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PROBLEM OF OPTIMAL CONTROL OF EPIDEMIC IN VIEW OF LATENT PERIOD

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The problem of optimal control of epidemic through vaccination and isolation, taking into account latent period is considered. The target function is minimized – functionality summarizing costs on epidemic prevention and treatment and also considering expenses on infected people left at the end of control T who may be a new source of epidemic. On the left endpoint of the integration segment initial data is given – quantity of infected and confirmed people at the moment t, the right endpoint is free. The dynamic constraints are written by way of a system of simple differential equations describing the speed of changes of number of subjected to infection and number of already infected. Besides the inhomogeneous community is considered, consisting of four age groups (babies, preschool children, school children and adults). The speed of vaccination (number of vaccinated per a time unit) and isolation speed are used as the control functions. There are some restrictions on control above and below. The latent period is described by the constant h and is part of the equation describing the contamination speed of people as a retarding in argument t, i.e. a person being in a latent period infects others not being aware of his disease. For problem solving Pontryagin maximum principle is used where it can be seen that the control is piecewise constant. The result of numerical implementation of discrete problem of optimal control is given. The conclusions are made that the latent period significantly influence the incidence rate and as consequence the costs on epidemic suppression. The programme based on the programming language Delphi gives an opportunity to estimate the scale of epidemic at different initial data and restrictions on control as well as to find an optimal control minimizing costs on epimedic suppression.

Key words: optimal control of epidemic, latent period, vaccination and isolation, minimization of epidemic elimination costs.

INTRODUCTION

Problems of optimal control of systems with delayed argument have extensive applications in engineering, economics, medicine, automatic control theory, theory of self-oscillatory systems and other sciences [1, p.78]. The development of approximate and numerical methods for solving such problems is a pressing issue. In this paper, taking into account latent period, we consider the problem of optimal control of the epidemic, which is described by a system of ordinary differential equations with delayed argument. The author constructed a model of the epidemic with a constant delay on the basis of Cermak-McKendrick model, formulated necessary conditions for optimality of the Pontryagin maximum principle, developed a numerical method for solving the problem for an inhomogeneous community, consisting of four groups, and carried out an analysis of the impact of the delay on optimal control.

RESEARCH METHODS AND METHODOLOGY

Let us consider the problem of optimal control of epidemic through vaccination and isolation in an inhomogeneous community, consisting of n age groups, taking into account the latent period h. The dynamics of the epidemic is described by the following system of differential equations with delay:

$$\begin{cases} \dot{x}_i(t) = -x_i(t)\sum_{j=1}^{n}\beta_{ij}y_j(t) - \mu_i x_i(t) - v_i(t) + \Lambda_i, & i=\overline{1,n}, \quad t\in[0;T], \\ \dot{y}_i(t) = x_i(t-h)\sum_{j=1}^{n}\beta_{ij}y_j(t-h) - \mu_i y_i(t) - \tilde{\mu}_i y_i(t) - \gamma_i y_i(t) - u_i(t), & i=\overline{1,n}, \quad t\in[0;T], \end{cases} \tag{1}$$

with the initial conditions on the interval of delay T_0 :

$$x_i(t) = x_{i0}(t), \quad y_i(t) = y_{i0}(t), \quad i = \overline{1, n}, \quad t \in T_0 = [-h;0], \tag{2}$$

where $x_i(t)$ – number of people exposed to infection in the i-group at time t ($i = \overline{1, n}$), $y_i(t)$ – number of people infected in the i-group, $\dot{x}_i(t)$ – rate of change in the number of people exposed to infection in the i-group at time t, $\dot{y}_i(t)$ – rate of change of the number of infected people in the i-group, $x_i(t)\sum_{j=1}^{n}\beta_{ij}y_j(t)$ – rate of infection of healthy people out of the i-group from the infected people of the j-group at time t, given the fact that the infection could occur from an infected person from any of the j-group ($j = \overline{1, n}$), $\gamma_i y_i(t)$ – number of patients in the i-group, regained their health without the action of external agents: quarantine, vaccination and so forth (γ^{-1} – average time of natural recovery for the given infectious disease), β_{ij} – growth coefficient, characterizing the frequency of meetings of healthy people out of the i-group with infected people out of the j-group and the probability of infection at the meeting, μ_i – natural mortality coefficient of people in the i-group, $\tilde{\mu}_i$ – mortality coefficient from the given infection in the i-group, Λ_i – average birth rate in the i-th group, h – constant quantity, characterizing the latent time of the disease. Let us denote $v_i(t)$ – population vaccination rate among those who are exposed to infection in i-group at time t, $u_i(t)$ – isolation rate of the infected in i-group at time t. Restrictions on the control functions are set in the following form:

$$0 \le v_i \le M_i, \quad i = \overline{1;n} \tag{3}$$

$$0 \le u_i \le N_i, \quad i = \overline{1;n} \tag{4}$$

where M_i, N_i – maximum rates of vaccination and isolation (are limited by technical and material possibilities) in the i-group.

Functional:

$$J(u,v) = \int_0^T \sum_{i=1}^{n} (Ay_i(t) + D_i v_i(t) + C_i u_i(t))dt + \sum_{i=1}^{n} B_i y_i(T) \to \inf \tag{5}$$

characterizes the aim of control, which is to minimize the cost of infection elimination, where A – the average cost per patient for the society per unit of time (known quantity, for Russia it is about \$ 50 [4, p. 7]), D_i – the cost of vaccination per person in the i-group, C_i – the cost of isolation per person in the i-group. The latter summand refers to the cost of residual patients, which may cause secondary infection, so their cost B_i ($i = \overline{1;n}$) should be large (as a penalty for undertreated patients). Unfortunately, in the latter summand we can not take into account the ones who are in incubation period, as they have not moved in the patients' group yet.

If we take A, the average cost of a patient for the society per a unit of time, equal to one standard monetary unit, then (5) can be rewritten as following:

$$J(u,v) = \int_0^T \sum_{i=1}^{n} (y_i(t) + d_i v_i(t) + c_i u_i(t))dt + \sum_{i=1}^{n} b_i y_i(T) \to \inf \tag{6}$$

where d_i – relative cost of vaccination per person in the i-group, c_i – relative cost of isolation of the patient in the i-group, b_i – relative cost of one undertreated patient in i-group at time T (and b > 1, since each undertreated patient can infect more people in the future).

Necessary conditions of optimality: let's construct Pontryagin's function:

$$H(x,y,g,z,v,u,p,q) = -\lambda_0 \sum_{i=1}^{n}(y_i(t) + d_i v_i(t) + c_i u_i(t)) + \sum_{i=1}^{n}(-x_i(t)\sum_{j=1}^{n}\beta_{ij} y_j(t) - \mu_i x_i(t) + \Lambda_i - v_i(t)) +$$
$$\sum_{i=1}^{n} q_i(t)(g_i(t)\sum_{j=1}^{n}\beta_{ij} z_j(t) - \mu_i y_i(t) - \tilde{\mu}_i y_i(t) - \gamma_i y_i(t) - u_i(t)),$$

where $g_i(t) = x_i(t-h), \quad z_i(t) = y_i(t-h), \quad i = \overline{1;n}$.

Switching functions:

$$\varphi_i(t) = -\lambda_0 d_i - p_i(t), \quad \psi_i(t) = -\lambda_0 c_i - q_i(t), \quad i = \overline{1;n}.$$

On the basis of the theorem about the necessary conditions of optimality in systems with after effects, formulated and proved in [2], [3], [6], we can write the necessary conditions of optimality for the previously constructed model.

If permissible process $\overline{w} = (\overline{x}, \overline{y}, \overline{v}, \overline{u})$ for each $t \in [0;T]$ is optimal in the problem (1)–(4), (6), then there exist not all at a time equal to zero number λ_0 and vector functions $p_i(t), q_i(t)$ such that the optimal control is determined by the following conditions:

$$\begin{cases} \overline{v}_i = 0, \quad if \quad (-\lambda_0 d_i - p_i(t)) < 0, \quad i = \overline{1;n} \\ \overline{v}_i = M_i, \quad if \quad (-\lambda_0 d_i - p_i(t)) > 0, \quad i = \overline{1;n} \\ 0 \le \overline{v}_i \le M_i, \quad if \quad (-\lambda_0 d_i - p_i(t)) = 0, \quad i = \overline{1;n} \end{cases} \tag{7}$$

$$\begin{cases} \overline{v}_i = 0, \quad if \quad (-\lambda_0 d_i - p_i(t)) < 0, \quad i = \overline{1;n} \\ \overline{v}_i = M_i, \quad if \quad (-\lambda_0 d_i - p_i(t)) > 0, \quad i = \overline{1;n} \\ 0 \le \overline{v}_i \le M_i, \quad if \quad (-\lambda_0 d_i - p_i(t)) = 0, \quad i = \overline{1;n} \end{cases} \tag{8}$$

and conjugate functions satisfy the system of differential equations (here and below $\lambda_0 = 1$):

$$\begin{cases} \dot{p}_l = -\left.\dfrac{\partial H}{\partial x_l}\right|_t - \left.\dfrac{\partial H}{\partial g_l}\right|_{t+h} = \left. p_l(\sum_{j=1}^{n}\beta_{lj} y_j + \mu_l)\right|_t + \left. q_l \sum_{j=1}^{n}\beta_{lj} z_j\right|_{t+h} = \\ = p_l(t)(\sum_{l=1}^{n}\beta_{lj} y_j(t) + \mu_i) + q_l(t+h)\sum_{j=1}^{n}\beta_{lj} z_j(t+h), \quad i = \overline{1,n} \\ \dot{q}_l = -\left.\dfrac{\partial H}{\partial y_l}\right|_t - \left.\dfrac{\partial H}{\partial z_l}\right|_{t+h} = 1 + \left.(\sum_{i=1}^{n}\beta_{il} x_i p_i + q_l(\mu_l + \tilde{\mu}_l + \gamma_l))\right|_t - \left.\sum_{i=1}^{n}\beta_{il} g_i q_i\right|_{t+h} = \\ = 1 + \sum_{i=1}^{n} p_i(t)\beta_{il} x_i(t) - \sum_{i=1}^{n} q_i(t+h)\beta_{il} x_i(t) + q_l(t)(\mu_l + \tilde{\mu}_l + \gamma_l), \quad i = \overline{1,n} \end{cases} \tag{9}$$

$$p_i(T) = 0; \;\; q_i(T) = -b_i; \;\; p_i(t) = 0, \;\; q_i(t) = 0, \;\; t > T. \tag{10}$$

(10) – transversality conditions at the right end of integration.

Numerical realization of the task: We divide the interval of integration [0; T] into q equal subintervals by the points $0 = t_0 < t_1 < ... < t_q = T$ so that the length of each subinterval is $\Delta t = t_{i+1} - t_i$, $i = \overline{0, q-1}$. Let's divide delay interval [–h; 0] with a step Δt, rounding the obtained result to an integer m > 0.

Integral $I(v,u)$ may be found by a numerical method of rectangles, the error is estimated by the formula:

$$|R| \le \max_{[a,b]} |f'(x)| \frac{(b-a)^2}{2n},$$

where f(x) – integrand, [a; b] – the integration interval, n is the number of elementary partition segments of [a; b] [9, p. 99], and differential equations – by the Euler method, the error is estimated by the formula $|y_i - y(x_i)| \le C_1 h\,(e^{C_2(x_i - x_0)} - 1)$, where $|y_i - y(x_i)|$ – deviation of the approximate solution from the exact one, C_1, C_2 – positive constants determined by the right side of the equation $y' = f(x,y)$ and its derivatives in the neighborhood of the point (x_i, y_i), h = const – step of the numerical method, from h → 0 should be uniform aspiration [8 , p. 37].

Then the problem (1)–(5) is approximated by the following discrete problem of optimal control with accuracy $O(\Delta t)$:

$$I(v,u) = \sum_{j=1}^{n}\sum_{i=0}^{q-1}(y_j^i + d_j v_j^i + c_j u_j^i)\Delta t + \sum_{j=1}^{n} b_j y_j^q \to \inf \tag{11}$$

$$\begin{cases} x_j^{i+1} = x_j^i - x_j^i \Delta t \sum_{k=1}^{n} \beta_{jk} y_k^i - \Delta t(v_j^i + \mu_j x_j^i - \Lambda_j), \quad j = \overline{1;n}, \quad i = \overline{0; q-1}, \\ y_j^{i+1} = y_j^i + x_j^{i-m} \Delta t \sum_{k=1}^{n} \beta_{jk} y_k^{i-m} - \Delta t((\gamma_j + \mu_j + \tilde{\mu}_j) y_j^i + u_j^i), \quad j = \overline{1;n}, \quad i = \overline{0; q-1}, \end{cases} \tag{12}$$

$$x_j^{i,0} = \zeta_j^i, \quad y_j^{i,0} = \zeta_j^i, \quad j = \overline{1,n}, \quad i = \overline{-m,0} \tag{13}$$

in the delay interval T_0

$$0 \le v_j^i \le A_j, \quad 0 \le u_j^i \le B_j, \quad j = \overline{1,n}, \quad i = \overline{0,q-1}. \tag{14}$$

The Lagrangian function:

$$\begin{aligned} L = \lambda_0 \left[\sum_{j=1}^{n}\sum_{i=0}^{q-1} \left(y_j^i + d_j v_j^i + c_j u_j^i \right) \Delta t + \sum_{j=1}^{n} b_j y_j^q \right] + \sum_{j=1}^{n}\sum_{i=0}^{q-1} p_j^{i+1} \Bigg(x_j^{i+1} - x_j^i + x_j^i \Delta t \sum_{k=1}^{n} \beta_{jk} y_k^i + \\ \Delta t \left(v_j^i + \mu_j x_j^i - \Lambda_j \right) \Bigg) + \sum_{j=1}^{n}\sum_{i=0}^{q-1} q_j^{i+1} \left(y_j^{i+1} - y_j^i - x_j^{i-m} \Delta t \sum_{k=1}^{n} \beta_{jk} y_k^{i-m} + \Delta t \left(\gamma_j + \mu_j + \mu_j \right) y_j^i + u_j^i \right). \end{aligned} \tag{15}$$

We calculate the derivatives of the Lagrangian function, write down stationary conditions in the problem (11)–(14):

$$\frac{\partial L}{\partial x_j^i} = p_j^i - p_j^{i+1} + p_j^{i+1}\Delta t\sum_{k=1}^{n}\beta_{jk}y_k^i + p_j^{i+1}\Delta t\mu_j - q_j^{i+1+m}\Delta t\sum_{k=1}^{n}\beta_{jk}y_k^i = 0$$

$$\frac{\partial L}{\partial y_j^i} = \Delta t + \Delta t\sum_{k=1}^{n}p_k^{i+1}\beta_{kj}x_k^i + q_j^i - q_j^{i+1} - \Delta t\sum_{k=1}^{n}q_k^{i+1+m}\beta_{kj}x_k^i + \Delta t q_j^{i+1}(\gamma_j + \mu_j + \tilde{\mu}_j) = 0$$

or

$$\begin{aligned} p_j^i &= p_j^{i+1} - p_j^{i+1}\Delta t\sum_{k=1}^{n}\beta_{jk}y_k^i - p_j^{i+1}\Delta t\mu_j + q_j^{i+1+m}\Delta t\sum_{k=1}^{n}\beta_{jk}y_k^i, \qquad j=\overline{1,n}, \quad i=\overline{0,q-1}, \\ q_j^i &= q_j^{i+1} - \Delta t - \Delta t\sum_{k=1}^{n}p_k^{i+1}\beta_{kj}x_k^i + \Delta t\sum_{k=1}^{n}q_k^{i+1+m}\beta_{kj}x_k^i - \Delta t q_j^{i+1}(\gamma_j + \mu_j + \tilde{\mu}_j), \quad j=\overline{1,n}, i=\overline{0,q-1}. \end{aligned} \tag{16}$$

$$p_j^q = \frac{\partial L}{\partial x_j^q} = 0, \;\; q_j^q = \frac{\partial L}{\partial y_j^q} = -\lambda_0 b_j \;\text{ if }\; i > q \quad p_j^i = 0, q_j^i = 0 \tag{17}$$

Partial derivatives of the Lagrangian function with respect to the control variable are the following:

$$\begin{aligned} &\varphi_j^i = \frac{\partial L}{\partial v_j^i} = \left(\lambda_0 d_j + p_j^{i+1}\right)\Delta t, \psi_j^i = \frac{\partial L}{\partial u_j^i} = \left(\lambda_0 c_j + q_j^{i+1}\right)\Delta t \\ &j=\overline{1,n}, i=\overline{0,q-1}. \end{aligned} \tag{18}$$

To build the solution to the discrete problem of optimal control (11)–(18) we use the gradient projection method [10].

RESULTS OF THE RESEARCH

To carry out the experiment on a real model there were used statistical data on influenza epidemic in the city of Arkhangelsk. The data were provided by the Territorial Administration of the epidemiological surveillance in the city of Arkhangelsk over the past twenty years. On the basis of these data there were allocated four age groups:

I group – children from 0 to 2 years old,
II group – children from 3 to 6 years old,
III group – children from 7 to 14 years old,
IV group – people over 15 years old.

Mortality coefficients (independent of the flu) for each group, calculated in accordance with statistical data for Arkhangelsk: μ_1 = 0.008, μ_2 = 0.001, μ_3 = 0.001, μ_4 = 0.028. $\tilde{\mu}_j$ = 0 ($j=\overline{1;4}$) – take death coefficients, where death occurred because of the flu, zero, as there were no registered deaths caused by the flu over the past twenty years in Arkhangelsk. Take one week per a unit of time. The average birth rate in the 1st group is 35 people a week, in the rest groups Λ_j = 0 ($j=\overline{2;4}$). γ_j – natural recovery coefficient, it can be taken equal to one, as γ_j^{-1} – the average time of natural recovery coefficient, as for flu can be taken equal to one week. The coefficients β_{jk} are found by solving the inverse problem:

$$\beta_{14} = 4{,}22 \cdot 10^{-5};\ \beta_{11} \approx \beta_{12} \approx \beta_{13} \approx 4{,}22 \cdot 10^{-6};$$
$$\beta_{22} = 6{,}50 \cdot 10^{-5};\ \beta_{21} \approx \beta_{23} \approx \beta_{24} \approx 6{,}50 \cdot 10^{-6};$$
$$\beta_{33} = 2{,}41 \cdot 10^{-5};\ \beta_{31} \approx \beta_{32} \approx \beta_{34} \approx 2{,}41 \cdot 10^{-6};$$
$$\beta_{44} = 3{,}07 \cdot 10^{-6};\ \beta_{41} \approx \beta_{42} \approx \beta_{43} \approx 3{,}07 \cdot 10^{-7};$$

The latent period of the flu disease is from 1 to 10 days (usually 3–5 days) [4, p. 2]. Let us consider the time period of 10 weeks (T = 10). The relative vaccination cost is d = 0,01 in all the groups. The relative isolation cost is c = 3 in all the groups. The calculations were made in Delphi. In case when $b_1 = b_2 = b_3 = b_4 = 0$ the solution of the problem is shown on the following graphs (the epidemic dynamics and optimal control for the first, second and third groups are similar, therefore the graphics are shown only for the third and fourth groups).

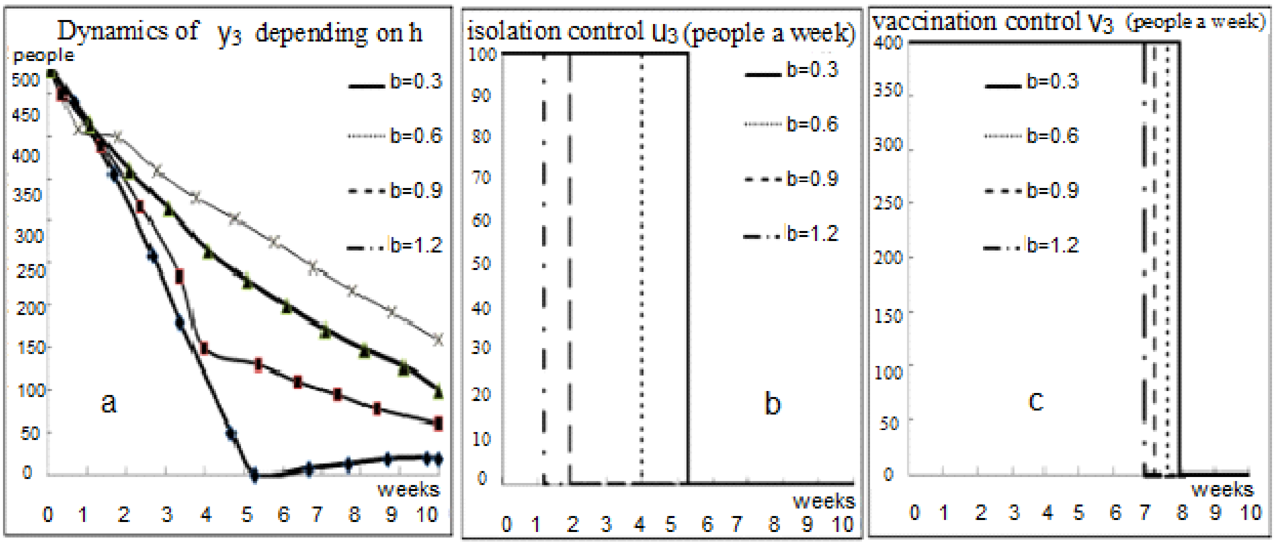

Fig. 1. Dynamics of the infected y_3 (a), isolation control u_3 (b), vaccination control v_3 (c) depending on h

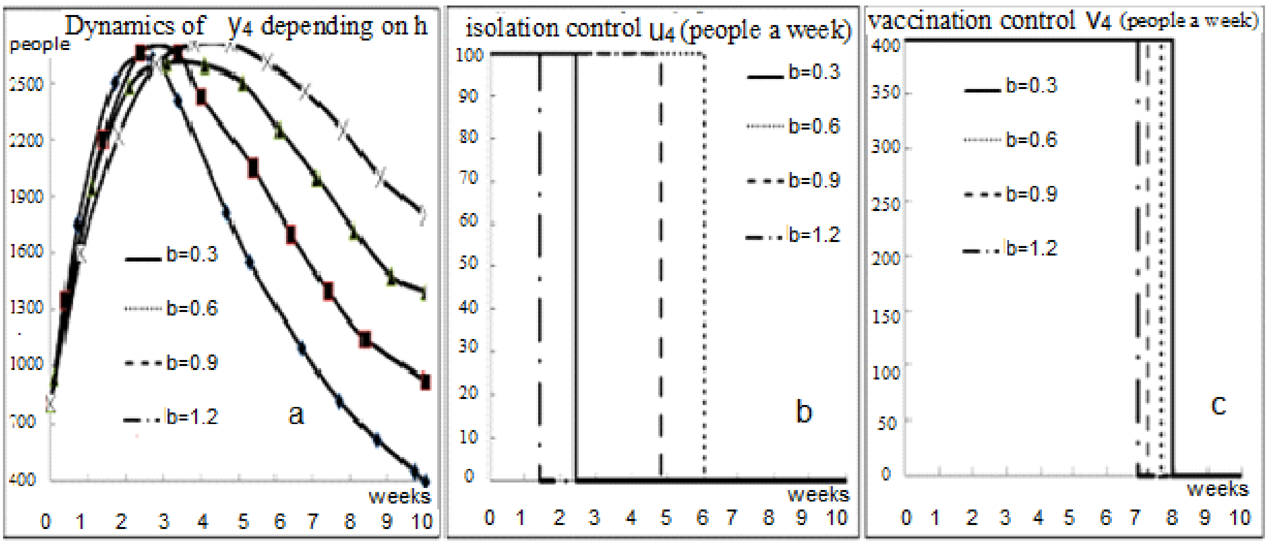

Fig. 2. Dynamics of the infected y_4 (a), isolation control u_4 (b), vaccination control v_4 (c) depending on h

Analysis of the results shows that with the growth of *h* increases the number of infected people $y_j\ \left(j = \overline{1,4}\right)$ on the interval [0; T], decreases duration of vaccination control as well as duration of isolation control, although not all the patients are isolated and cured. With the growth of h increase the total costs of infection elimination.

Now take $b_j \neq 0$ (j = 1,2,3,4), i.e. introduce a fine for undertreated patients. Let $b_j = 5$ (j = 1, 2, 3, 4).

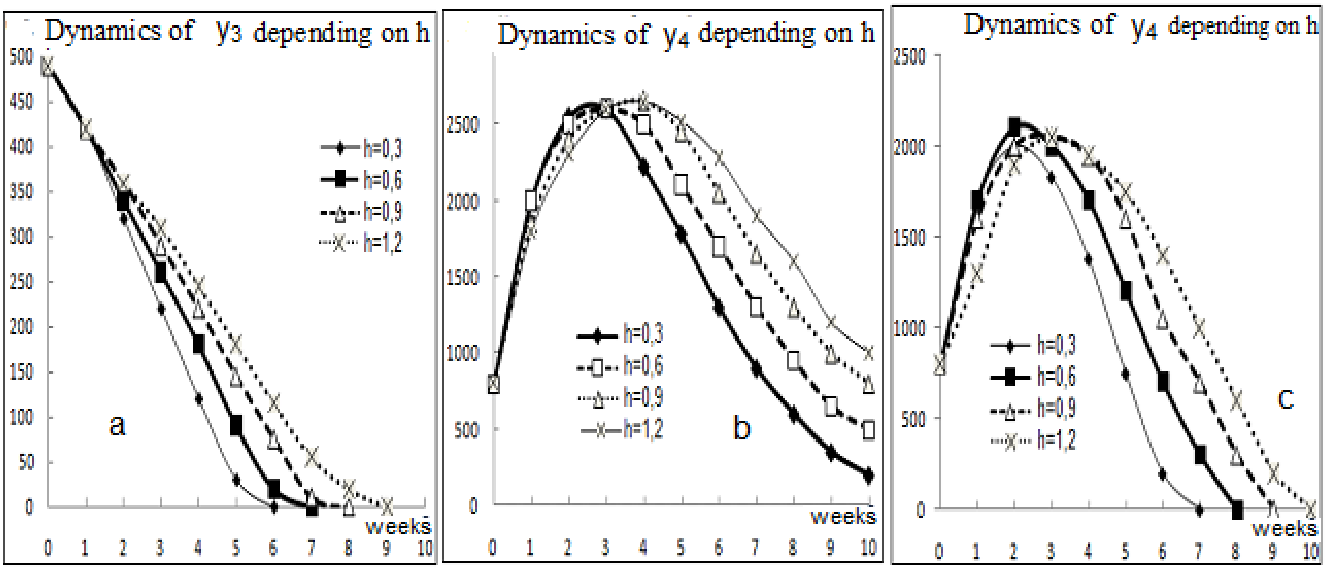

Fig. 3. Dynamics of the infected y_3(a) and y_4 (b) under constant isolation control $u_3 = u_4 = 100$ (pers./week) and dynamics of the infected y_4 (c) under constant isolation control $u_4 = 500$ (pers./week) depending on h

So now it is obvious that it is more profitable to heal the patients than to leave them undertreated, as they may cause secondary infection. Therefore, control should be of maximum rate and duration. Control in the first three groups is enough to eliminate the infection in the period under review (fig. 3a), in the fourth group – not enough (fig. 3b). To eliminate the infection in the fourth group, you have to either strengthen control or increase its duration. Increase in the isolation rate of patients up to five times gives the desired result – an epidemic in the fourth group will be eliminated within the required time frame (fig. 3c).

DISCUSSION OF OBTAINED RESULTS AND CONCLUSION

We have considered the problem of optimal control of epidemic through vaccination and isolation in an inhomogeneous community, consisting of four age groups, taking into account latent period. The aim of the control is to minimize the costs to fight the epidemic at existing control restrictions. The objective of numerical research is to reveal the impact of the latent period duration on program control. To carry out numerical experiment on a real model there were used statistical data on influenza epidemic in the city of Arkhangelsk. The obtained result shows that with the growth of latent period increases the number of the infected in all the groups, decreases duration of vaccination control as well as duration of isolation control, although not all the patients are isolated and cured. When introducing a fine for undertreated patients, control maximizes with respect to rate and duration, as it is more profitable to cure the patients rather than fight off the secondary infection.

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ЗАДАЧА ОПТИМАЛЬНОГО УПРАВЛЕНИЯ ЭПИДЕМИЕЙ С УЧЕТОМ ЛАТЕНТНОГО ПЕРИОДА

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Рассматривается задача оптимального управления эпидемией путём вакцинации и изоляции с учётом латентного периода. Минимизируется целевая функция – функционал, суммирующий затраты на лечение и профилактику эпидемии, а также учитывающий стоимость инфицированных людей, оставшихся на момент окончания управления T, которые могут явиться источником новой эпидемии. На левом конце отрезка интегрирования заданы начальные условия – количество инфицированных и подверженных заражению в момент времени t, правый конец – свободный. Динамические ограничения записаны в виде системы обыкновенных дифференциальных уравнений, описывающих скорость изменения числа подверженных заражению и числа уже зараженных. Причем рассматривается неоднородное общество, состоящее из четырех возрастных групп (младенцы, дошкольники, школьники, взрослые). В качестве управляющих функций взяты скорость вакцинации (число вакцинированных в единицу времени) и скорость изоляции. Имеются ограничения на управление сверху и снизу. Латентный период описывается константой h, и входит в уравнение, описывающее скорость инфицирования людей как запаздывание в аргументе t, то есть человек, находящийся в латентном периоде, заражает окружающих, не зная, что он уже болен. Для решения задачи записывается Принцип максимума Понтрягина, откуда видно, что управление является кусочно-постоянным. В работе приводится результат численной реализации дискретной задачи оптимального управления, сделаны выводы о том, что латентный период существенно влияет на рост заболеваемости и, как следствие, расходов на погашение эпидемии. Программа, написанная на языке программирования Delphi, дает возможность оценить масштабы эпидемии при различных начальных данных и ограничениях на управление, а также найти оптимальное управление, минимизирующее расходы на погашение эпидемии.

Ключевые слова: оптимальное управление эпидемией, латентный период, вакцинация и изоляция, минимизация затрат на погашение эпидемии.

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