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Energy cost of infection burden: An approach to understanding the dynamics of host–pathogen interactions

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Abstract

A mathematical model of long-term immune defense against infection was used to estimate the energy involved in the principal processes of immune resistance during periods of health and infection. From these values, an optimal level of energy was determined for immune response depending on infection burden. The present findings suggest that weak but prevalent pathogens lead to latent or chronic infection, whereas more virulent but less prevalent pathogens result in acute infection. This energy-based approach offers insight into the mechanisms of immune system adaptation leading to the development of chronic infectious diseases and immune deficiencies. Published by Elsevier Ltd.

Keywords: Infection burden; Immune defense; Energy cost; Adaptation; Trade-off

1. Introduction

Epidemiological, clinical and experimental data suggest that the immune system interacts with pathogens in the body in various but predictable ways. Non-specific arms (phagocytes, complement, interferon) and specific arms of immune defense (lymphocytes, antibodies) involve about 10^{12} cells and 10^{20} molecules in humans and cannot provide absolute protection against frequent infections caused by various microorganisms. Though the immune system adjusts its defense parameters to decrease substantially the rate and severity of infectious disease, why, nevertheless, does it maintain a level of defense which permits considerable morbidity? Usually, this question is treated as a problem of choice between defense as a resistance to infection and disease as a compromise (Gemmill and Read, 1998). It can be assumed that a strong immune response, resulting in prolonged periods of good health, and weak immune response, leading to frequent illness, are both too costly to an organism and lead to a decrease in fitness.

In this paper, energy is used as a cost measure of host–pathogen interactions. The relationship between the cost of immune resistance and disease-persistence may be considered as an example of a physiological trade-off (Stearns, 1992) and the problem of searching for immune defense strategies which are optimal for given environmental conditions can be formulated (Schmalhausen, 1949; Rashevsky, 1961).

The main processes of infectious pathology are: inflammation, immune response and damage to the target organ. Although we have a considerable understanding of inflammatory reaction, the role of inflammation in immune response is not completely understood (Fedoseev, 1998; Ley, 2000; MacDonald and Monteleone, 2005). Most mathematical models of infectious diseases describe the dynamics of specific immune responses (Marchuk, 1997; Nowak and May, 2000). Following from an analysis of mechanisms of common infections caused by opportunistic pathogens, the role of specific immune response during early stages of infection is not as crucial as immune response during final stages (Korol', 1983; Jakab, 1985; Karpov and Romanyukha, 1992). For opportunistic infections of the lungs, non-specific immune protection such as phagocytosis plays the principal role (Mayanski

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Table 1
Morphometric data characterizing size, structure and cellular composition of lungs in healthy human adults

Characteristics, dimension	Value	Reference
Total volume of lung airways (ml)	4500–5000	Weibel (1963)
Volume of lungs between the 1st and 8th airway generations (ml)	30–35	Weibel (1963)
Perimeter of trachea (mm)	50	Fedoseev (1998
Perimeter of terminal bronchioli (m)	30	Weibel (1963)
Surface area of conducting airways between trachea and bronchioli (m^2)	0.25	Mercer et al. (1994)
Diameter of respiratory bronchioli (μm)	600–700	Weibel (1963)
Diameter of alveoli (μm)	250–300	Weibel (1963)
Volume of lung respiratory compartment (ml)	3150	Weibel (1963)
Total volume of alveoli (ml)	2300–2900	Weibel (1963)
Total volume of lung capillaries (ml)	140	Weibel (1963)
Diameter of lung capillary (μm)	8	Weibel (1963)
Total number of alveoli	3×10^8	Weibel (1963)
Surface area of gas exchange in lungs (m^2)	81	Weibel (1963)
Surface area of alveoli (m^2)	70−80	Weibel (1963)
Surface area of lung capillaries (m^2)	70	Weibel (1963)
Minimal thickness of alveolar-capillary membrane (μm)	0.4	Weibel (1963)
Volume of alveolus (ml)	1.05×10^{-5}	Weibel (1963)
Number of epithelial cells in conducting airways	10.5×10^9	Mercer et al. (1994)
Number of cells in lower respiratory tract:		
Total number of cells in alveoli	1.9×10^{11}	Mercer et al. (1994)
Alveolar macrophages	2.2×10^{10}	Crapo et al. (1982)
Lymphocytes	$(2-5) \times 10^8$	Holt et al. (1986), Saltini et al. (1991)
Number of alveolar parenchyma cells:		
Epithelial cells type I	1.9×10^{10}	Crapo et al. (1982)
Epithelial cells type II	3.7×10^{10}	Crapo et al. (1982)
Endothelial cells	6.9×10^{10}	Crapo et al. (1982)
Interstitial cells	8.3×10^{10}	Crapo et al. (1982)
Interstitial lymphocytes	$(0.4-1.0) \times 10^{10}$	Holt et al. (1986)

and Mayanski, 1983). In many bacterial infections, phagocytes represent the only type of host cells capable of eliminating the pathogens. Few mathematical models exist which describe the dynamics of inflammatory reaction (Lauffenburger and Kennedy, 1981; Lauffenburger, 1985). Examples of specific and non-specific defense reactions can be found in Rudnev and Romanyukha (1995) and Marino and Kirschner (2004).

Pulmonary inflammation caused by a bacterial infection leads to a significant increase in the volume of alveolar fluid (a medical condition known as alveolar edema), but the influence of this phenomenon on the course of infection has yet to be studied. In this work, we describe a mathematical model of bacterial pneumonia which accounts for phagocytosis, edema, cellular infiltration and immune response, as well as damage to and the regeneration of target tissue. We identified model parameters using clinical data, estimated the values of energy cost for immune and pathological processes associated with pneumonia, and examined the minimum energy cost of immune defense regimens and their dependence on the parameters of infection burden.

2. Mathematical model of pneumonia

The lungs represent a principal site of invasion for many pathogens. In particular, respiratory infections cause about 30% of infection-related deaths each year (WHO, 2004). At present, there are much data available which characterize the anatomical structure, morphological organization and cellular composition of the human lungs; some of them are summarized in Table 1.

The lungs consist of two major compartments: conducting airways and bronchoalveolar respiratory tract. Conducting airways are protected against inhaled pathogens by various immune system agents. Among them: secretory antibodies (sIgA), lysozyme, lactoferrin, lactoperoxidase, and interferons. Microorganisms deposited on mucous membranes of the trachea, bronchi and terminal bronchioli are usually removed from the lungs within 1 day or less by mucociliary transport (Mims et al., 2001).

In contrast to the conducting airways, the lung respiratory compartment (target tissue in pneumonia) is protected mainly by alveolar macrophages (AMs). When these AMs become impaired, the lungs are more susceptible to bacterial infections (Reese and Betts, 1991; Caretzky et al., 1993).

An important difference between inflammatory reaction and immune response to pneumonia is found in their spatio-temporal organization (Fig. 1). An interaction between phagocytes and bacteria occurs in the lower respiratory tract, primarily in the alveoli (Fig. 1A, E). In the case of AM dysfunction, bacteria can grow more easily in number and cause a significant inflammatory reaction.

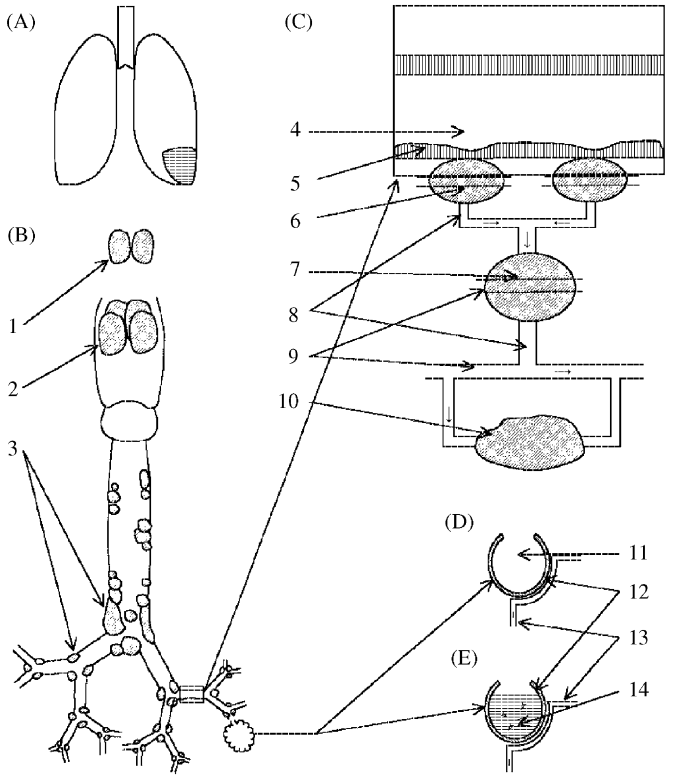

Fig. 1. Spatial organization of immune defense in the lungs: (A) Localization of bacterial infection in lungs. (B) Lymphatic tissues of the respiratory tract. 1, adenoids; 2, tonsils; 3, bronchus-associated lymphoid tissue, BALT. (C) Lung lymphatics. 4, airspace of bronchus or bronchiolus; 5, bronchial (bronchiolar) epithelium; 6, lymphatic nodule; 7, lymph node; 8, lymphatic vessels; 9, blood vessels; 10, spleen. (D) Normal alveolus. (E) Alveolus in the peak of pneumonia. 11, alveolar airspace; 12, alveolar membrane; 13, alveolar capillary; 14, alveolar edema fluid.

Damage of alveolar-capillary membranes leads to alveolar edema (Fig. 1D, E) and increases the influx of phagocytic cells from the blood (presumably neutrophils, phagocytic cells which slightly differ from AMs). These processes occur during the first hours and days of disease onset. At that time, bacterial antigens enter lymph nodes (LNs) (either directly or within dendritic cells or phagocytes, Fig. 1B, C) and induce an immune response. After 7–10 days, a considerable increase in the concentration of specific antibodies is typically observed. These antibodies enter damaged lung segments and bind to bacteria, thus increasing the rate at which phagocytic cells (alveolar macrophages and neutrophils) eliminate bacteria.

2.1. Model equations

Let us consider the following time-dependent variables of the mathematical model of pneumonia: $K(t)$, the concentration of bacteria in volume $V = V(t)$ of the alveolar fluid in segments where infection develops;[1] $M_A(t)$, the concentration of alveolar macrophages in $V(t)$; $N_A(t)$, the concentration of neutrophils in $V(t)$; $M_K(t)$, the concentration of stimulated antigen-presenting cells (macrophages and dendritic cells) in the LNs; $H_B(t)$, the concentration of antigen-specific Th2 cells in LNs; $B(t)$, concentration of antigen-specific B cells in LNs; $P(t)$, the concentration of plasma cells which produce antigen-specific antibodies (in LNs); $F(t)$, the concentration of antigen-specific antibodies in blood; $m(t)$, the concentration of damaged alveolar parenchyma cells in $V(t)$.

So the model of pneumonia can be written as a system of 10 ordinary nonlinear delay-differential equations:

$$\frac{dK}{dt} = \beta K - g(t)M_A K - hN_A K\frac{F}{F^*} - \frac{dV}{dt}\frac{K}{V}, \tag{1}$$

$$\frac{dM_A}{dt} = \gamma K + \alpha_M(M_A^* - M_A) - c_1 g(t)M_A K - \frac{dV}{dt}\frac{M_A}{V}, \tag{2}$$

$$\frac{dN_A}{dt} = \chi K M_A + \alpha_N(N_A^* - N_A) - c_2 h N_A K\frac{F}{F^*} - \frac{dV}{dt}\frac{N_A}{V}, \tag{3}$$

$$\frac{dV}{dt} = \delta(V^{max} - V)K + \alpha_V(V^* - V), \tag{4}$$

$$\frac{dM_K}{dt} = (M_K^{max} - M_K)\gamma_{MK}K - \alpha_{MK}M_K, \tag{5}$$

$$\frac{dH_B}{dt} = b_H[\rho_H M_K(t-\tau_H)H_B(t-\tau_H) - M_K H_B] - b_P M_K H_B B + \alpha_H(H_B^* - H_B), \tag{6}$$

$$\frac{dB}{dt} = b_P^B[\rho_B M_K(t-\tau_B)H_B(t-\tau_B)B(t-\tau_B) - M_K H_B B] + \alpha_B(B^* - B), \tag{7}$$

$$\frac{dP}{dt} = b_P^P \rho_P M_K(t-\tau_P)H_B(t-\tau_P)B(t-\tau_P) + \alpha_P(P^* - P), \tag{8}$$

$$\frac{dF}{dt} = \rho_F P + \alpha_F(F^* - F), \tag{9}$$

$$\frac{dm}{dt} = \sigma K + \alpha_m(m^* - m) - \frac{dV}{dt}\frac{m}{V}. \tag{10}$$

Initial conditions correspond to an infection initiation at time $t = 0$:

$$\begin{aligned} &K(0) = K_0, \quad M_A(0) = M_A^*, \quad N_A(0) = N_A^*,\\ &V(0) = V^*, \quad M_K(0) = 0,\\ &H_B(0) = H_B^*, \quad B(0) = B^*, \quad P(0) = P^*,\\ &F(0) = F^*, \quad m(0) = m^*,\\ &M_K(t)H_B(t) = 0 \quad \forall t \in [-\tau_H, 0);\\ &M_K(t)H_B(t)B(t) = 0 \quad \forall t \in [-\tau, 0), \quad \tau = \max(\tau_B, \tau_P). \end{aligned} \tag{11}$$

Let us now assume that the model parameters and initial values are nonnegative, and function $g(t)$ is sufficiently

[1]We assume that bacteria localize in two lung segments (typically, in the right lower lobe).

smooth. With these assumptions, it can be shown that a solution to the initial value problem (1)–(11) exists, and this solution is unique, nonnegative, and bounded on any finite time interval $[0, t]$, where $t > 0$. The following characteristic features of this model are outlined (see Rudnev, 2000 for details):

(1) This model consists of two sets of equations. The first set (Eqs. (1)–(4)) represents the dynamics of phagocytic response to infection in the lungs (modified from Lauffenburger, 1985), and describes the dilution of alveolar edema. The second set of equations (Eqs. (5)–(10)) describes the immune response using the Marchuk–Petrov mathematical model of humoral immune response (Marchuk, 1997). The first and the second set of model equations are related by their dependence on concentration of antibodies and bacteria.

(2) The model describes resistance to small, localized infection due to phagocytosis by the alveolar macrophages. Phagocytic cells can eliminate a limited number of microorganisms: 100–120 and 40–50 bacteria *S. aureus* for every AM or neutrophil, respectively (Leijh et al., 1986). If the ratio of bacteria to AMs is close to 100, the rate of bacterial elimination sharply decreases (third term of Eq. (2)). So, infectious dose will be small if it does not significantly disrupt the normal phagocytic activity of AMs, and the following healthy-state equilibrium condition holds: $\beta < gM_A + hN_A F/F^*$.

(3) A common mechanism of pneumonia initiation is described by this model: temporal suppression of phagocytosis. For this, we use an empirical function $g(t)$ (see Eqs. (1)–(2)). Based on experimental data which describe the influence of viral infection on the rate of bacterial clearance (Jakab, 1985; Nickerson and Jakab, 1990), we represent this function as

$$g(t) = g_0(1 - a\mathrm{e}^{-bt}), \tag{12}$$

where g_0 is the constant rate of bacterial phagocytosis by the AMs and parameters a and b characterize the degree to which AMs will be suppressed and the rate of recovery for AMs to eliminate bacteria, respectively.

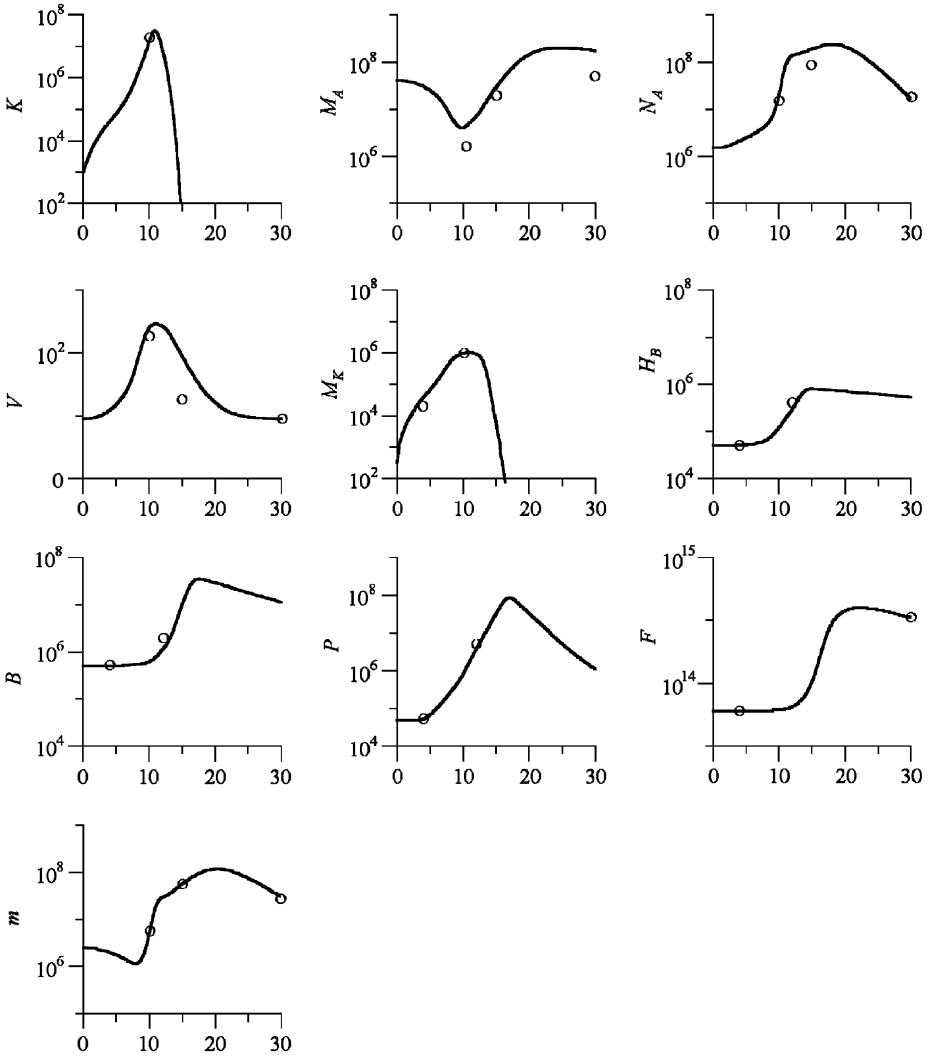

Fig. 2. Solution of the initial value problem (1)–(11): acute form of intermediate severity bacterial pneumonia in humans. Parameter values are shown in Table 2. *X*-axis represents the time after disease initiation (days). Data on generalized picture of pneumonia are shown with open circles.

2.2. Parameters identification and sensitivity analysis

Let us define the course of pneumonia in lungs generally using the variables of the quantitative model, as in the so-called generalized picture of Marchuk et al. (1991). We conceptualized pneumonia using clinical data on the dynamics of cell populations in bronchoalveolar lavage fluids for 36 patients having pneumonia of intermediate severity (Kop'eva et al., 1991) and clinical, morphological and experimental data from Weibel (1963, 1973), Marchuk and Berbentsova (1989), Kop'eva et al. (1991), Stanley et al. (1991), Stone et al. (1992). Boundaries of permissible values of the model parameters $\alpha^{(i)}$ were estimated as $0 < a_i \leqslant \alpha^{(i)} \leqslant b_i < \infty$. Parameter values were estimated using the objective function

$$F(\alpha) = \sum_{i,j} \left(\lg \left(\frac{x^i(t_j, \alpha)}{X_j^i} \right) \right)^2 \tag{13}$$

characterizing deviation of the model solutions from the data, where α is the vector of the model parameters, $x^i(t_j, \alpha)$ is the value of the ith variable of the model at time t_j, and X_j^i is the corresponding data of generalized picture.

The results of the model fitting to the data of generalized picture of pneumonia are shown in Fig. 2. The values of the model parameters after fitting are represented in Table 2.

We consider the following values in reference to the model solutions: $K_{max} = \max\{K(t) : t \geqslant 0\}$, maximum bacterial concentration in the lungs (characteristic of

Table 2
Estimated model parameters for simulation of acute bacterial pneumonia

Parameter	Physical meaning and dimension	Permissible values range	Estimate
β	Rate constant of bacteria multiplication (1/day)	0–37.6	2.7
g	Rate constant of phagocytosis by AMs (ml/(cell day))	10^{-7}–10^{-5}	1.36×10^{-7}
h	Rate constant of phagocytosis by neutrophils (ml/(cell day))	10^{-8}–10^{-6}	2.7×10^{-8}
γ	Rate constant of chemotaxis for monocytes (1/day)	10^{-4}–10^{0}	1.96×10^{-4}
χ	Rate constant of chemotaxis for neutrophils (ml/(cell day))	1.6×10^{-7}–1.3×10^{-4}	7.57×10^{-7}
δ	Rate constant of alveolar infiltration (ml/(cell day))	10^{-9}–10^{-5}	3.22×10^{-7}
γ_{MK}	Rate constant of macrophage stimulation (ml/(cell day))	10^{-8}–10^{-5}	3.7×10^{-6}
b_H	Rate constant of Th2 cells stimulation (ml/(cell day))	6.6×10^{-7}–5.0×10^{-6}	7.9×10^{-7}
b_P	Rate constant of Th2 cells differentiation (ml^2/($cell^2$ day))	2.8×10^{-15}–2.8×10^{-12}	1.7×10^{-14}
b_P^B	Rate constant of B cells stimulation (ml^2/($cell^2$ day))	2.8×10^{-13}–2.8×10^{-10}	2×10^{-12}
b_P^P	Rate constant of plasma cells production (ml^2/($cell^2$ day))	2.8×10^{-13}–2.8×10^{-10}	4×10^{-11}
σ	Rate constant of alveolar parenchyma cells damage (1/day)	0.01–1.0	0.71
a	Maximal relative decrease of the rate constant of phagocytosis by AMs	0.5–0.8	0.8
b	Rate of restoration AM's ability to eliminate bacteria (1/day)	0.1	0.1
c_1	Inverse value of maximal number of bacteria eliminated by one AM	8×10^{-3}–10^{-2}	10^{-2}
c_2	Inverse value of maximal number of bacteria eliminated by one neutrophil	0.02–0.025	0.02
α_M	Rate constant of natural death for AMs (1/day)	0.03–0.15	0.03
α_N	Rate constant of natural death for neutrophils (1/day)	0.2–1.0	0.32
α_V	Rate constant of alveolar edema resolution (1/day)	0.1–1.0	0.48
α_{MK}	Rate constant of stimulated state loss for macrophages (1/day)	1–3	3.0
α_H	Rate constant of activated state loss for Th2 cells (1/day)	0.01–0.1	0.03
α_B	Rate constant of natural death for B cells (1/day)	0.05–0.1	0.1
α_P	Rate constant of natural death for plasma cells (1/day)	0.33–0.5	0.4
α_F	Rate constant of natural death for antibodies (1/day)	0.043	0.043
α_m	Rate constant of damaged alveolar parenchyma cells elimination (1/day)	0.1–0.4	0.2
ρ_H	Number of Th2 cells created by division(s series)	2	2
ρ_B	Number of B cells created by division(s series)	10–18	16
ρ_P	Number of plasma cells created by division(s series) of B cells	2–5	3
ρ_F	Rate of IgG production per plasma cell (mol/(cell day))	10^6–5×10^7	10^6
M_A^*	Normal concentration of AMs (cell/ml)	4×10^7	4×10^7
N_A^*	Normal concentration of neutrophils (cell/ml)	1.5×10^6	1.5×10^6
V^*	Normal volume of alveolar surfactant in the target segments of lungs (ml)	9.0	9.0
V^{max}	Maximal volume of alveolar edema in the target segments of lungs (ml)	300	300
M_K^{max}	Concentration of antigen-presenting cells in LNs (cell/ml)	10^6	10^6
H_B^*	Normal concentration of antigen-specific Th2 cells in LNs (cell/ml)	10^4–1.5×10^5	5×10^4
B^*	Normal concentration of antigen-specific B cells in LNs (cell/ml)	10^5–1.5×10^6	5×10^5
P^*	Normal concentration of antigen-specific plasma cells in LNs (cell/ml)	10^4–1.5×10^5	5×10^4
F^*	Normal concentration of antigen-specific antibodies in blood (mol/ml)	5×10^{12}–1.5×10^{14}	6×10^{13}
m^*	Normal concentration of damaged alveolar parenchyma cells in lungs (cell/ml)	2.5×10^6	2.5×10^6
τ_H	Duration of Th2 cells division(s) (day)	0.4–0.8	0.4
τ_B	Duration of B cells division(s) (day)	2–3	3
τ_P	Duration of B cells division(s) and differentiation resulting in plasma cells appearance (day)	3–4	3

pneumonia severity); $\Delta T_{max} = \min\{t \geqslant 0 : K(t) = K_{max}\}$, minimal time corresponding to the maximum value of bacterial concentration (characteristic of the rate of pneumonia progression); $\Delta T_{infect} = \min\{t \geqslant 0 : K(t)V(t) \leqslant 1\}$, duration of infection.

The values of K_{max}, ΔT_{max}, and ΔT_{infect} depend to a large extent on the parameters of non-specific defense (Eqs. (1)–(4)) and on the level of antigen-specific antibodies in healthy-state (F^*). Current literature supports this view of the mechanisms of pathogenesis in opportunistic infections (Reese and Betts, 1991; Caretzky et al., 1993).

Initial estimates of parameter values for the models (1)–(10) vary in range: up to 100% for the rates of cells and factors elimination and phagocytic capacity of alveolar macrophages and neutrophils; 1–2 order for the rates of phagocytosis and rate of Th2 stimulation; and up to 3–4 order of magnitude for other parameters (see Table 2).

Eqs. (1)–(10) describe physical processes and one of the common characteristics of solution in this case is the rate of energy dissipation. More accurate estimates of the model's parameter values are possible with information about the rate of energy dissipation, but the dependence of this rate on the parameters regulating energy dissipation is still unknown.

Numerical experiments showed that a relatively small increase in the homeostatic concentration of AMs and in the concentration of specific antibodies can significantly reduce the severity and duration of infection. It is still unclear which factors and processes govern the level of immune protection and, particularly, why an organism does not maintain higher levels of AMs and antibodies for better immune resistance? One way of beginning to answer this question may be to consider it in terms of the theory of life history (Stearns, 1992). For this purpose, we evaluate the dependence of individual fitness on the level of immune defense. The life history approach is based on an idea of compromise, or trade-off between longevity and fertility (Zera and Harshman, 2001; Colditz, 2002; McDade, 2003). The cost of immune defense relates to the cost of maintenance, and it correlates positively with longevity and negatively with fertility. In this sense, we use the term "fitness" as a measure of immune system optimization (balance between the costs and benefits of defense) (Rashevsky, 1961).

The energy spent by the body on immune defense can be represented in terms of the metabolic costs on a life-long interval. It follows then, that we compare the energy costs for the immune system during base-line health maintenance and during response to infection.

3. Energy cost of pneumonia

Let us first consider equations for model-based estimates of host energy expenditures in pneumonia. The total energy cost of pneumonia E includes the following components: E_{id}, the energy needed for immune defense of the lungs (i.e. the production and maintenance of immune cells and antibodies); E_b, the energy of growth and metabolism for pathogens; E_r, the energy needed to repair damaged lung segments; E_{ed}, the energy needed for resolution of alveolar edema; and E_f, the metabolic cost of fever.[2] Thus,

$$E = E_{id} + E_b + E_r + E_{ed} + E_f. \tag{14}$$

The energy cost of immune defense of the lungs E_{id} can be represented variously as a sum of the following components:

- the energy cost of synthesis (E_s) and maintenance (E_m) of cells for immune defense:
$$E_{id} = E_s + E_m, \tag{15}$$
- the energy cost of maintaining homeostatic level of immune defense of the lungs (E_c), and induced immune defense caused by pneumonia (E_i):
$$E_{id} = E_c + E_i, \tag{16}$$
- the energy cost of non-specific lung resistance (E^n) and specific resistance (E^s) (the production and maintenance of antigen-presenting cells, lymphocytes, plasma cells, and antibodies):
$$E_{id} = E^n + E^s. \tag{17}$$

Using these general equations with the proper indexes, we can further distinguish the following energy costs of immune defense for pneumonia:

- $E^n_s = E^n_{sc} + E^n_{si}$, production of non-specific immune cells (phagocytes);
- $E^s_s = E^s_{sc} + E^s_{si}$, production of specific immune cells and antibodies;
- $E^n_m = E^n_{mc} + E^n_{mi}$, maintenance of non-specific resistance;
- $E^s_m = E^s_{mc} + E^s_{mi}$, maintenance of specific resistance;
- $E^n_c = E^n_{cs} + E^n_{cm}$, natural non-specific resistance;
- $E^s_c = E^s_{cs} + E^s_{cm}$, natural specific resistance;
- $E^n_i = E^n_{is} + E^n_{im}$, induced non-specific immune defense;
- $E^s_i = E^s_{is} + E^s_{im}$, induced specific immune defense.

Thus, we can write:

$$E_{id} = E^n_s + E^s_s + E^n_m + E^s_m = E^n_c + E^s_c + E^n_i + E^s_i. \tag{18}$$

Details concerning the calculations of these values, as well as other components of the equation for the energy cost of pneumonia, are described in Appendix.

In addition to energy costs, we denote the values of maximal power of considered processes by W with corresponding indexes.

[2]For simplicity, we do not account for some additional components of the total energy cost to the organism in response to pneumonia (for instance, organism cannot adapt to environmental challenges as easily or forage for food as efficiently during this time of infection).

4. Energy cost of infection burden

Let us next consider the energy cost E^* of host–pathogen interactions on life-long interval $[0, T^*]$ that includes both periods of infection and health. Assuming, for simplicity, that infections occur at a constant rate v[day^{-1}], we can write an expression for E^* such that

$$E^* = E^*(\alpha, v) = vT^*E(\alpha) + (1 - vT)T^*W(\alpha), \quad (19)$$

where α represents the vector of model parameters; and T represents the duration of infection. The term $vT^*E(\alpha)$ of Eq. (19) represents the energy cost of infection. $E(\alpha)$ is the energy cost of pneumonia from Eq. (14), and vT^* is the total number of infections. The second term $(1 - vT)T^*W(\alpha)$ represents the energy cost of immune defense in the lungs in absence of infection, and $W(\alpha)$ is the corresponding average rate of energy expenditure:

$$W(\alpha) = (E_c^n + E_c^s)/T. \quad (20)$$

The vector of model parameters α can be represented as (α', α''), where α' is the vector of the immune system parameters and α'' is the vector describing characteristics of pathogen.

Function E^* characterizes the general metabolic cost of immune protection (during homeostasis and during infection) and may be used as a measure of immune system adequacy or fitness. It depends on contributions of different arms of immunity that form a set of permissible strategies of immune defense. Since the immune system undergoes selection pressure the following condition determines optimal immune defense strategies $\tilde{\alpha}$ among all possible strategies:

$$E^*(\tilde{\alpha}, v) = \min_{\alpha'} E^*(\alpha, v). \quad (21)$$

Let us assume that all components of α' are fixed except value of M_A^* characterizing the normal level of non-specific immune defense (a critical parameter which determines the rate of progression and severity of pneumonia).

The dynamics of bacterial concentration corresponding to the optimal values of M_A^* (see Eq. (21)) for various values of v and $\beta = 2.7$ are shown in Fig. 3. Note that for $v = 1.5 \times 10^{-4}$ day^{-1} two different optimal solutions with the same value of E^* exist ("chronic" with $\tilde{M}_A^* = 4.3 \times 10^7$ and "acute" with $\tilde{M}_A^* = 2.3 \times 10^7$ cells/ml). Let us call this value of v an "equivalence point" since other values of v give only one optimal solution. Repeating these calculations for different β, one can obtain a set of equivalence points which separate optimal chronic infection dynamics from optimal acute ones (Fig. 4). It follows that for high prevalences of low-virulence infection the optimal dynamics correspond to a chronic condition (region I), while for low prevalences of infection with high bacterial virulence the optimal dynamics correspond to an acute condition (region II). This dependence between environmental factors and optimal infection dynamics holds for different values of parameters α'. The area between the dashed lines corresponds to the values of the rate of pneumonia in Russia (approximately 0.05 years^{-1} per capita (Krylov and Shatskaya, 1995)).

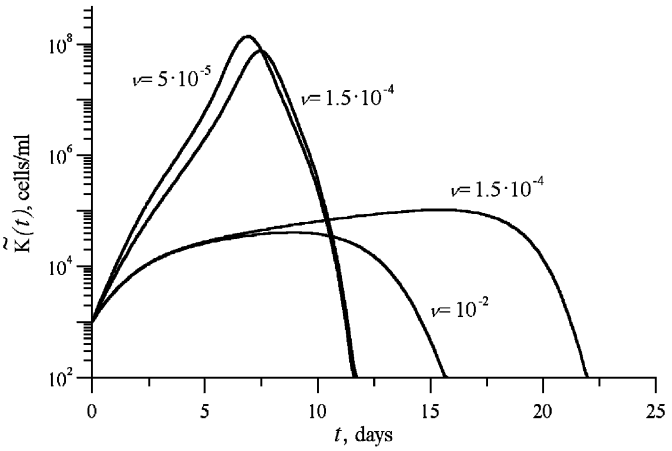

Fig. 3. Optimal trajectories of the bacterial concentration $\tilde{K}(t)$ for various rates of infection v. Threshold value $v = 1.5 \times 10^{-4}$ day^{-1} corresponds to two different solutions of the optimization problem (21): acute and chronic forms of infection.

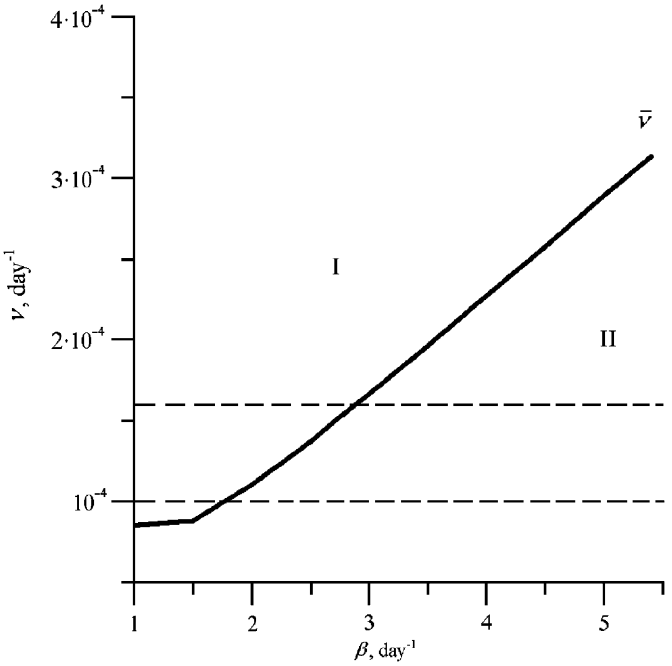

Fig. 4. Dependence of optimal immune defense regimens on the parameters of infection burden (bacterial virulence β and infection rate v): the region I and II corresponds to the chronic and acute form of infection, respectively. The area between dashed lines corresponds to the rate of pneumonia in Russia (approximately 0.05 years^{-1} per capita (Krylov and Shatskaya, 1995)).

5. Discussion

The high level of morbidity and mortality from infectious diseases is a vital issue for all countries in the world (WHO, 2004). One of the main reasons of high morbidity is the pervasiveness of widespread acquired

immune system deficiencies (Gerba et al., 1996). Diagnosis and correction of immune system deficiencies, therefore, has important practical value.

Treating such deficiencies requires first, an understanding of homeostasis in healthy organisms. Healthy-state immune control can be defined as the ability of the immune system to protect effectively against infectious disease. Epidemiological data suggest that in most cases, though, the immune system cannot provide complete protection against infection. So, we can define healthy-state, normal immune functioning as a state allowing, for instance, not more than 1–2 slight respiratory infections per year. To explain this only partial resistance to infection one can use a conception of the cost of immunity (Sheldon and Verhulst, 1996).

In this work, we consider the cost of mutual relations with the world of microbes as the energy an organism spends in response to infection and on maintenance of the immune system (note that the trophic chain human–microbes is not symmetric, $E_{id} + E_r + E_{ed} + E_f \gg E_b$). This approach takes notice of the energy needed in response to disease and the energy needed for baseline health maintenance. Although the energy needed for immunity is only a small part of basal metabolic rate (about 1–3%), it may vary in range and influence on reproduction, unlike the more stable house-keeping cost. Thus, the range of energy expenditure cannot be less than the cost of defense against infectious disease or higher than the cost of defense plus cost of reproduction (Demas et al., 1997; Moreno et al., 2001; Westendorp et al., 2001). An optimal strategy of the immune system is to redistribute the energy between different arms of the immune response, and this may occur through evolutionary and physiological adaptation (Franceschi et al., 1995). This adaptation includes hormone regulation of the immune system by various factors such as leptin, growth hormone and others (Moore et al., 2003; Xiao et al., 2003; Dixit et al., 2004). For example, a decrease in the total amount of exchangeable fat is associated with a decrease of energy expenditure for immune defense (Faggioni et al., 2001; van Crevel et al., 2002; Steinman et al., 2003).

In this work, we estimated parameter values of energy expenditure for defense against pneumonia. Several features of the energy budget for pneumonia appear in Table 3 which demonstrate the relative contribution of defense and pathological processes. Among them:

(1) a major part of the energy cost for bacterial pneumonia E is formed by a fever-induced increase in metabolic rate E_f (up to 90% of total energy cost of pneumonia);

(2) a major part of the energy need for immune defense in the lungs E_{id} is used for maintenance of phagocytes, which is about 8% of E;

(3) energy expenditures for normal (in the absence of infection) phagocytic defense and antibody production (including B and T cell maintenance) are of the same magnitude;

(4) the energy cost of specific immune responses is relatively low and comparable with the energy cost for regenerating lung parenchyma and resolving alveolar edema.

One can see that energy cost of fever and maintenance of phagocyte system are the basic factors for pneumonia. It can be assumed that more frequent acute infections in humans (including viral and viral–bacterial infections of the upper respiratory tract) are characterized by similar energy budgets. For chronic infections, however, the energy budget should be different; energy consumption decreases for fever but increases for the return to homeostasis, for specific and non-specific defense. Because predicting the energy cost for different infections is difficult, we suggest a general formula for energy cost of infection (Eqs. (14) and (18)). For any particular infection, however, it is necessary to account for the main components of energy cost which are typical for this infection.

A hypothetical mechanism explaining the transition from acute to chronic infection (as a result of minimizing the cost of anti-infectious defense) is shown in Fig. 4. As the frequency of infection increases it becomes more profitable to the immune system to tolerate pathogens in the body rather than attempt to eliminate them. The transition from acute to chronic-form infection depends also on characteristics of an organism's systems of defense and on properties of the pathogen. Thus, the frequency of chronic disease increases as a result of age-related decreases in the efficacy of immune-specific defense. Also, less virulent pathogens are more likely to produce chronic infection. Chronic infections, then, are the result of the body's optimal adaptive response so as to minimize total energy cost while still maintaining sufficient health.[3]

It should be mentioned that fitness and the energy cost of defense against infection are closely related. However, under some conditions this relation is not always so. For instance, sustained immune defense over a long period of time decreases the fitness less than defense against acute infection (assuming equal values of total cost for both cases). We observe this relationship because the intensive costs increase abruptly (nonlinearly) as the probability of death increases. Therefore, not only is energy cost important but the efficacy of this cost is important too.

Fig. 5 represents qualitatively the relation between energy expenditure for immune defense and loss of energy because of disease. Curve #1 corresponds to the condition when only one parameter of immune response varies (M_A^*). When external conditions are changed (e.g. when the rate of infection or the virulence of a pathogen is increased) the interaction with pathogens leads to an increase in energy consumption (curve #2). Points A, B and the dashed line

[3]From this point of view, some immune deficiency states can be considered as a result of normal physiological adaptation. Usually, acute bacterial infection is initiated by viral infection(s). So decrease of frequency of viral infections is effective method of chronic bacterial infection treatment (Marchuk and Berbentsova, 1989).

Table 3
Model-based energy cost estimates of defense and pathological processes for pneumonia

	Physical meaning and dimension	Estimate
E_f	Loss of energy in pneumonia due to fever-induced increase in metabolic rate (J) (Eq. (28))	9.4×10^{6}
E_r	Energy needed for regeneration of damaged lung tissues (J) (Eq. (26))	3.8×10^{3}
E_{ed}	Energy needed for resolution of alveolar edema (J) (Eq. (27))	2.2×10^{3}
E_b	Energy needed for growth and metabolism of bacterial population in lungs during pneumonia (J) (Eq. (22))	1.2
E_s^n	Energy cost of the production of lung phagocytes (J) (Eq. (23))	1.3×10^{4}
E_c^n	Energy cost of constant non-specific immune defense (J): $E_c^n = V_{tot}^* T[(\alpha_2\alpha_M+\beta_1)M_A^* + (\alpha_3\alpha_N+\beta_2)N_A^*]$	6.2×10^{5}
E_m^n	Energy cost of maintenance of phagocytes (J) (Eq. (25))	7.9×10^{5}
E_i^n	Energy cost of induced non-specific lung immune defense (J): $E_i^n = \alpha_2\int_0^T[\gamma K(t)V(t)+\alpha_M M_A^*(V(t)-V^*)]\,dt + \alpha_3\int_0^T[\chi K(t)M_A(t)V(t) + \alpha_N N_A^*(V(t)-V^*)]\,dt + \beta_1\int_0^T(M_A(t)V(t)-M_A^*V^*)\,dt + \beta_2\int_0^T(N_A(t)V(t)-N_A^*V^*)\,dt$	1.8×10^{5}
E_s^s	Energy cost of the production of specific immune cells and antibodies (J) (Eq. (24))	1.7×10^{5}
E_c^s	Energy cost of constant specific lung immune defense (J): $E_c^s = LT[(\alpha_5\alpha_M+\beta_3)M_K^{max} + (\alpha_6\alpha_H+\beta_4)\kappa H_B^* + (\alpha_7\alpha_B+\beta_5)\kappa B^* + (\alpha_8\alpha_P+\beta_6)\kappa P^*] + \alpha_9\alpha_F\kappa F^* L' T$	3.9×10^{5}
E_m^s	Energy cost of the maintenance of specific immune defense (J): $E_m^s = \beta_3 L M_K^{max} T + \beta_4 L\int_0^T(H_B(t)+\kappa H_B^*)\,dt + \beta_5 L\int_0^T(B(t)+\kappa B^*)\,dt + \beta_6 L\int_0^T(P(t)+\kappa P^*)\,dt$	2.3×10^{5}
E_i^s	Energy cost of the induced specific immune defense (J): $E_i^s = \alpha_6 L\int_0^T b_H[\rho_H M_K H_B|_{t-\tau_H} - M_K(t)H_B(t)]\,dt + \alpha_7 L\int_0^T b_P^B[\rho_B M_K H_B B|_{t-\tau_B} - M_K(t)H_B(t)B(t)]\,dt + \alpha_8 L\int_0^T(b_P^P\rho_P M_K H_B B|_{t-\tau_P})\,dt + \alpha_9 L'\int_0^T\rho_F P(t)\,dt + \beta_4 L\int_0^T(H_B(t)-H_B^*)\,dt + \beta_5 L\int_0^T(B(t)-B^*)\,dt + \beta_6 L\int_0^T(P(t)-P^*)\,dt$	3.0×10^{3}
W_f	Maximal rate of energy loss due to fever-induced increase in metabolic rate (W)[a]	65
W_r	Maximal rate of energy expenditure for regeneration of damaged lung tissues (W)	6.4×10^{-3}
W_{ed}	Maximal rate of energy expenditure for resolution of alveolar edema (W)	4.5×10^{-3}
W_b	Maximal rate of energy loss due to growth and metabolism of the bacterial population in lungs (W)	8.3×10^{-6}
W_s^n	Maximal rate of energy expenditure for production of non-specific immune cells (W)	3.6×10^{-2}
W_c^n	Maximal rate of energy expenditure for constant non-specific immune defense (W)	7.2×10^{-2}
W_m^n	Maximal rate of energy expenditure for maintenance of phagocytes (W)	0.27
W_i^n	Maximal rate of energy expenditure for induced non-specific immune defense (W)	0.21
W_s^s	Maximal rate of energy expenditure for production of antigen-specific cells, plasma cells and antibodies (W)	2.1×10^{-2}
W_c^s	Maximal rate of energy expenditure for constant specific immune defense (W)	4.6×10^{-2}
W_m^s	Maximal rate of energy expenditure for maintenance of specific immune defense (W)	3.1×10^{-2}
W_i^s	Maximal rate of energy expenditure for induced specific immune defense (W)	6.0×10^{-3}

[a]Equations for W can be obtained from equations for corresponding components of E.

between them represent a set of minimal values of host's energy expenditure.

The present approach is similar to the trade-offs analysis in evolutionary and ecological physiology (Stearns, 1992; McDade, 2003). One may assume that evolutionary and physiological adaptation leads to a diminished total energy cost of host–pathogen interactions (shown by arrows in Fig. 5). Additionally, processes of natural selection in pathogens can modify the targeted extreme values for a host which results in host–pathogen co-adaptation (Nowak and May, 2000; Diekmann et al., 2002; Frank, 2002).

An example of such adaptation is shown in the transition between chronic and acute forms of infection obtained using the model framework. With this hypothetical

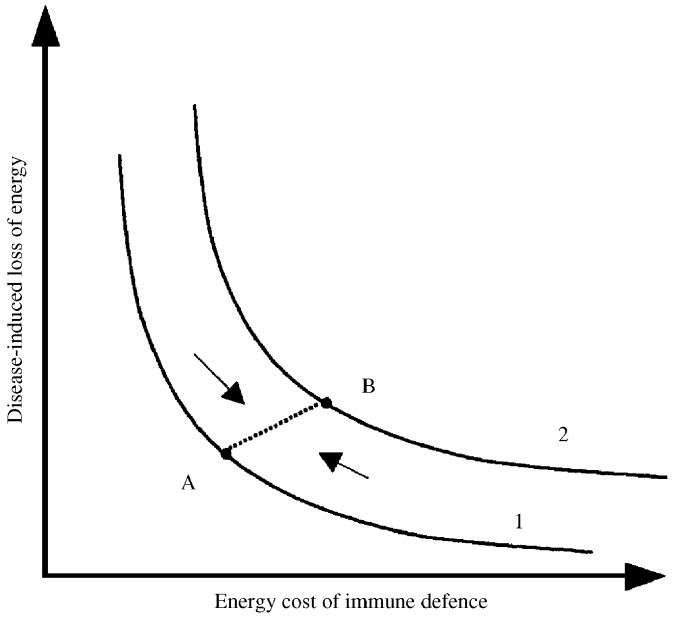

Fig. 5. Scheme of trade-off between energy cost of immune defense and disease-related penalties. Points A and B show optimal immune defense energy allocation for different values of infection burden.

mechanism of forming chronic infection, we can conclude that the normal state of the immune system depends on heterogeneous life conditions, and therefore, several normal states of the immune system can coexist in a given population.

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Appendix. Energy cost of pneumonia

Let us consider the values of energy expenditures for the production of bacterium (α_1), alveolar macrophage (α_2), neutrophil (α_3), antigen-presenting cell (α_5), Th2 cell (α_6), B cell (α_7), plasma cell (α_8), antibody (α_9), and lung parenchyma cell (α_{10}). Let α_4 be the specific energy cost of lung edema resolution. Similarly, let the parameters β_1–β_6 be the corresponding powers of maintenance of AM, neutrophil, antigen-presenting cell, Th2 cell, B cell and plasma cell, respectively, and β_7 be the specific energy loss due to fever (coefficient which shows dependence between fever and metabolic rate). Let T denote the duration time of pneumonia. If the energy consumed by an exponentially growing population of microorganisms is used mainly for bacterial division, the expression for E_b (see Eq. (14)) can be written as

$$E_b = \alpha_1 \int_0^T \beta K(t) V(t)\, \mathrm{d}t, \tag{22}$$

where $\beta K(t)V(t)$ is the time-dependent intrinsic rate of bacterial growth in the lungs (see Eq. (1)).

The energy cost for production of lung phagocytes (E_s^n) can be written as

$$\begin{aligned} E_s^n = {} & \alpha_2 \int_0^T (\gamma K(t) + \alpha_M M_A^*) V(t)\, \mathrm{d}t \\ & + \alpha_3 \int_0^T (\chi K(t) M_A(t) + \alpha_N N_A^*) V(t)\, \mathrm{d}t \\ & + \alpha_2 \alpha_M M_A^* (V_{tot}^* - V^*) T + \alpha_3 \alpha_N N_A^* (V_{tot}^* - V^*) T. \end{aligned} \tag{23}$$

The right-hand side of this equation is the sum of the energy expenditures for production of monocytes and neutrophils which accumulate in damaged lung segments (first and second terms), and unaffected lung segments during infection (third and fourth terms). Parameter V_{tot}^* is the normal volume of alveolar surfactant in the lungs (according to Weibel, 1973 it is about 90 ml).

Similarly, we can write an expression for energy cost for the production of specific immune cells and antibodies (E_s^s):

$$\begin{aligned} E_s^s = {} & \alpha_5 \alpha_M L M_K^{max} T + \alpha_6 L \int_0^T [b_H(\rho_H M_K H_B|_{t-\tau_H} \\ & - M_K(t) H_B(t)) + \alpha_H \kappa H_B^*]\, \mathrm{d}t \\ & + \alpha_7 L \int_0^T [b_P^B(\rho_B M_K H_B B|_{t-\tau_B} \\ & - M_K(t) H_B(t) B(t)) + \alpha_B \kappa B^*]\, \mathrm{d}t \\ & + \alpha_8 L \int_0^T [b_P^P \rho_P M_K H_B B|_{t-\tau_P} + \alpha_P \kappa P^*]\, \mathrm{d}t \\ & + \alpha_9 L' \int_0^T (\rho_F P(t) + \alpha_F \kappa F^*)\, \mathrm{d}t, \end{aligned} \tag{24}$$

where L is the volume of the lymph nodes in lungs ($L \sim 12$ ml (Sapin and Borzyak, 1982)), L' is the plasma volume ($L' \sim 3500$ ml, Smith and Kampine, 1990); κ is the ratio between the total number of B cells and antigen-specific B cells (both in the LNs). According to Monteil et al. (1990), $\kappa \sim 2 \times 10^3$. The first term in the right-hand side of Eq. (24) describes the energy cost of production of antigen-presenting cells. The second, third, and fourth terms describe the energy cost for the production of Th2-, B-, and plasma-cells in the LNs, respectively. The last term describes the energy cost for production of antibodies. For simplicity, we assume that the relative frequency of antigen-specific antibodies in blood is equal to the relative frequency of lymphocytes of the same specificity in the LNs.

The following expression describes the energy cost of maintenance of lung phagocytes:

$$E_m^n = \beta_1 \int_0^T M_A(t)V(t)\,dt + \beta_2 \int_0^T N_A(t)V(t)\,dt + \beta_1 M_A^*(V_{tot}^* - V^*)T + \beta_2 N_A^*(V_{tot}^* - V^*)T. \quad (25)$$

The right-hand side of Eq. (25) describes the energy cost of maintenance of phagocytes in damaged (first and second terms) and healthy lung segments (third and fourth terms). Expressions for other energy cost components of immune defense in the lungs can be obtained in a similar way (see Table 4).

Using Eq. (10) and the definition of the parameter α_{10}, one can estimate the energy cost for regenerating alveolar parenchyma cells (E_r):

$$E_r = \alpha_{10} \int_0^T \alpha_m(m(t) - m^*)V(t)\,dt. \quad (26)$$

Similarly, using Eq. (4) and the definition of the parameter α_4, we can calculate E_{ed} as

$$E_{ed} = \alpha_4 \int_0^T \alpha_V(V(t) - V^*)\,dt. \quad (27)$$

The development of acute infectious disease in an organism results in the increase of basal metabolic rate (BMR), which is proportional to the relative increase of body temperature: about 11.3% of the normal BMR value per each 1 °C over 37 °C (Long et al., 1979). We assume that the value of E_f is proportional to the total amount of pathogens in the lungs:

$$E_f = \beta_7 \int_0^T K(t)V(t)\,dt. \quad (28)$$

Estimates of parameters are shown in Table 4. They were obtained using the following data and assumptions:

- The energy cost of the bacterial division is equal to 0.3 J/1 mg of bacteria dry weight (Gunsalus and Shuster, 1961; Lehninger, 1971). The dry weight of bacteria corresponds to about 20% of their total weight (Spector, 1956). Bacterial protein content equals to 50–70% of their dry weight.
- The fraction of energy expenditures for protein synthesis in cells is equal to approximately the relative content of protein per unit of its dry weight (Gunsalus and Schuster, 1961).
- The percent of major biochemical compounds (i.e. proteins, nucleic acids, lipids, and polysaccharides) of dry weight bacteria and leukocytes are similar (Gunsalus and Schuster, 1961; Flindt, 1988); the dry weight of eukaryotic cell corresponds to about 30% of its total weight.
- The average energy cost of leukocytes maintenance is about 5×10^{-3} W/g (Ivanov, 1990).
- The resting and activated cells of the immune system have similar specific energy expenditures for metabolism per unit of their weight.
- The specific energy expenditure to clear the alveolar edema is equal to the energy expenditure for liquid filtration in the kidneys, i.e. about 2.9 J/ml (Flindt, 1988; Rolfe and Brown, 1997).
- The relative value of basal metabolic rate in the peak of pneumonia of intermediate severity equals 125% of its normal value (Liggett and Renfro, 1990; Vermeeren et al., 1997).

Table 4
Range of permissible values for specific energy cost of various processes of immune defense in the LNs in healthy state and for bacterial pneumonia

	Physical meaning and dimension	Permissible values range	Value
α_1	Energy cost of bacterium production (J/cell)	8×10^{-12}–7×10^{-11}	3×10^{-11}
α_2	Energy cost of the production of alveolar macrophage (J/cell)	9×10^{-8}–8×10^{-7}	3.6×10^{-7}
α_3	Energy cost of the production of neutrophil (J/cell)	2×10^{-8}–2×10^{-7}	8.1×10^{-8}
α_4	Specific (per ml) energy cost of lung edema resolution (J/ml)	1–6	2.9
α_5	Energy cost of the production of antigen-presenting cell (J/cell)	2×10^{-8}–2×10^{-7}	$9 \times 10^{-}8$
α_6	Energy cost of the production of Th2 cell (J/cell)	7×10^{-9}–6×10^{-8}	2.7×10^{-8}
α_7	Energy cost of the production of B cell (J/cell)	7×10^{-9}–6×10^{-8}	2.7×10^{-8}
α_8	Energy cost of the production of plasma cell (J/cell)	2×10^{-8}–2×10^{-7}	9×10^{-8}
α_9	Energy cost of the production of antibody (J/mol)	5×10^{-17}–10^{-16}	9×10^{-17}
α_{10}	Energy cost of the production of lung parenchyma cell (J/cell)	9×10^{-8}–8×10^{-7}	3.6×10^{-7}
β_1	Power of the maintenance of alveolar macrophage (J/(cell day))	4×10^{-7}–4×10^{-6}	1.7×10^{-6}
β_2	Power of the maintenance of neutrophil (J/(cell day))	10^{-7}–9×10^{-7}	3.8×10^{-7}
β_3	Power of the maintenance of antigen-presenting cell (J/(cell day))	10^{-7}–10^{-6}	4.3×10^{-7}
β_4	Power of the maintenance of Th2 cell (J/(cell day))	3×10^{-8}–3×10^{-7}	1.3×10^{-7}
β_5	Power of the maintenance of B cell (J/(cell day))	3×10^{-8}–3×10^{-7}	1.3×10^{-7}
β_6	Power of the maintenance of plasma cell (J/(cell day))	10^{-7}–10^{-6}	4.3×10^{-7}
β_7	Coefficient which links fever and metabolic rate (J/(cell day))	2×10^{-4}–10^{-3}	6.3×10^{-4}

In general, the above-mentioned values depend on the efficiency of ATP production, consumption of energy by the immune cells under normal and pathological conditions, as well as other factors. The data published in Lehninger (1971), Ivanov (1990), Johnson (1991) suggest that the relative variation of each of these factors can be estimated as 50%. In our calculations, we used parameter values shown in the last column of Table 4. These estimates allow to scale roughly the principal components of the energy cost of pneumonia, as well as immune system functioning in healthy state. The results of calculations are shown in Table 3 and described in the text.

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