DISCUSSION

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Characteristics of self-regulation of the epidemic process of infection caused by the Epstein–Barr virus (Herpesviridae: *Lymphocryptovirus*, HHV-4)

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Introduction. Among the available scientific literature, there are no publications addressing processes of self-regulation in the parasite-host population systems with reference to chronic infections, including the infection caused by the Epstein–Barr virus (EBV infection).
The aim of the study is to assess manifestations of the epidemic process of chronic EBV infection through the lens of the basic tenets of the theory of self-regulation of parasitic systems.
Materials and methods. The study was performed using data from scientific publications selected from such database sources as Scopus, Web of Science, Cochrane Library, PubMed, CyberLeninka, RSCI, etc. The list of analyzed publications included published articles of the authors of this study, reporting the results of the retrospective epidemiological analysis of the incidence of infectious mononucleosis in Russia in general and in Moscow in particular, as well as the results of the laboratory tests regarding the detection frequency of specific antibodies to EBV proteins.
Results. The chronic course of EBV infection promotes a close long-term interaction between the pathogen and the host. The genetic variability of the pathogen and the functions of specific and nonspecific human immune defense systems play a key role in the interaction between two heterogeneous populations and underlie their phasal self-transformation. A variety of social and natural factors (adverse chemical, physical, biological, climatic impacts, etc.) trigger the reactivation of chronic EBV infection, thus providing the continuous existence of additional sources of infection in the host population.
Conclusion. The analysis of the manifestations of chronic EBV infection in the context of the theory of self-regulation of parasitic systems promotes the understanding of the factors underlying the unevenness of its epidemic process. The obtained data can be adjusted for other infections having similar transmission mechanisms and virus life cycles (including other herpes infections) to map out strategies to control the epidemic process of chronic infections spread by aerosol transmission of the pathogen.

Keywords: *Epstein–Barr virus; epidemic process; theory of self-regulation; V. Belyakov; heterogeneity of parasite and host populations; dynamic variability; regulatory role of factors*

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ОРИГИНАЛЬНОЕ ИССЛЕДОВАНИЕ
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Особенности саморегуляции эпидемического процесса инфекции, вызванной вирусом Эпштейна–Барр (Herpesviridae: *Lymphocryptovirus*, HHV-4)

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Введение. В доступной научной литературе отсутствуют работы, описывающие процессы саморегуляции в системе популяций «паразит–хозяин» для инфекций, имеющих хроническое течение, к которым в том числе относится инфекция, вызванная вирусом Эпштейна–Барр (ВЭБ-инфекция).
Цель работы – оценить проявления эпидемического процесса хронической ВЭБ-инфекции с позиции основных положений теории саморегуляции паразитарных систем.
Материалы и методы. Материалом для исследования послужили данные научных публикаций, поиск которых осуществляли по базам данных Scopus, Web of Science, The Cochrane Library, PubMed, CyberLeninka, РИНЦ и др. В перечень проанализированных работ вошли ранее опубликованные статьи авторов настоящего исследования, в том числе описывающие результаты ретроспективного эпидемиологического анализа заболеваемости инфекционным мононуклеозом в Российской Федерации в целом и Москве в частности и данные проведенных лабораторных исследований, отражающие частоту выявления специфических антител к белкам ВЭБ.
Результаты. Хроническое течение ВЭБ-инфекции способствует тесному длительному взаимодействию возбудителя и хозяина. Генетическая вариабельность патогена и особенности функционирования систем специфической и неспецифической иммунной защиты человека определяют взаимодействие двух гетерогенных популяций и лежат в основе их фазовой самоперестройки. Отдельные социальные и природные факторы (неблагоприятные химические, физические, биологические, климатические воздействия и др.) являются триггерами реактивации хронической ВЭБ-инфекции, что обеспечивает постоянное наличие в популяции хозяина дополнительных источников инфекции.
Заключение. Оценка проявлений хронической ВЭБ-инфекции с позиций теории саморегуляции паразитарных систем способствует пониманию причин неравномерности течения ее эпидемического процесса. Полученные данные могут быть аппроксимированы на другие инфекции со сходным механизмом передачи и аналогичным жизненным циклом возбудителя (в т.ч. иные герпетические заболевания), что позволит определить возможные направления контроля за эпидемическим процессом хронических инфекций с аэрозольным механизмом передачи возбудителя.

Ключевые слова: *вирус Эпштейна–Барр; эпидемический процесс; теория саморегуляции; В.Д. Беляков; гетерогенность популяции паразита и хозяина; динамическая изменчивость; регулирующая роль условий*

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Introduction

The Epstein-Barr virus (EBV) belongs to the *Herpesviridae* family*,* the *Gammaherpesvirinae* subfamily; its structure and life cycle have been quite extensively studied. Most people acquire an infection caused by EBV (EBV infection) during childhood. The pathogen is generally transmitted via the aerosol route. Primary infection can be asymptomatic or can cause pronounced clinical manifestations typical of infectious mononucleosis [1]. Subsequently, the virus remains for life in the human body, and the infectious process becomes chronic. Latent phases alternate with phases of reactivation [2].

Although the variants of the clinical course of EBV infection are described in detail in modern scientific literature, no effective etiotropic therapy has been developed so far [3–5]. The pathogen's ability to evade the host immune response poses challenges to the development of vaccines [6]. The lack of efficient treatment strategies and specific prevention methods contributes to the ubiquitous spread of EBV in the human population. Currently, up to 90% of the world's population is infected with EBV [7].

Most of the scientific studies addressing EBV infection delve into clinical characteristics and immunological aspects of the disease. The studies focusing on epidemiology aspects in Russia tend to be narrowed down to the analysis of incidence of infectious mononucleosis in some regions [8, 9]. In the meantime, the reports of this specific disease do not include any etiological decoding of the diagnosis, thus leading to distortion and incorrect interpretation of the data [10].

Generally, there are no statistical reports on EBV-caused diseases in other countries. Rare articles discussing the epidemiological characteristics of EBV infection are based on anamnestic data or laboratory test results for individual population cohorts. For example, the analysis of the detection frequency of infectious mononucleosis in different age groups in Denmark was based on the survey conducted among blood donors who informed about the presence or absence of the above disease. The obtained results demonstrating higher infection rates among younger children and adolescents cannot be seen as reliable, since the collected information did not include medical documentation with laboratory test data [11].

A more detailed analysis was conducted in the United Kingdom, where researchers studied the incidence of infectious mononucleosis hospital admissions, which tended to increase in 2002–2013. Serological markers for EBV infection were studied using serum samples from 2,366 individuals aged 1 to 25 years, among which chronic latent EBV infection was found in 85.3% of cases. The authors arrived at the conclusion that there was a direct relationship between the frequency of detection of virus infection markers and the age of the study participants [12].

The above situation highlights the importance of the analysis of the main characteristics of the epidemic process of EBV infection, which should be studied through the lens of fundamental theoretical generalizations [13–15]. The pandemic of novel coronavirus infection (COVID-19) has prompted the global community to look at the processes occurring in the interacting parasite and host populations through the prism of the theory of self-regulation of parasitic systems, which was proposed by Russian epidemiologist Vitaly Belyakov in the 1980s. This theory encompasses the mechanisms underlying self-regulation, namely: the heterogeneity of interacting populations through relations between each other; their dynamic variability; the phasal development of the parasite; the regulatory role of social and natural factors in phasal changes of parasitic systems [13].

The validity of Belyakov's theory has been consistently proven by examples of acute infections, when upon completion of the infectious process, the pathogen leaves the host [14]. The theory of self-regulation of the epidemic process was developed using the example of acute anthroponotic airborne infections, such as acute respiratory infections, streptococcal infections, diphtheria, etc. [16, 17]. The theory of self-regulation of parasitic systems has been used to describe the epidemic process of influenza and other acute respiratory tract infections [18, 19]. Special attention is given to the nature of the interaction between SARS-CoV-2, the causative agent of the novel coronavirus infection, and the human host at the population level [20–23]. At the same time, there are no research publications that would incorporate theoretical epidemiology into the description of interaction processes in the parasite-host system for chronic infections with the aerosol transmission mechanism.

The **aim** of the study is to assess manifestations of the epidemic process of chronic EBV infection through the lens of the basic tenets of the theory of self-regulation of parasitic systems.

To achieve the aim, we planned to check the presence or absence of phasal transformation, considering the changes in biological properties of the host and pathogen populations during their interaction, and to identify the role of social and natural factors responsible for unevenness and intensity of the development of the epidemic process and its self-regulation.

Materials and methods

The study was undertaken as theoretical research and was focused on the epidemic process of EBV infection, which was analyzed though the lens of the basic tenets of Belyakov's theory of self-regulation of parasitic systems.

The study was performed using data from scientific publications selected from such database sources as Scopus, Web of Science, Cochrane Library, PubMed, CyberLeninka, RSCI, etc. In our search, we also used Researchgate and reference lists of review articles. The keywords were as follows: Epstein-Barr virus, EBV, infectious mononucleosis, self-regulation of the epidemic process, epidemic process of EBV infection. A total of 5,562 publications were selected using the keyword search to be further narrowed down to 183 abstracts. The abstracts were independently assessed for relevance and shortlisted for further search for full-text articles. The final list of full-text articles included 48 publications. The search was not limited to any geographical location. The search timespan was 50 years. The search started on April 7, 2023, and ended on June 21, 2023.

The list of analyzed publications included published articles of the authors of this study, reporting the results of the retrospective epidemiological analysis of the incidence of infectious mononucleosis in Russia in general and in Moscow in particular, as well as the results of the laboratory tests regarding the detection frequency of specific antibodies to EBV proteins: immunoglobulin M antibodies to the capsid antigen (VCA IgM) and immunoglobulin G antibodies to early, capsid, and nuclear antigens (EA IgG, VCA IgG, and EBNA IgG). The above data provided a visual illustration of the tenets of the theory of self-regulation with reference to the studied infection and prompted assumptions regarding phasal variability of the host population during interaction with EBV.

The data were analyzed using formal logic methods. Microsoft Excel software for Windows was used to create graphical representations. All diagrams are borrowed from the previously published articles.

Results

Heterogeneity of EBV and human populations and their interaction

The Epstein-Barr virus, also known as human herpesvirus type 4, exhibits a tropism for different host lymphoid and epithelial cells; it causes a chronic infectious process with alternating phases of latency and reactivation.

The EBV genome encodes more than 85 proteins. The virus population is heterogeneous: There are two types distinguished by the differences in the *EBNA2* gene and several variants distinguished by the gene encoding the latent membrane protein (*LMP1*) [24]. The variability of other genes has been described, including the gene encoding the surface glycoprotein, gp350, which mediates the virus entry into a cell [25]. The scientific literature provides data on the heterogeneity of EBV within one host, which can increase significantly during the reactivation of chronic infection and decrease during the transition to the phase of latency [24]. Since the diversity level is highly associated with the stability of any biological system, the diversity of the EBV population should be analyzed in two aspects concurrently – the heterogeneity of pathogens circulating among the host population and their heterogeneity within one individual, depending on the phase of development of the infectious process. The life-long persistence of EBV in the host cannot be maintained in the latent state. Preservation of biological species requires periodic reproduction of viral progeny [13]. In the meantime, the absence of heterogeneity of the pathogen during reactivation could result in its prompt recognition and elimination by the host immune system. Therefore, EBV heterogeneity is a prerequisite for reactivation and, consequently, for effective circulation in the host population.

Diversity in the host population is governed by functions of the systems responsible for specific and nonspecific susceptibility to EBV. Studies have shown that patients with EBV-caused infectious mononucleosis demonstrated a decrease in the induced IFN-α and IFN-γ production [26, 27]. Primary EBV infection and reactivation of chronic infection are associated with changes in the cellular component of the immune system – elevated levels of cytotoxic $CD8^{+}$ T cells that can recognize and destroy infected host cells, as well as the pronounced deficiency of B cells that are principal EBV targets. Regardless of their age, in patients having clinical manifestations of infectious mononucleosis, the number of B cells with phenotypes «$CD19^{+}$, $CD21^{+}$, $CD81^{+}$», «$CD19^{+}$, $CD21^{-}$, $CD81^{+}$», and «$CD19^{+}$, $CD21^{+}$, $CD81^{-}$» is significantly reduced compared to healthy individuals [28, 29].

The humoral immune response is mediated by specific immunoglobulin antibodies to EBV proteins. The evaluation of the serological status of patients is generally based on qualitative and quantitative detection of VCA IgM, VCA IgG, EA IgG, and EBNA IgG. The detection of VCA IgM and EA IgG antibodies correlates with different phases of primary infection or reactivation of chronic EBV infection, while the presence of VCA IgG and EBNA IgG antibodies is indicative of a chronic latent process [30]. The previous study revealed the existence of a strong inverse correlation between the changes in the VCA IgG and EBNA IgG seroprevalence rates and the intra-annual dynamics of the incidence of infectious mononucleosis. At the same time, the incidence rates did not rise above the upper range of the estimated threshold during months characterized by high detection frequencies for the above markers [31].

Dynamic variability and phases of development of interacting populations

According to Belyakov's theory of self-regulation, the interaction between the parasite and host populations is rooted in their variability, which governs the uneven development of the epidemic process. The phases that the pathogen population goes through are as follows: reservation, epidemic transformation, epidemic spread, and reservation transformation [13]. The interaction of all elements of the system leads not only to an infectious process, but also to development of population or herd immunity. Thus, the host population also goes through several phases, which do not have specific names and can be defined as phases of a high level of herd immunity, a decreasing level of herd immunity, a low level of herd immunity, and an increasing level of herd immunity. During the interaction, the changes in one population will correspond to the changes in the other. The comparison of changes during the epidemic process of EBV infection is presented in the **Table**.

It should be noted that the concept of herd immunity is generally associated with specific immunoprophylaxis strategies. Vaccination is a highly effective measure that can significantly reduce the burden of infectious diseases, morbidity, and mortality [15]. However, there is currently no vaccine against EBV infection, and the level of immune protection required for prevention of the epidemic spread of the pathogen has not been identified [6, 32]. Therefore, this article is focused solely on post-infection immunity, leaving out quantitative assessment of its level, which requires an individual study.

The table demonstrates that a variety of functional humoral and cellular defense mechanisms have been accumulated during the phase of a high level of herd immunity, preventing the transition of the pathogen from the latent existence to replication (reactivation) during chronic EBV infection. The above phase is characterized by a high prevalence of the pathogen among the population, while the proportion of individuals exposed to risk of primary infection remains at the lowest level. Since most of the individuals have a high level of immune protection, the host population has low heterogeneity and low susceptibility to EBV.

Without intense circulation of the pathogen, the human immune system gradually "forgets" it, and its alertness decreases. The proportion of children born to non-immune mothers increases [32]. As the susceptibility to EBV decreases, some individuals develop conditions for reactivation of chronic EBV infection. The heterogeneity of the host population increases. The sources of infection accumulate, demonstrating the trend typical of the phase of a decreasing level of herd immunity. According to the theory of self-regulation, the respective changes in the

Table. Interaction-induced phase variability of the EBV and human populations
Таблица. Фазовая изменчивость популяции ВЭБ и человека в результате взаимодействия

EBV population Популяция ВЭБ		Interaction range Область взаимодействия	Human population Популяция человека	
phase фаза	description характеристика	manifestations of the epidemic process through the incidence dynamics проявления эпидемического процесса на примере динамики заболеваемости	description характеристика	phase фаза
Reservations Резервации	Low heterogeneity and virulence Гетерогенность и вирулентность низкая	Interepidemic period (low incidence rates) Межэпидемический период (показатели заболеваемости низкие)	Low heterogeneity and susceptibility (the highest level of specific immune protection against EBV in individuals with chronic infection – the latent phase of the disease; the lowest proportion of seronegative individuals in the total population – low risk of infection) Гетерогенность и восприимчивость низкая (максимальный уровень специфической иммунной защиты в отношении ВЭБ у лиц с хронической инфекцией – латентная фаза болезни; минимальная доля серонегативных лиц в общей популяции – низкий риск инфицирования)	High level of herd immunity Высокого уровня популяционного иммунитета
Epidemic transformation Эпидемического преобразования	Increasing heterogeneity and virulence Рост гетерогенности и вирулентности	Increasing incidence Подъем заболеваемости	Increasing heterogeneity and susceptibility (Decreasing level of specific immune protection against EBV in people with chronic infection – reactivation; increase in the proportion of seronegative individuals) Рост гетерогенности и восприимчивости (Снижение уровня специфической иммунной защиты в отношении ВЭБ у лиц с хронической инфекцией – реактивация; рост удельного веса серонегативных лиц)	Decreasing level of herd immunity Снижения уровня популяционного иммунитета
Epidemic spread Эпидемического распространения	Decreasing heterogeneity and high virulence Снижение гетерогенности на фоне высокой вирулентности	Persistent high incidence Стагнация показателей заболеваемости на высоком уровне	Decreasing heterogeneity and high virulence (The lowest level of specific immune protection against EBV in people with chronic infection; the highest proportion of seronegative individuals in the population) Снижение гетерогенности на фоне высокой восприимчивости (Минимальный уровень специфической иммунной защиты в отношении ВЭБ у лиц с хронической инфекцией; максимальная доля серонегативных лиц в популяции)	Low level of herd immunity Низкого уровня популяционного иммунитета
Reservation transformation Резервационного преобразования	Increasing heterogeneity along with decreasing virulence and the number Рост гетерогенности на фоне снижающейся вирулентности и численности	Decline in the incidence Спад заболеваемости	Increasing heterogeneity and decreasing susceptibility (Increasing level of specific immune protection against EBV in people with chronic infection; a decrease in the proportion of seronegative individuals) Рост гетерогенности и снижение восприимчивости (Повышение уровня специфической иммунной защиты в отношении ВЭБ у лиц с хронической инфекцией; снижение удельного веса серонегативных лиц)	Increasing level of herd immunity Нарастания уровня популяционного иммунитета

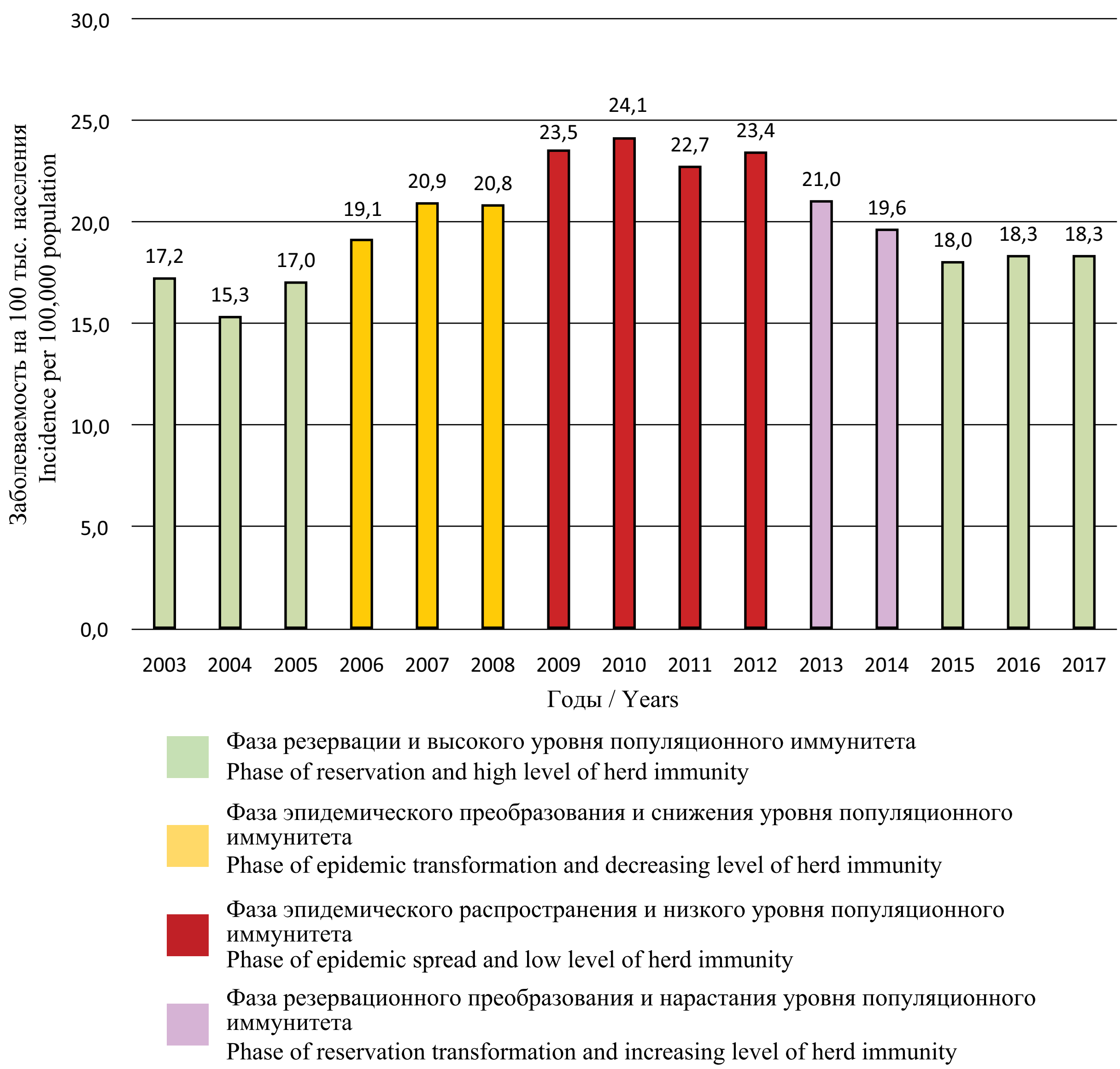

Fig. 1. Multi-year dynamics of the infectious mononucleosis incidence in Moscow in 2003–2017 (per 100,000 population)
Рис. 1. Многолетняя динамика заболеваемости инфекционным мононуклеозом в Москве в 2003–2017 гг. (на 100 тыс. населения)

pathogen population correspond to the phase of epidemic transformation and are associated with increasing heterogeneity and virulence of the virus [13].

The phase of a low level of herd immunity promotes ideal conditions for activation of the transmission mechanism: There is a sufficient number of sources of infection and susceptible individuals. All of them have the lowest levels of immune protection against EBV, thus contributing to the low heterogeneity and the high susceptibility of the host population. Individuals previously not exposed to EBV get infected and individuals with chronic EBV infection develop superinfection (epidemic spread of the pathogen).

In some individuals, the development of primary EBV infection, superinfection, or reactivation of chronic EBV infection triggers an increase in the level of herd immunity. Although there are multiple sources of infection during this period, the pathogen keeps spreading until the peak of heterogeneity is reached. Then, the proportion of susceptible individuals decreases dramatically, and EBV gradually loses its virulence and moves into a latent state.

The aforesaid is confirmed by the results of the previous retrospective epidemiological analysis [31]. **Figure 1** presents a fragment of multi-year dynamics of the infectious mononucleosis incidence in Moscow; the timespan between two troughs (2004 and 2015) was 11 years. The lowest incidence rates (2003–2005 and 2015–2017) correspond to the phases of reservation in the pathogen population and high level of herd immunity in host population. The increase in the incidence in 2006–2008 resulted from the increased heterogeneity of interacting populations (phases of epidemic and infection transformation). The highest rates were reported in 2009–2012 and corre-

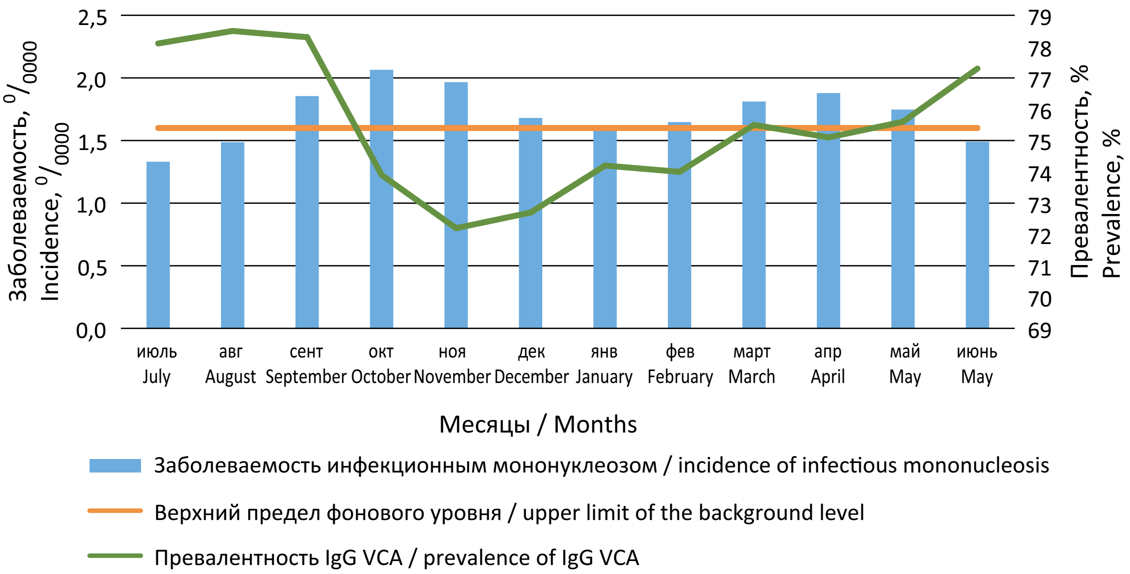

Fig. 2. Intra-annual dynamics of the infectious mononucleosis incidence and VCA IgG prevalence in Moscow: The multi-year average rates in 2010–2022.

Рис. 2. Внутригодовая динамика заболеваемости инфекционным мононуклеозом и превалентность IgG VCA в Москве: средние многолетние уровни за период 2010–2022 гг.

spond to the phases of epidemic spread and low level of herd immunity. The decrease in the pathogen virulence and host population susceptibility explains the decrease in the incidence in 2013–2014 (phases of reservation transformation and increasing level of herd immunity).

Similar trends are observed in the intra-annual dynamics of the incidence of infectious mononucleosis, which generally demonstrates a slight seasonal upswing during cold months **(Fig. 2)**. The multi-year average rates overshooting the upper range of the background rates were recorded from September to May. The slight decrease in the incidence in January could be caused both by the disconnection of the host population and by the reduction in the reported number of cases of infectious mononucleosis during New Year holidays [31, 33, 34]. Fig. 2 presents the infectious mononucleosis incidence rates compared to the VCA IgG prevalence among Moscow residents. In June–September, the VCA IgG detection frequency demonstrated the highest levels, thus implying low incidence rates among the population. In October–November, the prevalence rates decreased significantly, while the incidence increased. In April–May, on the contrary, while the number of cases of infectious mononucleosis was decreasing, the frequency of detection of the above marker was gradually increasing. The above data provide a vivid illustration of phase transformations, which occur in the host population during the interaction with EBV.

Regulatory role of conditions (social and natural factors)

Based on the tenets of the theory of self-regulation, all social and natural factors can be divided into three groups depending on the type of their impact on the phase nature of development of the epidemic process [13]:

– factors affecting the vertical (through succession of generations) and the horizontal (migration, emergence of new groups) "mixing" of people;

– factors activating the mechanism of pathogen transmission;

– factors decreasing immunity and resistance.

By "mixing" we mean interaction between the individuals who have not been previously exposed to EBV (or any of its genetic variants) and infected people. Note that the highest proportion of individuals who are not immune to EBV is observed in the age group of children younger than 2 years old [32]. With increasing age, the seroprevalence rates tend to increase and reach the highest level by the age of 30–40 years, demonstrating a slight decrease by the age of 50–60 years [7]. The above patterns illustrate the role of demographic changes in the structure of the population as one of the factors regulating the intensity of the epidemic process [14].

The frequency and intensity of contacts among individuals depend on their social activity, which is lowest among younger children and older people. Social processes contributing to horizontal mixing include migration of population, including daily commuting by public transport, formation of new organized groups (for example, through conscription), and restarting of the previously established groups, for example, after summer vacations (preschool and school educational organizations) [35, 36]. In the case of EBV, the main prerequisite for horizontal mixing is the existence of territorial patterns of the spread of its genetic variants [24].

In addition to the aforesaid, the role of horizontal mixing in the regulation of the epidemic process can depend on the population density of a certain area. The analysis of data on EBV infection did not demonstrate any significant correlation between the VCA IgM and EA

IgG detection frequency and the population density in regions of Russia. At the same time, there is a linear relationship of moderate strength between the multi-year average incidence rates of infectious mononucleosis and the population density. The explanation can be found in the fact that the closeness of contacts among individuals has an impact on the EBV spread among non-immune individuals, while having no significant effect on reactivation of chronic infection, which is triggered by other factors [37]. The analysis of the causes underlying changes in the incidence of infectious mononucleosis in 2020 shows that the restrictive measures aimed at disconnection of the population and reduction of the risk of aerosol transmission of SARS-CoV-2 resulted in reduction of intensity of the epidemic process of EBV infection [38].

An important role in the epidemic spread of the pathogen is played by factors inducing the activation of transmission mechanisms. The aerosol transmission is the main transmission route for EBV; it requires the presence of the pathogen in the upper respiratory tract as well as factors inducing the formation of the aerosol.

It has been found that the EBV DNA detection frequency in the saliva of the examined individuals does not have significant differences during warm and cold seasons of the year, while the incidence of infectious mononucleosis is characterized by an autumn-spring seasonal upswing [33] concurrent with the peaks of other upper respiratory tract infections [34]. It should be noted that infectious mononucleosis develops without pronounced catarrhal symptoms, which, in their turn, contribute to the formation of an infectious aerosol. During seasonal upswings, EBV co-circulates in the host population with other pathogens that cause upper respiratory tract infections. The previous studies have shown that during cold months of the year, EBV was detected in nasopharyngeal and oropharyngeal swabs in 33.7–37.1% of individuals examined during the influenza and ARVI monitoring, and in 16.3–18.6% of individuals, it was detected together with other pathogens. In co-infections, a runny nose and cough result in the formation of an infectious aerosol containing EBV, along with other pathogens [39, 40].

Note that pathogens of other infectious diseases not only have a significant role in activation of the aerosol transmission mechanism, but also trigger the reactivation of chronic EBV infection, since they significantly change immunological reactivity and can enter a competitive relationship with EBV, having tropism for the same cells. Scientific publications describe cases of reactivation of EBV infection in patients with HIV infection [41, 42], hepatitis B [43], tuberculosis [44, 45], and COVID-19 [46].

In addition to pathogenic microorganisms, EBV reactivation can be induced by different types of ionizing radiation, as, for example, demonstrated in astronauts during spaceflights [47]. In the experiment, the cell culture containing the EBV-positive cell line was exposed to 4 different types of radiation: ^{137}Cs gamma rays, 150-MeV protons, 600 MeV/n carbon ions, and 600 MeV/n iron ions at doses of 0.1, 0.5, 1.0, and 2.0 Gy. It was found that the EBV lytic gene transcription and, consequently, EBV reactivation occurred for all types and doses of radiation 4 days after the exposure. Gamma rays were most effective in inducing reactivation. The researchers also found that EVB reactivation could occur due to the effect of different types of radiation on latently infected cells in the absence of changes in the host immune system [48].

Among other factors that have a direct impact on the parasite-host system we can single out the climatic impact. It has been found that in Russia, areas with high seroprevalence rates for IgG EBNA antibodies among adults are located in unfavorable climatic zones. For example, the Republic of Kalmykia, Astrakhan and Orenburg Regions (the zones of steppes, semi-deserts, and deserts) have a continental climate with sharp daily and seasonal variations in temperature. The Murmansk Region and the Republic of Sakha (Yakutia), which are located in the tundra zone, are characterized by the combination of low temperatures and high humidity [37].

Thus, various natural and social factors are the main drivers regulating the epidemic process, having an impact on its intensity and dynamics, and, consequently, on the heterogeneity of parasite and host populations. V. Belyakov believed that the ability to control these factors should form the core of preventive and epidemic control measures [13]. At the same time, the best results are achieved by measures aimed at enhancement of the host immune protection [14].

Currently, there are no approved vaccines for preventing EBV infection. Vaccine candidates are being developed in different countries; however, none of them have brought the desired result [6]. Therefore, the measures aimed at enhancement of immune protection should include preventive vaccination against other pathogens that play a critical role in the reactivation of chronic EBV infection as well as nonspecific immunoprophylaxis. Reduction of the impact of other factors contributing to reactivation is of high importance, including prevention and timely treatment of concomitant somatic diseases, minimization of adverse household, job-related and other impacts, promotion of healthy lifestyle.

To prevent the activation of the transmission mechanism, the measures should include such key components as disinfection and sterilization (disinfection of indoor air, household items, utensils, surfaces; disinfection, pre-cleaning, and sterilization of medical equipment and instruments; disinfection of epidemiologically dangerous medical waste), as well as personal respiratory protective equipment to be used in crowded places, especially during seasonal peaks in the incidence of upper respiratory tract infections.

The factors contributing to mixing of people are less responsive to man-made impacts. At the same time, the ban on travel across countries and regions, which was imposed during the COVID-19 pandemic, played a crucial role in the implementation of public health measures against the novel infection and can be used in emergency situations caused by other diseases.

Conclusion

The analysis has shown that the chronic course of EBV infection promotes a close long-term interaction between the pathogen and the host. The genetic variability of the pathogen and the functions of specific and nonspecific human immune defense systems play a key role in the interaction between two heterogeneous populations and underlie their phasal self-transformation. A variety of social and natural factors (adverse chemical, physical, biological, climatic impacts, etc.) trigger the reactivation of chronic EBV infection, thus providing the continuous existence of additional (along with patients with primary infection) sources of infection in the host population.

The analysis of the manifestations of chronic EBV infection in the context of the theory of self-regulation of parasitic systems promotes understanding of the factors underlying the unevenness of its epidemic process. The obtained data can be adjusted for other infections having similar transmission mechanisms and virus life cycles (including other herpes infections) to map out strategies for control over the epidemic process of chronic infections spread by aerosol transmission of the pathogen.

REFERENCES

1. Agaeva M.I., Agaeva Z.A. Characteristic features of the course of herpesvirus infections during pregnancy. *Klinicheskiy razbor v obshchey meditsine.* 2022; (1): 49–55. https://doi.org/10.47407/kr2022.3.1.00118 (in Russian)
2. Solomay T.V., Semenenko T.A., Karazhas N.V., Rybalkina T.N., Kornienko M.N., Bosh'yan R.E., et al. Assessing risks of infection with herpes viruses during transfusion of donor blood and its components. *Analiz riska zdorov'yu.* 2020; (2): 135–42. https://doi.org/10.21668/health.risk/2020.2.15.eng https://elibrary.ru/mjiicr
3. Fedorova I.M., Koteleva S.I., Kapustin I.V., Blyakher M.S., Tul'skaya E.A., Zvereva N.N., et al. Hormone therapy affecting interferon defense in children with infectious mononucleosis. *Infektsiya i immunitet.* 2021; 11(5): 943–50. https://doi.org/10.15789/2220-7619-TSC-1350 https://elibrary.ru/dnyuor (in Russian)
4. Ivanov A.A., Kulichenko T.V. Polypharmacy in infectious mononucleosis management: case series. *Pediatricheskaya farmakologiya.* 2022; 19(5): 412–6. https://doi.org/10.15690/pf.v19i5.2462 https://elibrary.ru/zxqiuy (in Russian)
5. Vikulov G.Kh., Oradovskaya I.V., Kolobukhina L.V. Herpesvirus infections in children: prevalence, incidence, clinical forms, and management algorithm. *Voprosy prakticheskoy pediatrii.* 2022; 17(6): 126–41. https://doi.org/10.20953/1817-7646-2022-6-126-140 (in Russian)
6. Solomay T.V., Semenenko T.A., Filatov N.N., Kostinov M.P., Il'ina N.I. Epstein–Barr virus: vaccine development. *Immunologiya.* 2020; 41(4): 381–90. https://doi.org/10.33029/0206-4952-2020-41-3-381-390 https://elibrary.ru/kmmvgr (in Russian)
7. Solomay T.V., Semenenko T.A., Blokh A.I. Prevalence of Epstein–Barr virus antibodies in different age groups in Europe and Asia: a systematic review and meta-analysis. *Zdravookhranenie Rossiyskoy Federatsii.* 2021; 65(3): 276–86. https://doi.org/10.47470/0044-197X-2021-65-3-276-286 https://elibrary.ru/sljyeb (in Russian)
8. Burmagina I.A., Pozdeeva M.A., Agafonov V.M. Infectious mononucleosis in the northern region. *Sanitarnyy vrach.* 2014; (11): 38–41. https://elibrary.ru/szojrb (in Russian)
9. Solomay T.V., Semenenko T.A. Epstein–Barr viral infection is a global epidemiological problem. *Voprosy virusologii.* 2022; 67(4): 265–77. https://doi.org/10.36233/0507-4088-122 https://elibrary.ru/cnyvgi (in Russian)
10. Solomay T.V. Dynamics of morbidity and territorial spread of infectious mononucleosis. *Zdravookhranenie Rossiyskoy Federatsii.* 2019; 63(4): 186–92. https://doi.org/10.18821/0044-197X-2019-63-4-186-192 https://elibrary.ru/aymphv (in Russian)
11. Rostgaard K., Balfour H.H. Jr., Jarrett R., Erikstrup C., Pedersen O., Ullum H., et al. Primary Epstein–Barr virus infection with and without infectious mononucleosis. *PLoS One*. 2019; 14(12): e0226436. https://doi.org/10.1371/journal.pone.0226436
12. Kuri A., Jacobs B.M., Vickaryous N., Pakpoor J., Middeldorp J., Giovannoni G., et al. Epidemiology of Epstein–Barr virus infection and infectious mononucleosis in the United Kingdom. *BMC Public Health.* 2020; 20(1): 912. https://doi.org/10.1186/s12889-020-09049-x
13. Belyakov V.D. General laws of functioning of parasitic systems (mechanisms of self-regulation). *Parazitologiya*. 1986; 20(4): 249–55. (in Russian)
14. Briko N.I., Mindlina A.Ya., Polibin R.V. Universality of changes in epidemic process manifestations of anthroponosis infections in recent decades. *Zhurnal mikrobiologii, epidemiologii i immunobiologii.* 2015; 55(5): 12–20. https://elibrary.ru/zqjycd (in Russian)
15. Briko N.I. Theoretical generalizations in epidemiology: from history to the present. *Epidemiologiya i vaktsinoprofilaktika.* 2018; 17(5): 5–16. https://doi.org/10.31631/2073-3046-2018-17-5-5-16 https://elibrary.ru/pkowvr (in Russian)
16. Belyakov V.D., Yafaev R.Kh. *Epidemiology [Epidemiologiya].* Moscow: Meditsina; 1989. (in Russian)
17. Semenenko T.A., Akimkin V.G., Burtseva E.I., Nozdracheva A.V., Simonova E.G., Tutel'yan A.V., et al. Characteristics of the epidemic situation associated with acute respiratory viral infections in the Russian Federation during the pandemic spread of COVID-19. *Epidemiologiya i vaktsinoprofilaktika.* 2022; 21(4): 4–15. https://doi.org/10.31631/2073-3046-2022-21-4-4-15 https://elibrary.ru/zovuqr (in Russian)
18. Rednenko V.V., Semenov V.M., Korobov G.D. Epidemiological analysis of the annual dynamics of respiratory infections in a closed group. *Mediko-biologicheskie i sotsial'no-psikhologicheskie problemy bezopasnosti v chrezvychaynykh situatsiyakh.* 2011; (1): 24–8. https://elibrary.ru/qjhktx (in Russian)
19. Kolesin I.D. An analysis of the displacement mechanism of predecessors by a pandemic strain. *Biofizika.* 2016; 61(6): 985–8. https://doi.org/10.1134/S0006350916060105 https://elibrary.ru/yvhdgd (in Russian)
20. Akimkin V.G., Semenenko T.A., Ugleva S.V., Dubodelov D.V., Kuzin S.N., Yatsyshina S.B., et al. COVID-19 in Russia: epidemiology and molecular genetic monitoring. *Vestnik Rossiyskoy akademii meditsinskikh nauk.* 2022; 77(4): 254–60. https://doi.org/10.15690/vramn2121 https://elibrary.ru/dozijs (in Russian)
21. Bilev A.E., Bileva N.A., Chupakhina L.V., Vandysheva T.V., Ariskina M.A. Is the theory of self-regulation of the epidemic process acceptable for the new coronavirus infection COVID-19? *Vestnik meditsinskogo instituta «REAVIZ». Reabilitatsiya, Vrach i Zdorov'e.* 2022; (4): 12–8. https://doi.org/10.20340/vmi-rvz.2022.4.COVID.2 (in Russian)
22. Akimkin V.G., Kuzin S.N., Semenenko T.A., Ploskireva A.A., Dubodelov D.V., Tivanova E.V., et al. Characteristics of the COVID-19 epidemiological situation in the Russian Federation in 2020. *Vestnik Rossiyskoy akademii meditsinskikh nauk.* 2021; 76(4): 412–22. https://doi.org/10.15690/vramn1505 https://elibrary.ru/zmowbe (in Russian)
23. Akimkin V.G., Popova A.Yu., Ploskireva A.A., Ugleva S.V., Semenenko T.A., Pshenichnaya N.Yu., et al. COVID-19: the evolution of the pandemic in Russia. Report I: Manifestations of the COVID-19 epidemic process. *Zhurnal mikrobiologii, epidemiologii i immunobiologii*. 2022; 99(3): 269–86. https://doi.org/10.36233/0372-9311-276 https://elibrary.ru/zxgtfd (in Russian)
24. Popkova M.I., Utkin O.V. Genetic diversity of the Epstein–Barr virus: a modern view of the problem. *Zhurnal mikrobiologii, epidemiologii i immunobiologii.* 2022; 99(1): 93–108. https://doi.org/10.36233/0372-9311-228 https://elibrary.ru/kbfbkm (in Russian)
25. Solomay T.V., Malakhova M.V., Shitikov E.A., Bespyatykh D.A., Veselovskiy V.A., Semenenko T.A., et al. Epstein–Barr virus: evaluation of gp350 and EBNA2 gene variability. *Molekulyarnaya genetika, mikrobiologiya i virusologiya.* 2022; 40(3): 32–40. https://doi.org/10.17116/molgen20224003132 https://elibrary.ru/dmfrxl (in Russian)
26. Kukushkina E.A., Koteleva S.I., Blyakher M.S., Fedorova I.M., Ramazanova Z.K., Zvereva N.N., et al. Altered interferon de-

fense in children with dynamically changed infectious mononucleosis. *Infektsiya i immunitet.* 2021; 11(1): 157–64. https://doi.org/10.15789/2220-7619-TIP-1349 https://elibrary.ru/asboym (in Russian)
27. Ershov F.I., Ospel'nikova T.P., Narovlyanskiy A.N. Interferon status as a method of determination of nonspecific biomarkers of human immunopathology. *Zhurnal mikrobiologii, epidemiologii i immunobiologii.* 2019; (3): 91–9. https://doi.org/10.36233/0372-9311-2019-3-91-99 https://elibrary.ru/jmogdb (in Russian)
28. Trisko A.A., Kolesnikova N.V., Avdeeva M.G., Chudilova G.A., Lomtatidze L.V. Peculiarities of cellular immunity in acute Epstein–Barr virus infection. *Epidemiologiya i infektsionnye bolezni.* 2015; 20(4): 13–5. https://elibrary.ru/uhyruv (in Russian)
29. Chuykova K.I., Popova O.A. Improvement of treatment of infectious mononucleosis in children. *Detskie infektsii.* 2012; 11(4): 48–51. https://elibrary.ru/phgfzl (in Russian)
30. Nagovitsyna E.B. Modern approaches to diagnostics and treatment of Epstein–Barr virus infectious mononucleosis. *Dal'nevostochnyy meditsinskiy zhurnal.* 2016; (3): 45–50. https://elibrary.ru/wmwfkx (in Russian)
31. Solomay T.V., Semenenko T.A., Tutel'yan A.V., Bobrova M.V. Epidemiological features of infection caused by the Epstein–Barr virus. *Zhurnal mikrobiologii, epidemiologii i immunologii.* 2021; 98(6): 685–96. https://doi.org/10.36233/0372-9311-139 https://elibrary.ru/cyuyrd (in Russian)
32. Solomay T.V., Semenenko A.V., Nikitina G.Yu., Shuvalov A.N. Predictive scenarios for the development of the epidemic process of Epstein–Barr virus infection in the absence of specific prevention measures and their implementation. *Epidemiologiya i infektsionnye bolezni. Aktual'nye voprosy.* 2023; 13(1): 60–9. https://doi.org/10.18565/epidem.2023.13.1.60–9 (in Russian)
33. Solomay T.V., Filatov N.N. Seasonality of infection caused by the Epstein–Barr virus. *Zhurnal infektologii.* 2020; 12(4): 93–100. https://doi.org/10.22625/2072-6732-2020-12-4-93-100 https://elibrary.ru/dshwxp (in Russian)
34. Solomay T.V., Filatov N.N., Kaira A.N., Lavrov V.F., Kuzin A.A., Lantsov E.V. Similarity of manifestations of epidemic processes of infectious mononucleosis and upper respiratory tract infections. *Vestnik Rossiyskoy Voenno-meditsinskoy akademii.* 2020; (3): 46–51. https://elibrary.ru/fwocgg (in Russian)
35. Korotchenko S.I. Problems of immunization of persons subject to military conscription. *Sanitarnyy vrach.* 2016; (12): 8–13. https://elibrary.ru/xrmzgv (in Russian)
36. Gotvyanskaya T.P., Mukasheva E.A., Nozdracheva A.V., Sipacheva N.B., Semenenko A.V., Ignat'eva A.V., et al. Incidence and population immunity to influenza and ARVI in the context of the COVID-19 pandemic. *Sanitarnyy vrach.* 2023; (3): 153–63. https://doi.org/10.33920/med-08-2303-03 (in Russian)
37. Solomay T.V., Semenenko T.A., Kuzin S.N., Akimkin V.G. Territorial features of the epidemic process of infection caused by the Epstein–Barr virus. *Epshteyna-Barr. Infektsionnye bolezni: novosti, mneniya, obuchenie.* 2021; 10(4): 81–9. https://doi.org/10.33029/2305-3496-2021-10-4-81-89 https://elibrary.ru/zsblzm (in Russian)
38. Solomay T.V., Semenenko T.A., Isaeva E.I., Vetrova E.N., Chernyshova A.I., Romenskaya E.V., et al. COVID-19 and the risk of herpesvirus reactivation. *Epidemiologiya i infektsionnye bolezni. Aktual'nye voprosy.* 2021; 11(2): 55–62. https://doi.org/10.18565/epidem.2021.11.2.55-62 https://elibrary.ru/rgixoj (in Russian)
39. Solomay T.V., Semenenko T.A., Filatov N.N., Kolbutova K.B., Oleynikova D.Yu., Karazhas N.V. The role of children and adults as a reservoir of pathogens during the seasonal rise in the incidence of upper respiratory tract infections. *Detskie infektsii.* 2020; 19(3): 5–11. https://doi.org/10.22627/2072-8107-2020-19-3-5-11 https://elibrary.ru/zchyjf (in Russian)
40. Gralton J., Tovey E., McLaws M.L., Rawlinson W.D. The role of particle size in aerosolised pathogen transmission: a review. *J. Infect.* 2011; 62(1): 1–13. https://doi.org/10.1016/j.jinf.2010.11.010
41. Farisyi M.A., Sufiawati I. Detection of Epstein–Barr virus DNA in saliva of HIV-1-infected individuals with oral hairy leukoplakia. *Oral Dis.* 2020; 26(Suppl. 1): 158–60. https://doi.org/10.1111/odi.13400
42. Koshy E., Mengting L., Kumar H., Jianbo W. Epidemiology, treatment and prevention of zoster: A comprehensive review. *Indian J. Dermatol. Venereol. Leprol.* 2018; 84(3): 251–62. https://doi.org/10.4103/ijdvl.IJDVL_1021_16
43. Suarez F., Lortholary O., Hermine O., Lecuit M. Infection-associated lymphomas derived from marginal zone B cells: a model of antigen-driven. *Blood.* 2006; 107(8): 3034–44. https://doi.org/10.1182/blood-2005-09-3679
44. Sinitsyn M.V., Bogorodskaya E.M., Rodina O.V., Kubrakova E.P., Romanova E.Yu., Bugun A.V. The damage of the central nervous system in the patients with tuberculosis in modern epidemiological conditions. *Infektsionnye bolezni: novosti, mneniya, obuchenie.* 2018; 7(1): 111–20. https://doi.org/10.24411/2305-3496-2018-00015 https://elibrary.ru/yshtny (in Russian)
45. Mordyk A.V., Sitnikova S.V., Puzyreva L.V., Nazarova O.I., Fursevich L.N. Manifestations of HIV infection associated with the results of treatment of tuberculosis in patients admitted to a specialized hospital. *VICh-infektsiya i immunosupressii.* 2015; 7(1): 69–75. https://elibrary.ru/tnbset (in Russian)
46. Solomay T.V., Semenenko T.A., Filatov N.N., Vedunova S.L., Lavrov V.F., Smirnova D.I., et al. Reactivation of Epstein–Barr virus (Herpesviridae: Lymphocryptovirus, HHV-4) infection during COVID-19: epidemiological features. *Voprosy virusologii.* 2021; 66(2): 152–61. https://doi.org/10.36233/0507-4088-40 https://elibrary.ru/nhbzyr (in Russian)
47. Rooney B.V., Crucian B.E., Pierson D.L., Laudenslager M.L., Mehta S.K. Herpes virus reactivation in astronauts during spaceflight and its application on earth. *Front. Microbiol.* 2019; 10: 16. https://doi.org/10.3389/fmicb.2019.00016
48. Mehta S.K., Bloom D.C., Plante I., Stowe R., Feiveson A.H., Renner A., et al. Reactivation of latent Epstein–Barr virus: a comparison after exposure to gamma, proton, carbon, and iron radiation. *Int. J. Mol. Sci.* 2018; 19(10): 2961. https://doi.org/10.3390/ijms19102961

ЛИТЕРАТУРА

1. Агаева М.И., Агаева З.А. Характерные особенности течения герпесвирусных инфекций во время беременности. *Клинический разбор в общей медицине.* 2022; (1): 49–55. https://doi.org/10.47407/kr2022.3.1.00118
2. Соломай Т.В., Семененко Т.А., Каражас Н.В., Рыбалкина Т.Н., Корниенко М.Н., Бошьян Р.Е. и др. Оценка риска инфицирования герпесвирусами при переливании донорской крови и ее компонентов. *Анализ риска здоровью.* 2020; (2): 136–42. https://doi.org/10.21668/health.risk/2020.2.15 https://elibrary.ru/hrzyly
3. Федорова И.М., Котелева С.И., Капустин И.В., Бляхер М.С., Тульская Е.А., Зверева Н.Н. и др. Влияние гормонотерапии на состояние интерфероновой защиты у детей, больных инфекционным мононуклеозом. *Инфекция и иммунитет.* 2021; 11(5): 943–50. https://doi.org/10.15789/2220-7619-TSC-1350 https://elibrary.ru/dnyuor
4. Иванов А.А., Куличенко Т.В. Полипрагмазия при лечении инфекционного мононуклеоза: серия клинических случаев. *Педиатрическая фармакология.* 2022; 19(5): 412–6. https://doi.org/10.15690/pf.v19i5.2462 https://elibrary.ru/zxqiuy
5. Викулов Г.Х., Орадовская И.В., Колобухина Л.В. Герпесвирусные инфекции у детей: распространенность, заболеваемость, клинические формы и алгоритм ведения. *Вопросы практической педиатрии.* 2022; 17(6): 126–41. https://doi.org/10.20953/1817-7646-2022-6-126-140
6. Соломай Т.В., Семененко Т.А., Филатов Н.Н., Костинов М.П., Ильина Н.И. Вирус Эпштейна–Барр: разработка вакцин. *Иммунология.* 2020; 41(4): 381–90. https://doi.org/10.33029/0206-4952-2020-41-3-381-390 https://elibrary.ru/kmmvgr
7. Соломай Т.В., Семененко Т.А., Блох А.И. Распространённость антител к вирусу Эпштейна–Барр в разных возрастных группах населения Европы и Азии: систематический обзор и метаанализ. *Здравоохранение Российской Федерации.* 2021; 65(3): 276–86. https://doi.org/10.47470/0044-197X-2021-65-3-276-286 https://elibrary.ru/sljyeb
8. Бурмагина И.А., Поздеева М.А., Агафонов В.М. Инфекционный мононуклеоз в северном регионе. *Санитарный врач.* 2014; (11): 38–41. https://elibrary.ru/szojrb
9. Соломай Т.В., Семененко Т.А. Эпштейна–Барр вирусная инфекция – глобальная эпидемиологическая проблема. *Вопросы вирусологии.* 2022; 67(4): 265–77. https://doi.org/10.36233/0507-4088-122 https://elibrary.ru/cnyvgi
10. Соломай Т.В. Многолетняя динамика заболеваемости и территориальное распространение инфекционного мононуклеоза.

Здравоохранение Российской Федерации. 2019; 63(4): 186–92. https://doi.org/10.18821/0044-197X-2019-63-4-186-192 https://elibrary.ru/aymphv

11. Rostgaard K., Balfour H.H. Jr., Jarrett R., Erikstrup C., Pedersen O., Ullum H., et al. Primary Epstein–Barr virus infection with and without infectious mononucleosis. *PLoS One*. 2019; 14(12): e0226436. https://doi.org/10.1371/journal.pone.0226436
12. Kuri A., Jacobs B.M., Vickaryous N., Pakpoor J., Middeldorp J., Giovannoni G., et al. Epidemiology of Epstein–Barr virus infection and infectious mononucleosis in the United Kingdom. *BMC Public Health*. 2020; 20(1): 912. https://doi.org/10.1186/s12889-020-09049-x
13. Беляков В.Д. Общие закономерности функционирования паразитарных систем (механизмы саморегуляции). *Паразитология*. 1986; 20(4): 249–55.
14. Брико Н.И., Миндлина А.Я., Полибин Р.В. Универсальность изменений в проявлениях эпидемического процесса антропонозных инфекций за последние десятилетия. *Журнал микробиологии, эпидемиологии и иммунобиологии*. 2015; 55(5): 12–20. https://elibrary.ru/zqjycd
15. Брико Н.И. Теоретические обобщения в эпидемиологии: от истории к современности. *Эпидемиология и вакцинопрофилактика*. 2018; 17(5): 5–16. https://doi.org/10.31631/2073-3046-2018-17-5-5-16 https://elibrary.ru/pkowvr
16. Беляков В.Д., Яфаев Р.Х. *Эпидемиология*. М.: Медицина; 1989.
17. Семененко Т.А., Акимкин В.Г., Бурцева Е.И., Ноздрачева А.В., Симонова Е.Г., Тутельян А.В. и др. Особенности эпидемической ситуации по острым респираторным вирусным инфекциям с учетом пандемического распространения COVID-19. *Эпидемиология и вакцинопрофилактика*. 2022; 21(4): 4–15. https://doi.org/10.31631/2073-3046-2022-21-4-4-15 https://elibrary.ru/zovuqr
18. Редненко В.В., Семенов В.М., Коробов Г.Д. Эпидемиологический анализ годовой динамики заболеваемости респираторными инфекциями в закрытом коллективе. *Медико-биологические и социально-психологические проблемы безопасности в чрезвычайных ситуациях*. 2011; (1): 24–8. https://elibrary.ru/qjhktx
19. Колесин И.Д. Анализ механизма вытеснения пандемическим штаммом своих предшественников. *Биофизика*. 2016; 61(6): 1190–3. https://elibrary.ru/xknvon
20. Акимкин В.Г., Семененко Т.А., Углева С.В., Дубоделов Д.В., Кузин С.Н., Яцышина С.Б. и др. COVID-19 в России: эпидемиология и молекулярно-генетический мониторинг. *Вестник Российской академии медицинских наук*. 2022; 77(4): 254–60. https://doi.org/10.15690/vramn2121 https://elibrary.ru/dozijs
21. Билёв А.Е., Билёва Н.А., Чупахина Л.В., Вандышева Т.В., Арискина М.А. Приемлема ли теория саморегуляции эпидемического процесса для новой коронавирусной инфекции COVID-19? *Вестник медицинского института «РЕАВИЗ». Реабилитация, Врач и Здоровье*. 2022; (4): 12–8. https://doi.org/10.20340/vmi-rvz.2022.4.COVID.2
22. Акимкин В.Г., Кузин С.Н., Семененко Т.А., Плоскирева А.А., Дубоделов Д.В., Тиванова Е.В. и др. Характеристика эпидемиологической ситуации по COVID-19 в Российской Федерации в 2020 г. *Вестник Российской академии медицинских наук*. 2021; 76(4): 412–22. https://doi.org/10.15690/vramn1505 https://elibrary.ru/zmowbe
23. Акимкин В.Г., Попова А.Ю., Плоскирева А.А., Углева С.В., Семененко Т.А., Пшеничная Н.Ю. и др. COVID-19: эволюция пандемии в России. Сообщение I: проявления эпидемического процесса COVID-19. *Журнал микробиологии, эпидемиологии и иммунобиологии*. 2022; 99(3): 269–86. https://doi.org/10.36233/0372-9311-276 https://elibrary.ru/zxgtfd
24. Попкова М.И., Уткин О.В. Генетическое разнообразие вируса Эпштейна–Барр: современный взгляд на проблему. *Журнал микробиологии, эпидемиологии и иммунобиологии*. 2022; 99(1): 93–108. https://doi.org/10.36233/0372-9311-228 https://elibrary.ru/kbfbkm
25. Соломай Т.В., Малахова М.В., Шитиков Е.А., Беспятых Д.А., Веселовский В.А., Семененко Т.А. и др. Вирус Эпштейна–Барр: оценка вариабельности генов gp350 и EBNA2. *Молекулярная генетика, микробиология и вирусология*. 2022; 40(3): 32–40. https://doi.org/10.17116/molgen20224003132 https://elibrary.ru/dmfrxl
26. Кукушкина Е.А., Котелева С.И., Бляхер М.С., Федорова И.М., Рамазанова З.К., Зверева Н.Н. и др. Изменение состояния интерфероновой защиты у детей, больных инфекционным мононуклеозом, в динамике заболевания. *Инфекция и иммунитет*. 2021; 11(1): 157–64. https://doi.org/10.15789/2220-7619-TIP-1349 https://elibrary.ru/asboym
27. Ершов Ф.И., Оспельникова Т.П., Наровлянский А.Н. Интерфероновый статус как метод определения неспецифических биомаркеров иммунопатологии человека. *Журнал микробиологии, эпидемиологии и иммунобиологии*. 2019; (3): 91–9. https://doi.org/10.36233/0372-9311-2019-3-91-99 https://elibrary.ru/jmogdb
28. Триско А.А., Колесникова Н.В., Авдеева М.Г., Чудилова Г.А., Ломтатидзе Л.В. Особенности клеточного иммунитета при острой инфекции, вызванной вирусом Эпштейна–Барр. *Эпидемиология и инфекционные болезни*. 2015; 20(4): 13–5. https://elibrary.ru/uhyruv
29. Чуйкова К.И., Попова О.А. Совершенствование терапии инфекционного мононуклеоза у детей. *Детские инфекции*. 2012; 11(4): 48–51. https://elibrary.ru/phgfzl
30. Наговицына Е.Б. Современные подходы к диагностике и лечению инфекционного мононуклеоза Эпштейна–Барр-вирусной этиологии. *Дальневосточный медицинский журнал*. 2016; (3): 45–50. https://elibrary.ru/wmwfkx
31. Соломай Т.В., Семененко Т.А., Тутельян А.В., Боброва М.В. Эпидемиологические особенности инфекции, вызванной вирусом Эпштейна–Барр. *Журнал микробиологии, эпидемиологии и иммунологии*. 2021; 98(6): 685–96. https://doi.org/10.36233/0372-9311-139 https://elibrary.ru/cyuyrd
32. Соломай Т.В., Семененко А.В., Никитина Г.Ю., Шувалов А.Н. Прогнозные сценарии развития эпидемического процесса инфекции, вызванной вирусом Эпштейна–Барр, на этапе отсутствия мер специфической профилактики и при их внедрении. *Эпидемиология и инфекционные болезни. Актуальные вопросы*. 2023; 13(1): 60–9. https://doi.org/10.18565/epidem.2023.13.1.60–9
33. Соломай Т.В., Филатов Н.Н. Сезонность инфекции, вызванной вирусом Эпштейна–Барр. *Журнал инфектологии*. 2020; 12(4): 93–100. https://doi.org/10.22625/2072-6732-2020-12-4-93-100 https://elibrary.ru/dshwxp
34. Соломай Т.В., Филатов Н.Н., Каира А.Н., Лавров В.Ф., Кузин А.А., Ланцов Е.В. Сходство проявлений эпидемических процессов инфекционного мононуклеоза и инфекций верхних дыхательных путей. *Вестник Российской Военно-медицинской академии*. 2020; (3): 46–51. https://elibrary.ru/fwocgg
35. Коротченко С.И. Проблемы иммунопрофилактики лиц, подлежащих призыву на военную службу. *Санитарный врач*. 2016; (12): 8–13. https://elibrary.ru/xrmzgv
36. Готвянская Т.П., Мукашева Е.А., Ноздрачева А.В., Сипачева Н.Б., Семененко А.В., Игнатьева А.В. и др. Заболеваемость и популяционный иммунитет к гриппу и ОРВИ в условиях пандемии COVID-19. *Санитарный врач*. 2023; (3): 153–63. https://doi.org/10.33920/med-08-2303-03
37. Соломай Т.В., Семененко Т.А., Кузин С.Н., Акимкин В.Г. Территориальные особенности эпидемического процесса инфекции, вызванной вирусом Эпштейна–Барр. *Инфекционные болезни: новости, мнения, обучение*. 2021; 10(4): 81–9. https://doi.org/10.33029/2305-3496-2021-10-4-81-89 https://elibrary.ru/zsblzm
38. Соломай Т.В., Семененко Т.А., Исаева Е.И., Ветрова Е.Н., Чернышова А.И., Роменская Э.В. и др. COVID-19 и риск реактивации герпесвирусной инфекции. *Эпидемиология и инфекционные болезни. Актуальные вопросы*. 2021; 11(2): 55–62. https://doi.org/10.18565/epidem.2021.11.2.55-62 https://elibrary.ru/rgixoj
39. Соломай Т.В., Семененко Т.А., Филатов Н.Н., Колбутова К.Б., Олейникова Д.Ю., Каражас Н.В. Роль детей и взрослых как резервуара возбудителей в период сезонного подъема заболеваемости инфекциями верхних дыхательных путей. *Детские инфекции*. 2020; 19(3): 5–11. https://doi.org/10.22627/2072-8107-2020-19-3-5-11 https://elibrary.ru/zchyjf
40. Gralton J., Tovey E., McLaws M.L., Rawlinson W.D. The role of particle size in aerosolised pathogen transmission: a review. *J. Infect*. 2011; 62(1): 1–13. https://doi.org/10.1016/j.jinf.2010.11.010
41. Farisyi M.A., Sufiawati I. Detection of Epstein–Barr virus DNA in saliva of HIV-1-infected individuals with oral hairy leukoplakia. *Oral Dis*. 2020; 26(Suppl. 1): 158–60. https://doi.org/10.1111/odi.13400
42. Koshy E., Mengting L., Kumar H., Jianbo W. Epidemiology, treatment and prevention of zoster: A comprehensive review. *Indian J. Dermatol. Venereol. Leprol*. 2018; 84(3): 251–62. https://doi.org/10.4103/ijdvl.IJDVL_1021_16

43. Suarez F., Lortholary O., Hermine O., Lecuit M. Infection-associated lymphomas derived from marginal zone B cells: a model of antigen-driven. *Blood*. 2006; 107(8): 3034–44. https://doi.org/10.1182/blood-2005-09-3679
44. Синицын М.В., Богородская Е.М., Родина О.В., Кубракова Е.П., Романова Е.Ю., Бугун А.В. Поражение центральной нервной системы у больных туберкулезом в современных эпидемических условиях. *Инфекционные болезни: новости, мнения, обучение.* 2018; 7(1): 111–20. https://doi.org/10.24411/2305-3496-2018-00015 https://elibrary.ru/yshtny
45. Мордык А.В., Ситникова С.В., Пузырева Л.В., Назарова О.И., Фурсевич Л.Н. Оценка проявлений ВИЧ-инфекции и результатов лечения пациентов от туберкулеза в специализированном стационаре. *ВИЧ-инфекция и иммуносупрессии.* 2015; 7(1): 69–75. https://elibrary.ru/tnbset
46. Соломай Т.В., Семененко Т.А., Филатов Н.Н., Ведунова С.Л., Лавров В.Ф., Смирнова Д.И. и др. Реактивация инфекции, вызванной вирусом Эпштейна–Барр (*Herpesviridae: Lymphocryptovirus*, HHV-4), на фоне COVID-19: эпидемиологические особенности. *Вопросы вирусологии.* 2021; 66(2): 152–61. https://doi.org/10.36233/0507-4088-40 https://elibrary.ru/nhbzyr
47. Rooney B.V., Crucian B.E., Pierson D.L., Laudenslager M.L., Mehta S.K. Herpes virus reactivation in astronauts during spaceflight and its application on earth. *Front. Microbiol.* 2019; 10: 16. https://doi.org/10.3389/fmicb.2019.00016
48. Mehta S.K., Bloom D.C., Plante I., Stowe R., Feiveson A.H., Renner A., et al. Reactivation of latent Epstein–Barr virus: a comparison after exposure to gamma, proton, carbon, and iron radiation. *Int. J. Mol. Sci.* 2018; 19(10): 2961. https://doi.org/10.3390/ijms19102961