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BIOPHYSICS OF COMPLEX SYSTEMS

Analysis of the Mechanism of a Three-Wave Influenza A Virus Epidemic Cycle

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Abstract—A three-wave epidemic cycle caused by a new influenza A virus serotype has been simulated. The mechanism of a stepwise decrease in the cohort of susceptible persons has been examined. A group of asymptomatic infected individuals and an antigen activity index (regulating the intensity of input fluxes to the groups of infected persons) are introduced into the model. The morbidity rate is additionally regulated by virulence. The model is identified according to the observations of a three-wave cycle of the Hong-Kong serotype (H3N2). The simulation results suggest a leading role of asymptomatic infected persons in replenishment of the morbid group.

Keywords: serotype, antigenicity, virulence, epidemic cycle, asymptomatic infected individual, clinically infected individual, internal regulation, mathematical model

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Seasonal increases in the morbidities of acute respiratory viral infections are as a rule accompanied by an increase in the relative share of asymptomatic infection forms [1]. A large cohort of asymptomatic infected persons involved in the seasonal increases contributes to the complex pattern of the epidemic process and in the case of a sequence of outbreaks caused by a new serotype, this raises the question of the role of asymptomatic carriers in retaining the antigenic novelty of the pathogen throughout the entire epidemic cycle. The attempt to resolve this question, as well as to get a better understanding of how the epidemic process develops, leads to the concept of epidemic self-regulation, that is, the theory of the self-regulation of epidemic processes by Belyakov [2]. The experimental data that underlie this theory relate the variations in the host and pathogen populations to the internal mechanisms that function in a parasitic system. However, these facts are insufficient to explain the long-term circulation of the pandemic agent (for an attempt to explain this, see [3]). In order to expand our understanding of the mechanism that provides the internal regulation, as well as to clarify the role of asymptomatic cohort, it is reasonable to examine a three-wave manifestation of a new influenza A virus serotype.

According to [1] (p. 67), the successive epidemic outbreaks of 1959–1980 formed a series that is united by the antigenic relatedness of the pathogen. Such series are referred to as epidemic cycles. Each cycle contained several epidemic waves, creating a stepwise pattern of the decrease in the size of the susceptible cohort. A putative mechanism of this phenomenon was described by Ivanova et al. [4]. Note that a three-wave epidemic cycle of influenza A virus is determined by either the emergence of a new serotype (shift) or its renewal (semishift). In both cases, the number of asymptomatic individuals increases during the first epidemic and two subsequent ones, which is accompanied by an increase in virulence.

The large number of asymptomatic patients suggests that the main cohort of clinically infected individuals is formed via transition of an asymptomatic infection course to a clinical form, while only an insignificant share of susceptible individuals is infected from clinical cases. However, within a family the disease is most frequently transmitted from infected family members. Thus, we introduce the second assumption on the role of an asymptomatic cohort as a reservoir for the emergence of the virulent agent. Verification of these assumptions would allow for a better clarification of the role of asymptomatic individuals in the development of repeated epidemics.

The data that are necessary for verification of this idea were obtained by a team of epidemiologists with Il'enko as a major contributor in a unique 4-year observations of a constant cohort of students [4, 5]. Once the data on the morbidity dynamics in each epidemic wave are available, it is possible to search for systemic relationships between the pathogen and host populations so that their totality, as represented by a mathematical model, will be able to reproduce the

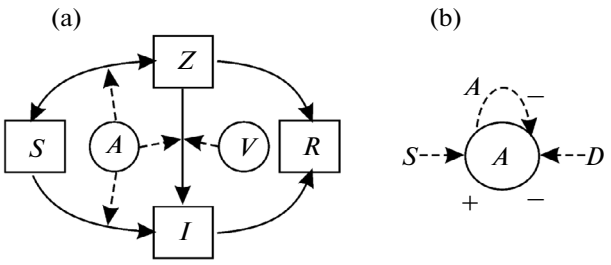

Fig. 1. A scheme of the fluxes and regulatory links in the parasitic system that reflects the interactions between pathogen and host populations (a) without feedback and (b) feedback alone: A is the antigen-activity index of the pathogen; S, Z, I, and R are the numbers of susceptible, asymptomatic infected, clinically infected, and immune individuals, respectively; V, virulence; and D, antigenic drift.

stepwise development of an epidemic cycle. Note that the ratio of the model coefficients will give some idea of the degree of matching between the assumptions and real data. The goal of this work was to construct such a model, test its adequacy, and clarify the role of the asymptomatic infected cohort.

THE MATHEMATICAL MODEL

The introduction of two of the most important characteristics of pathogen variation, viz., virulence and immune resistance, to the model present certain difficulty associated with a periodic change in the former and aperiodic (for one pandemic) change in the latter. This problem could be resolved by introducing two variables. However, the fact that the changes in virulence occur ahead of the changes in morbidity level, as was noted by Belyakov [2], allows for another solution. Since the number of asymptomatic individuals changes ahead of the clinically infected patients (and, correspondingly, of clinical morbidity), the number of asymptomatic individuals (which vary in agreement with virulence) may be used as an equivalent of periodically changing virulence. This simplification allows an additional variable to be avoided.

Another difficulty consists in finding a measurable characteristic that would be equivalent to the immune resistance of a pathogen (the ability to escape the host immune response). Since this characteristic changes concurrently with the host immunogenicity [2] and immunogenicity is determined by the protective level (titer) of antibodies, the changes in the titer may serve as a characteristic for the changes in immune resistance.

The increase in antibody titer during three epidemics and the fact that it is proportional to the total infection intensity for clinical and asymptomatic forms ([2], p. 203) make it possible to relate the immune resistance and infection rate and to introduce the generalized characteristic of the pathogen strength, which we refer to as the antigen activity index of the pathogen.

Let S, I, and R be the numbers of susceptible, clinically infected, and immune individuals, respectively; Z, the number of asymptomatic individuals (with an infection that is not apparent); A, the antigen-activity index; and V, its virulence, correlating with Z. The antigenic activity is associated with the antibody titer 1: k via k, taking initial A value as the unit for measuring k:

$$k = A/A(0).$$

We take the fact into account that an asymptomatic circulation (in a form that is not apparent) of a pathogen is accompanied by transitory carrying of the virus (a short-term presence of the pathogen in the host's body [1]). The liberation from the pathogen is reflected by an opposite flux to the susceptible cohort: $Z \to S$. Thus, the pre-epidemic circulation, as the most important stage in the epidemic process, when the virulence of the pathogen is periodically restored, is included in the general scheme of processes in a parasitic system.

We assume that for a random mixing of susceptible and infected individuals, some of the susceptible persons acquire an asymptomatic infection and some of them acquire a (clinically) manifested infection. In addition, a repeated infection frequently transfers part of the asymptomatic individuals to the cohort with a manifested infection. We also assume that the contact of susceptible individuals with asymptomatic infected persons results in asymptomatic infections and a contact with manifested cases results in manifested infections. The contacts of asymptomatic individuals with manifested cases brings the asymptomatic individuals into the cohort of manifested infection. These transitions are shown in Fig. 1a as solid arrows. The transition intensities (dashed arrows) are regulated by the antigenic factor A, which, in turn, is regulated by the host population (positive effect of transitory transmissions in the susceptible cohort), as well as being subject to their own changes. In addition, the transition of individuals from the susceptible to the clinically infected cohort is regulated by the virulence, V, which is commensurable with Z without any scaling. The transitions $S \leftrightarrow Z$ reflect the processes during the pre-epidemic period.

We refer to the set of these factors as the mechanism that underlies the adaptation of the pathogen population to the varying characteristics of the host population (Fig. 1b). Using this mechanism, the pathogen increases and decreases its antigenicity potential following the immunological variation in the host population, as well as periodically restoring its virulence following the periodic changes in the number of asymptomatic individuals. As is seen in Fig. 1, the mathematical model is specified as

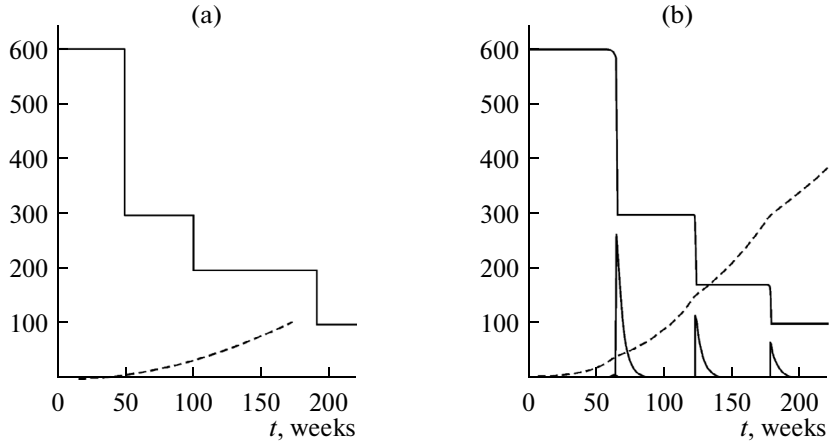

Fig. 2. The three-step decrease in the number of susceptive individuals over a 3-year circulation of the Hong Kong serotype (H3N2) according to (a) observation data and (b) simulation results; the outbursts of three epidemic waves and an increase in the pathogen immune resistance (dashed line) are shown; the initial values of variables are $S(0) = 600$, $Z(0) = 3$, $I(0) = 2$, $R(0) = 0$, $A(0) = 100$; $\alpha_0 = \alpha_1 = 0.12 \cdot 10^{-5}$, $\alpha_2 = 0.225 \cdot 10^{-4}$, $\beta = 0.1$, $c = 0.000175$, $m_0 = 0.005$, $m_1 = 0$, $p = 0.45$, $q = 0.4$; the abscissa shows t (weeks; scale 1 : 2) and the ordinate, S, I, and Z (number of individuals; scale 1 : 65).

$$\begin{aligned}
\frac{dS}{dt} &= -\alpha_0 AVSI - \alpha_1 ASZ + \beta Z,\\
\frac{dZ}{dt} &= \alpha_1 ASZ - \alpha_2 AZI - qZ - \beta Z,\\
\frac{dI}{dt} &= \alpha_0 AVSI + \alpha_2 AZI - pI,\\
\frac{dR}{dt} &= pI + qZ, \quad V = Z,\\
\frac{dA}{dt} &= (cS - m_1 A - m_0)A,\\
S + Z + I + R &= H = \text{const},\\
S(0) > 0, \quad Z(0) > 0, \quad I(0) > 0, \quad R(0) &\geq 0,
\end{aligned} \tag{1}$$

where α_0, α_1, and α_2 are empirical coefficients; $q = 1/T_q$ and $p = 1/T_p$, where T_q and T_p are the characteristic duration for asymptomatic and clinically manifested infections; $\beta = 1/T_r$, where T_r is characteristic duration for pre-epidemic circulation; c is the empirical coefficient of the positive host population effect on the increase in the pathogen immune resistance; $m_0 = 1/T_0$, where T_0 is the characteristic duration for retention of antigenic novelty; and m_1 is the empirical coefficient of pathogen self-inhibition.

MATERIALS AND METHODS

The data from a 4-year observation of a constant group of students ([5]; [6], p. 200) were used for numerical identification of the model. According to these data, 605 students of the 610 examined had no antibodies to the pandemic influenza virus A/Hong Kong/68 (which caused three epidemic waves in 1969, 1970, and 1971–1972) before the beginning of the pandemic that was caused by this pathogen. During the first wave (1969), 309 persons either got the disease or were infected; 282 of them became unsusceptible. During the second wave (1970), 108 students of the remaining 323 students who did not become ill in 1969 got the disease. During the third wave (1971–1972), 103 of 202 students became ill (Fig. 2a). The level of protective antibodies was measured before each epidemic ([6], p. 200). The increase in the antibody titer average for the group from a level of 1 : 10 to 1 : 80 and higher is represented by the sequence of k values that equal 10, 20, 40, and 80, where the first value refers to the beginning of the pre-epidemic period and the three subsequent values refer to the beginning of each of the three epidemics. It is necessary to demonstrate that model (1), which was identified using these data, is able to reproduce the described pattern of the epidemic process. After verification of the adequacy of the model, the next task is to test the above-described assumptions. The testing method is based on the following considerations.

The observation data, which show that the ratio of asymptomatic to clinically manifested influenza forms is on average 1 : 1 ([6], p. 160), suggest that we set $\alpha_0 = \alpha_1$. For α_2, we assume that the large asymptomatic cohort elevates the probability of reinfection and, correspondingly, the probability of the transition of an asymptomatic into a clinically manifested form, suggesting that we set $\alpha_2 > \alpha_0$. If identification of the model actually demands that $\alpha_0 = \alpha_1 < \alpha_2$, then the first of the above assumptions is rather likely; moreover, if the condition $V = Z$ is met, the second assumption is also valid.

RESULTS AND DISCUSSION

Identification of the model using the above-described data resulted in a pattern that was close to real (Fig. 2b), which suggests that the model is adequate. The ratio of α_0, α_1, and α_2 obtained by identification meets the actual ratio:

$$\alpha_0 = 0.12 \cdot 10^{-5}, \quad \alpha_1 = 0.12 \cdot 10^{-5},$$

$$\alpha_2 = 0.225 \cdot 10^{-4} \ (\alpha_0 = \alpha_1 < \alpha_2).$$

It follows that it is quite likely that the clinically infected cohort is formed via the partial transition of asymptomatic forms to the clinical variant. The absence of any data on the intensity of such a transition prevents us from stating that this is actually true. In addition, the need to introduce a periodically varying virulence V suggests that the second assumption is also confirmed (otherwise, the modeled pattern would be far from the real one). Consequently, both assumptions are true; correspondingly, the role of asymptomatic infected individuals consists in fulfilling two functions. The misfit between the real and model intervals between the second and third epidemics is more likely associated with diverse weather conditions rather than with internal regulation of the epidemic process. A process of epidemic outbreak development that is more expanded in time demonstrates that the Z peak appears ahead of the I peak.

As is evident from Fig. 2b, the immune resistance of a new serotype increases starting from a low level. However, the increase in immune resistance slows with an increase in host immunogenicity leading to a turning point at a certain moment (this moment is beyond the figure). This leads to a rapid decrease in the immune resistance of the pathogen and eventually to its displacement by a new serotype. Although the proposed model does not reflect the change in serotypes but rather focuses on the replacement of epidemic waves within the same serotype, it still shows the variation of the pathogen throughout the epidemic cycle. The number of epidemic waves in an epidemic cycle can be both larger and smaller than three depending on the model parameters, which complies with the real situation [1]. However, the emergence of a new serotype is hardly associated with the number of epidemic outbreaks, e.g., the three-wave cycles of 1959–1980 were replaced by a two-wave cycle in 2009–2011 with the emergence of a new serotype, *A*(H1N1)pnf [7–9].

Taking the cohort of asymptomatic infected individuals into account becomes important when searching for a strategy of vaccine prophylaxis [10], since the existence of asymptomatic illness gives grounds for a considerable part of a population to refuse vaccination with the risk of getting the clinical disease form in the case of an "unlucky" infection. In conclusion, we note that the interest in the mechanism of a stepwise decrease in the size of the susceptible cohort has brought about some curious explanations. In particular, Hauduroy, a French virologist, explained the fact that only a certain quota of the susceptible cohort within each wave is affected by a kind of "gentlemen's agreement" between the host and pathogen populations, which supposedly provides the preservation of the pathogen population in the case of the moderate "spending" of the susceptible cohort ([11], p. 54). This type of romantic explanation fails to answer the question of the nature of such a quota but stimulates the search for its discovery, which we have attempted in this paper.

CONCLUSIONS

(1) A mathematical model is proposed that explains the mechanism of a stepwise decrease in the cohort of individuals who are susceptible to infection as a result of internal regulation of pathogen immune resistance and virulence, which influence the host population and are influenced by it.

(2) A mechanism that underlies the internal regulation is proposed; this mechanism relates the infection rates to the changing antigenic activity of pathogens and in the case of clinical infection, with virulence as well, which depends on the size of the asymptomatic cohort.

(3) The numerical model identification based on observation data demonstrates the leading role of the asymptomatic carriers in the renewal of the pathogen virulence potential (after each period between epidemics) and an auxiliary role in the replenishment of the clinically ill cohort.

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