0-10)</td>
<td>10</td>
<td>0 - 10</td>
</tr>
<tr>
<td>Maximal daily rate of vaccinees in risk groups (%), RiskVac</td>
<td>20 (0-50)</td>
<td>5</td>
<td>0 - 32</td>
</tr>
<tr>
<td>Number of medics/paramedics involved in AEA, NoMedPer</td>
<td>2000 (100-10000)</td>
<td>100</td>
<td>332 - 2990</td>
</tr>
<tr>
<td>Number of teams searching for and isolating infected cases and contacts, NoMedSt</td>
<td>100 (10-500)</td>
<td>200</td>
<td>57 - 281</td>
</tr>
<tr>
<td>Number of patients/contacts detected by one team per day, NoContSup</td>
<td>20 (5-100)</td>
<td>50</td>
<td>8 - 68</td>
</tr>
<tr>
<td>Number of vaccination stations, NoVacpoin</td>
<td>50 (0-300)</td>
<td>200</td>
<td>1 - 300</td>
</tr>
<tr>
<td>Number of vaccinees immunized at one station per day, NoVacPer</td>
<td>500 (0-3000)</td>
<td>50</td>
<td>520 - 1056</td>
</tr>
<tr>
<td>Reserve of vaccine doses for mass vaccination, NoVacSup</td>
<td>10000 (0-100000)</td>
<td>2</td>
<td>0 - 362075</td>
</tr>
<tr>
<td>Reserve of drugs in hospitals (for one treatment course), DrugDoses, 3</td>
<td>1000 (0-50000)</td>
<td>3</td>
<td>895 - 1684</td>
</tr>
<tr>
<td>Bed capacity for strict isolation, NoRemPl, 100</td>
<td>300 (100-1000)</td>
<td>100</td>
<td>420 - 771</td>
</tr>
<tr>
<td>Bed capacity in provisional hospitals, NoSupPl, 50</td>
<td>2500 (100-10000)</td>
<td>50</td>
<td>2197 - 6315</td>
</tr>
<tr>
<td>Bed capacity in quarantine departments for contacts, NoContPl, 70</td>
<td>1000 (100-10000)</td>
<td>70</td>
<td>100 - 1815</td>
</tr>
<tr>
<td>Values of the optimization criterium</td>
<td>92185380</td>
<td></td>
<td>43391115 - 46574888</td>
</tr>
</tbody>
</table>

1. The third column in Table lists the minimal and maximal values for optimization factors obtained after five iterations of the procedure.
2. The limit permissible values are boldfaced.

### 3. Results and Discussion

When studying the effect of AEA optimization, the interventions were optimized for all the infections to which the model is adapted. All the default model parameters were used for computing the dynamics of epidemics. The costs for optimization factors were also equal in all the calculations as well as the weights for the losses caused by epidemics in the optimization criterion. Except for influenza, all computations started from the primary infected cohort of 500 persons, which, in principle, corresponds to a mass bioterrorism attack or a large-scale accident in a facility dealing with pathogens. The computations were performed on the server of the model. The parameters that characterize infections and their justification are available on the server.

One of the factors, namely, rate of immune persons, was
discarded from optimization since its influence is so great, that it took on the maximally permissible values for all infections. In the case of plague, the rates of isolated patients in the third noninfectious stage, initially amounting to zero, were also not optimized.

Since the genetic algorithm of optimization is based on random processes of mutations, recombinations, and selection of parental pairs, the optimization was repeated five times for each pathogen. In this process, the criterion values for each infection after optimization fell in a rather narrow range, thereby demonstrating stability of optimization, based on a random process (Fig. 1). The following value was used to assess the sensitivity to optimization:

\[ S = 100\times(1 - C_i/C_0), \]  

(2)

where \( C_i \) and \( C_0 \) are the values of criterion after and before optimization, respectively.

Consider in more detail the results obtained by optimizing interventions for two infections, smallpox and plague (pneumonic form).

In a sense, these two selected infections are opposite. The smallpox incubation and infectious periods are long enough versus very short periods of plague. Efficient preventive and emergency vaccinations are possible for smallpox, whereas there is no anti-plague vaccine for mass immunization; however, the latter is compensated for by preventive administration of therapeutics (antibiotics) in the case of a plague epidemic. A rather high average number of the persons infected from one smallpox patient (\( R_0 \approx 8 \); this estimate has been obtained by adapting the model to the data on smallpox outbreaks in European cities [11]) and a relatively low transmission potential for plague (\( R_0 \approx 3 \) [14]) are leveled by that the duration of “generations” in the case of plague is short, so that one plague patient over one month can have more following infected persons than a smallpox patient.

Both the plague and smallpox appeared to be rather sensitive to the optimization of interventions. In particular, the optimization criterion for smallpox decreases more than twofold over 43–112 generations and for plague, sixfold over 48–58 generations.

The sets of “optimal” values for the factors are listed in Tables 1 (plague) and 2 (smallpox). It is evident that the minimal values of the criterion in the case of plague are attained provided that most of the factors run into the boundaries of permissible values. As for the isolation rates, these are the maximal values. For the remaining factors, most diverse values minimizing the value of the criterion have been obtained in individual implementations.

Low optimal values of several factors (for example, reserves of prevention drugs) are explainable by that, according to default settings, all resource restrictions are removed in the case of strict AEA, which is launched for plague approximately on day 10. Thus, all resources from that moment on are obtainable “free of cost”, so there is no need to maintain expensive mobilization preparedness for several factors. Note that all these reasoning is true only taking into account the “default” modeling parameters. Once a user considerably changes the time for implementation of AEA, costs for the factors, and weights of losses, the final conclusions may appear quite different.

As for the results of optimizing intervention in the case of local smallpox epidemics, the overall pattern is similar on the background of differences in absolute values, namely, close values of optimization criterion are attained at considerably different values of the parameters (Tables 1 and 2). Relative scattering of the epidemic (outbreak) parameters per se after several iterations of optimization procedure is only slightly higher than the relative scattering of optimization criterion (Tables 3 and 4).

| Table 3. Indices of epidemics used for calculations of losses for plague |
|-----------------|----------------|-----------------|-----------------|
| Indices                     | Weights of indices | Values for default parameters | Values after optimization |
| Total number of infected persons | 100 | 31664 | 5001–5177 |
| Person days of isolated patients | 1 | 380615 | 42111–45543 |
| Person days of observed contacts | 0.5 | 171874 | 24886 |
| Person days of observed suspects | 0.5 | 1405548 | 169 358–184422 |
| Quarantine (days) | 100 | 90 | 35 |
| Total number of lethal cases | 10 000 | 21 709 | 4103–4229 |
| Took preventive treatment | 0.1 | 408838 | 288240–322180 |
Table 4. Indices of epidemics used for calculations of losses for smallpox

<table>
<thead>
<tr>
<th>Indices</th>
<th>Weights of indices</th>
<th>Values for default parameters</th>
<th>Values after optimization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of infected persons</td>
<td>100</td>
<td>5552</td>
<td>4539–4865</td>
</tr>
<tr>
<td>Person days of isolated patients</td>
<td>1</td>
<td>103378</td>
<td>87 536–94 575</td>
</tr>
<tr>
<td>Person days of observed contacts</td>
<td>0.5</td>
<td>71012</td>
<td>13777–17101</td>
</tr>
<tr>
<td>Person days of observed suspects</td>
<td>0.5</td>
<td>3104620</td>
<td>2 471357–411417</td>
</tr>
<tr>
<td>Quarantine (days)</td>
<td>100</td>
<td>53</td>
<td>42–44</td>
</tr>
<tr>
<td>Total number of lethal cases</td>
<td>10000</td>
<td>863</td>
<td>412–449</td>
</tr>
<tr>
<td>Total number of vaccinees</td>
<td>0.1</td>
<td>733933</td>
<td>770730–857717</td>
</tr>
</tbody>
</table>

When the optimal values of factors run into the permissible limits, a dilemma emerges whether the limits should be expanded or, if the limits are real, the values of the corresponding factors should be fixed to the boundaries, the factors should be discarded from optimization, and the optimization procedure should be repeated for the remaining factors.

3. Conclusions

The universal model for epidemics, constructed at the State Research Center of Virology and Biotechnology Vector, makes it possible to study in an integrated manner the effects of manifold parameters on dynamics of a local epidemic or an outbreak, the range of parameters spanning from characteristics of pathogens to availability of necessary resources, which is most important for timely and comprehensive implementation of anti-epidemic activities.

One of the provided options is optimization of interventions. In this procedure, user may change the initial values of optimization factors and their permissible limits as well as the “weights” for the contributions of the factors and some epidemic parameters to the optimization criterion. The weights should be specified most accurately, since underestimated weights actually exclude the influence of factors or parameters on the value of the criterion as compared with the others. On the contrary, overestimated weights level the effects of the remaining factors.

This is vividly demonstrated by the fact that the “optimal” values of several factors may coincide with their lower limits despite their evident importance for the dynamics of an epidemic. This is explainable by that a default condition implies that any resource restrictions on the scale of interventions are canceled when the third-level strict anti-epidemic activities are switched on. This allows the constant and expensive maintenance of preparedness for several factors to be canceled too.

In general, the computations demonstrate that the model allows for efficient optimization of interventions. The optimization leads to a considerable decrease in all the parameters contributing to estimation of the losses caused by epidemics, such as the total number of infected persons and lethality.

Individual infections display different sensitivities to the optimization procedure. It appears expectable that the more transmissive the infection, the more sensitive is the epidemic it causes to the optimization of anti-epidemic activities. Influenza has emerged to be the most sensitive to optimization of interventions (the criterion decreases almost 100-fold) as well as pneumonic plague (the criterion decreases by over 80%). Marburg hemorrhagic fever, a weakly transmissible disease, and nontransmissible anthrax are least sensitive to the optimization.

Thus, by specifying permissibility limits of the factors determining the intervention efficiency and the costs for their maintenance or implementation, it is possible to obtain close to optimal values of the factors and to estimate feasibility of a full-fledged implementation of the anti-epidemic activities for several acute infectious diseases and even any acute infectious diseases, provided by a user high qualified in epidemiology, for which it is possible to ignore sex-related differences, age, and other sociodemographic characteristics of population cohorts.

Acknowledgements

The work was partially supported by the Federal Target Program “National System of Chemical and Biological Safety of the Russian Federation for 2009–2014.”

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