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Epidemiological characteristics of Epstein–Barr virus infection

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Abstract

Introduction. The Epstein–Barr virus (EBV) is one of the most common pathogens — it infects 90% of the world's population. However, specific characteristics of the EBV infection epidemic process remain unidentified. The previous studies focusing on assessment of incidence rates for infectious mononucleosis (IM) tend to ignore the serological status of the population.

The **aim** of the study was to identify epidemiological characteristics and assess the prevalence of serological markers for EBV infection for further epidemic control measures development.

Materials and methods. In Moscow, the thorough analysis was performed using the data on IM incidence (Form 2 "Data on Infectious and Parasitic Diseases") and test results for 138,232 people checked for presence of VCA IgG, EBNA IgG, VCA IgM, EA IgG, and EBV DNA in their blood and saliva in 2011–2020.

Results. The periodic pattern of IM incidence was discovered, demonstrating the repetitive peaks every 9 to 11 years and a strong direct correlative relationship with detection rates for active EBV infection markers. The intra-annual dynamics of IM incidence is characterized by a seasonal upswing during cold seasons of the year, reaching its peaks in October, November, or February and associated with a marked decrease in the VCA IgG and EBNA IgG seroprevalence. Children within the 1 to 17-year age range are groups at risk for acquiring primary infection, demonstrating significantly lower detection rates for chronic EBV infection (VCA IgG and EBNA IgG) markers and higher rates for VCA IgM and EBV DNA markers in blood compared to adults. The contribution of adult population to the epidemic process is formed through reactivation of chronic infection, which is observed primarily among women.

Conclusion. The identified characteristics are essential for comprehensive understanding of the EBV infection epidemic process and can be used for developing preventive and anti-epidemic measures.

Keywords: *Epstein–Barr virus, infectious mononucleosis, seroprevalence, incidence, epidemiological characteristics*

Ethics approval. The study was conducted with the informed consent of the patients. The research protocol was approved by the Bioethics Committee of the Institute of Federal State Burdgetarry Institution "I. Mechnikov Research Institute of Vaccines and Sera" (Protocol No.1, March 23, 2021).

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Эпидемиологические особенности инфекции, вызванной вирусом Эпштейна–Барр

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Аннотация

Введение. Вирус Эпштейна–Барр (ВЭБ) — один из самых распространённых патогенов — поражённость им населения достигает 90%. В то же время не установлены особенности эпидемического процесса ВЭБ-инфекции. Ранее проведённые исследования посвящены оценке показателей заболеваемости инфекционным мононуклеозом (ИМ) без учёта серологического статуса населения.

Цель работы — выявить эпидемиологические особенности и оценить превалентность серологических маркеров ВЭБ-инфекции для последующей разработки комплекса противоэпидемических мероприятий.

Материалы и методы. В Москве анализу подвергнуты данные заболеваемости ИМ (форма № 2 «Сведения об инфекционных и паразитарных заболеваниях») и результаты обследования 138 232 человек на наличие IgG VCA, IgG EBNA, IgM VCA, IgG EA, ДНК ВЭБ в образцах крови и слюны в 2011–2020 гг.

Результаты. Впервые установлены периодичность заболеваемости ИМ с интервалом 9–11 лет и её сильные прямые значимые корреляционные связи с выявлением маркеров активной ВЭБ-инфекции. Для внутригодовой динамики заболеваемости ИМ характерен сезонный подъём в холодный период года с максимальными показателями в октябре, ноябре или феврале, обусловленный выраженным снижением серопревалентности IgG VCA и IgG EBNA. Группами риска по заболеваемости первичной инфекцией являются дети 1–17 лет, что подтверждается достоверно более низкой, по сравнению со взрослыми, частотой выявления маркеров хронической ВЭБ-инфекции (IgG VCA и IgG EBNA) и высокой — IgM VCA и ДНК ВЭБ в крови. Вклад взрослого населения в эпидемический процесс формируется за счёт реактивации хронической инфекции, преимущественно у женщин.

Заключение. Выявленные особенности позволяют дать развёрнутую характеристику эпидемического процесса ВЭБ-инфекции и могут быть использованы для разработки комплекса профилактических и противоэпидемических мероприятий.

Ключевые слова: *вирус Эпштейна–Барр, инфекционный мононуклеоз, серопревалентность, заболеваемость, эпидемиологические особенности*

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Источник финансирования. Авторы заявляют об отсутствии внешнего финансирования при проведении исследования.

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

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Introduction

Although the infection caused by the Epstein-Barr virus (EBV) has been known for a long time, its epidemiological characteristics are poorly studied. It has been found that people get infected with EBV through the contact with a person having primary acute infection or reactivated chronic infection [1, 2]. The virus is transmitted through the air, through contact with saliva, and saliva-contaminated items [1, 3], vertically from the mother to the fetus [4], through the transplanted organs and tissues [5], through transfused blood and its components that were not put through pathogen reduction and leukocyte filtration [6, 7]. The incubation period is 42 days on average for patients with primary acute EBV infection [8]; chronic infection develops in patients, following primary infection [9]. Thus, EBV stays in a human body for life; the latent phase can be reactivated, and the virus will start replicating [1, 2].

Epidemiologically, primary acute infection and chronic infection reactivation known as active EBV infection are the focus of concern [10]. During the latent phase of the chronic infection, EBV stays as a circular episome within the host cell nucleus [11]. The factors contributing to the switch from latency to reactivation are being currently discussed. There are assumptions that the switch can be triggered by external factors of physical, chemical, and biological nature [12]. Some researchers assume that viral replication is preceded by the decreased immune responsiveness of the host organism, which, in its turn, can also be caused by the impact of adverse external factors [13].

EBV is found all over the world; more than 90% of the adults have chronic infection markers – IgG antibodies to capsid (VCA IgG) and nuclear (EBNA IgG) viral antigens. EBV infection is diagnosed as active when tests detect the viral DNA in blood and/or saliva, IgM to capsid (VCA IgM) and IgG to early (EA IgG) antigens [7]. Infectious mononucleosis (IM) is a clinically symptomatic form of an active EBV infection, though the infection can be subclinical and asymptomatic [14, 15].

IM cases have been statistically documented in Russia since 1990. The incidence rates monitored within the entire period demonstrated a clear upward trend. The rates vary significantly across the country; the explanation can be found in patterns of the epidemic process as well as in the associated diagnostic and reporting errors [16].

Most of the Russian and foreign studies addressing EBV infection, in general, and IM, in particular, have a clinical or immunological focus. There were too few epidemiological studies to identify a clear-cut periodic pattern of peaks and troughs in the incidence [14, 17, 18]. The most plausible reason for this comes from the approach based on estimation of incidence rates without regard for the serological status of the population within the studied region. Consequently, in the context of population heterogeneity, special significance should be attached to estimation of prevalence of virus infection markers using serological monitoring, which is a constituent part of the information system in epidemiological surveillance of the incidence [19]. The performed studies have shown that preschool and school children constitute the main groups of risk in terms of IM incidence [14, 18, 20, 21]. The contribution of adult population to the EBV infection epidemic process is poorly studied; no gender-related assessment has been conducted. All the above highlight the importance and open the door for focused research in specific characteristics of the EBV infection epidemic process.

The **aim** of the study was to identify epidemiological characteristics and assess the prevalence of serological markers for EBV infection for further epidemic control measures.

Materials and methods

The city for this study was selected by ranking regions of Russia by multiannual average IM incidence rates, with Moscow being assigned to areas reporting average rates within the $M \pm \sigma$ interval [16]. The wide range of healthcare facilities and laboratories performing diagnostic tests for detection of EBV infection markers was an additional factor supporting the decision to perform the study in the capital (metropolitan city).

For the analysis during this study, we used IM statistics data for Moscow and Russia for the 2000–2019 period (Form 2 "Data on Infectious and Parasitic Diseases") and summarized data for test results for presence of chronic latent EBV infection markers (VCA IgG and EBNA IgG) and active EBV infection markers (VCA IgM, EA IgG, EBV DNA in blood and saliva) in Moscow residents during 2011-2020; the data were provided by INVITRO Independent Laboratory, LLC. A total of 134,462 biological samples from men and women from different age groups were examined for VCA IgG within the 2011-2020 period; 138,232 samples were examined for EBNA IgG; 161,285 samples and 82,556 samples were tested for VCA IgM and EA IgG, respectively. Tests for presence of EBV DNA in blood and saliva were introduced to practice only in 2014. During 2014-2020, a total of 39,683 blood samples and 13,702 saliva samples were examined for presence of EBV DNA. The samples re-collected from the same people were not included in the study.

The incidence statistics data and laboratory test results were assessed using retrospective epidemiological analysis followed by statistical analysis. IM incidence rates were calculated as cases per 100,000 population; the detection rate for EBV infection markers was calculated per 100 examined people (%). Multiannual average rates were estimated, including their 95% confidence intervals (CI). Any differences were considered significant at any evidence against the true null hypoth-

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esis (p) of less than 5%, i.e. at $p < 0.05$. The upper limit for the baseline value for intra-annual incidence was calculated using the method [22].

To identify the relationship between the detection rates for EBV infection markers and IM incidence rates, we used Spearman's rank correlation coefficient (r). The relationship was considered strong at r equal to ± 0.7 or higher. The negative value of the coefficient was indicative of inverse correlation, while its positive value meant that there was a direct correlation.

Results

During 2000-2020, the IM incidence among the Moscow population was insignificantly higher than the incidence in Russia (**Fig. 1**); multiannual average rates were 19.5 (95% CI 11.1–27.9) and 13.8 (95% CI 7.7–19.9) per 100,000 population, respectively; any differences were not statistically significant. The 2015-2018 period was an exception, as the total Russian incidence was slightly higher than the incidence in the capital.

The comparison of multiannual dynamics trends showed that the IM incidence in Russia during 2000-2019 was increasing steadily. At the same time, Moscow demonstrated the repetitive occurrence of incidence peaks and troughs every 9 to 11 years. The highest rates were recorded in 2010 and 2019 (24.11 and 24.73 per 100,000 population, respectively); the lowest rates were reported in 2004 and 2015 (15.3 and 18.0 per 100,000, respectively). The sharp drop in IM incidence in 2020 compared to 2019, both in Moscow and Russia, can be explained by an actual decrease in the number of cases as well as by lower detection rates for this infection during the COVID-19 pandemic.

The intra-annual dynamics of IM incidence in Moscow during 2014-2020 was characterized by a seasonal upswing during the cold period of the year, from October to April. The highest average rates during this time span were reported in October, November, and February (1.86; 1.89 and 1.82 per 100,000 population, respectively; **Fig. 2**). Note that the seasonal incidence peak was not observed in any other months of the year. In 2014 and 2020, the highest rates were recorded in February (2.05 and 2.23 per 100,000 population, respectively), in 2015 and 2019 – in November (1.79 and 2.73), in 2016–2018 – in October (2.07; 1.99; 2.23). The lowest incidence rates in October and November were recorded in 2020 (0.93 and 1.41 per 100,000 population, respectively); the highest rates were reported in 2019 (2.31 and 2.73). In February, the lowest rates were recorded in 2017 (1.36); the highest rates were recorded in 2020 (2.23).

During all years, the highest IM incidence rates were recorded among the child population in age groups of 1–2, 3–6, 7–14, and 15–17-year-olds. Individuals aged 18 years and older as well as infants under 1 year were involved in the epidemic process to a lesser extent.

The comparison between the period with the higher IM incidence rates (2009–2013) and the period characterized by the lower rates (2014–2018) revealed statistically significant differences in multiannual average rates for all age groups ($p < 0.05$) except for people aged 18 years and older ($p > 0.05$). The multiannual average incidence rates for total population during 2009–2013 and 2014–2018 did not demonstrate any statistically significant differences ($p > 0.05$; **Fig. 3**).

At the same time, changes were observed in the age structure of patients. Compared to 2009–2013, the years showing lower incidence rates (2014–2018) demonstrated a statistically significant decrease in the

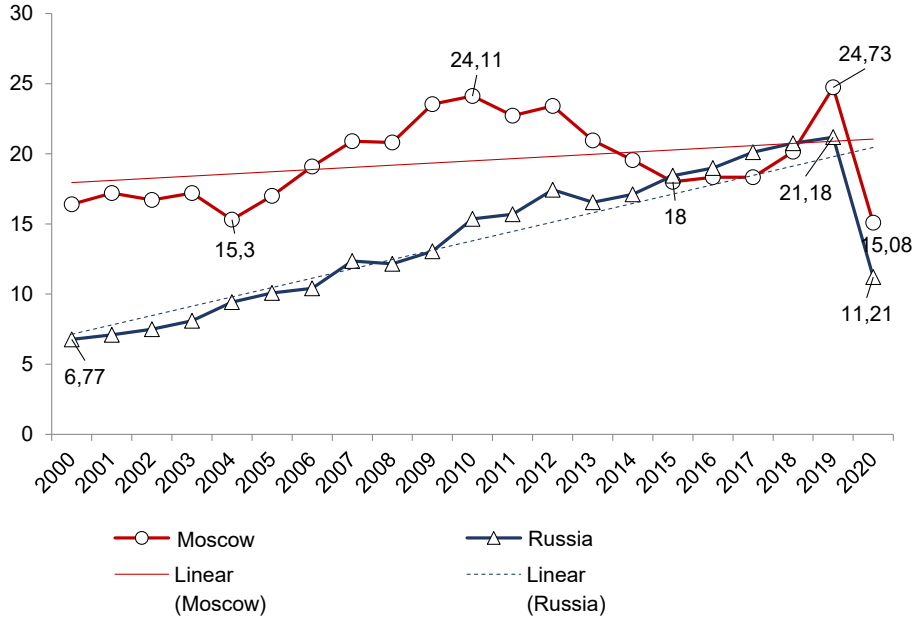

Fig. 1. IM incidence among the population in Moscow and Russia during 2000-2020 (per 100,000 population).

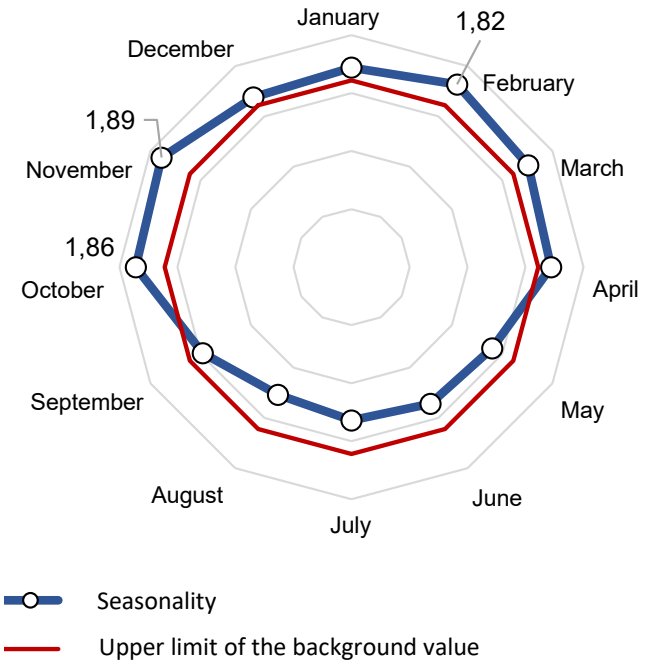

Fig. 2. Intra-annual dynamics of IM incidence in Moscow: multiannual average rates during 2014–2020 (per 100,000 population).

proportion of cases aged 1–2 years - from 12.4 (95% CI 11.9–12.95) to 11.0% (95% CI 10.5–11.6) and those aged 15–17 years – from 14.4 (95% CI 13.8–15.0) to 12.4 (95% CI 11.8–13.0) and a statistically significant increase in the proportion of cases among people aged 18 years and older – from 28.6% (95% CI 27.8–29.4) to 31.1% (95% CI 30.3–31.9).

The analysis of test results for the presence of chronic latent EBV infection markers revealed high prevalence of VCA IgG and EBNA IgG among Moscow residents. During the studied period, among the total population, the VCA IgG seroprevalence was significantly ($p < 0.05$) higher than that of EBNA IgG – 74.9% (95% CI 74.7–75.1) and 70.4% (95% CI 70.2–70.7), respectively. The highest rate among the total population for VCA IgG was recorded in 2019 – 76.1% (95% CI 75.5–76. 8), the lowest rate was recorded in 2013 (73.6%; 95% CI 72.9–74.3; $p < 0.05$). For EBNA IgG, it was 72.1% (95% CI 71.2–72.9) in 2011 and 69.0 (95% CI 68.2-69.7; $p < 0.05$) in 2013. When the multiannual IM incidence dynamics and changes in the seroprevalence rates during 2011–2020 were compared, Spearman's rank correlation coefficient (r) was 0.35 for VCA IgG and 0.3 for EBNA IgG. In both cases, the correlation was estimated as weak, direct and insignificant.

The intra-annual dynamics analysis for 2014–2020 showed that the highest VCA IgG seroprevalence rates were recorded from June to September; the highest rate was reached in September – 78.4% (95% CI 77.6–79.3). During the same months, the highest rates were also recorded for EBNA IgG (the highest rate of 73.1% in August (95% CI 72.1–74.0)). The lowest rates were recorded in November – 71.9% (95% CI 71.1–72.7) and 67.7% (95% CI 66.9–68.5), respectively (**Fig. 4**). The differences between the highest and the lowest rates for each marker were statistically significant.

The month-to-month comparison between the intra-annual IM incidence dynamics and the changes in the VCA IgG and EBNA IgG seroprevalence rates during 2014-2020 demonstrated a significant, strong inverse correlation: Spearman's rank correlation coefficient (r) was –0.8 and –0.77, respectively. The seasonal upswing in the incidence was accompanied by a sharp decrease in the seroprevalence for both markers.

The seroprevalence rates in the age group of 0–17-year-olds (VCA IgG 54.9% and EBNA IgG 48,8%) were significantly lower than among 18-39-year-olds (VCA IgG 95.0% and EBNA IgG 92.6%), 40–59-year-olds (VCA IgG 96.8% and EBNA IgG 93.2%), 60-year-olds and older people (VCA IgG 97.0% and EBNA IgG

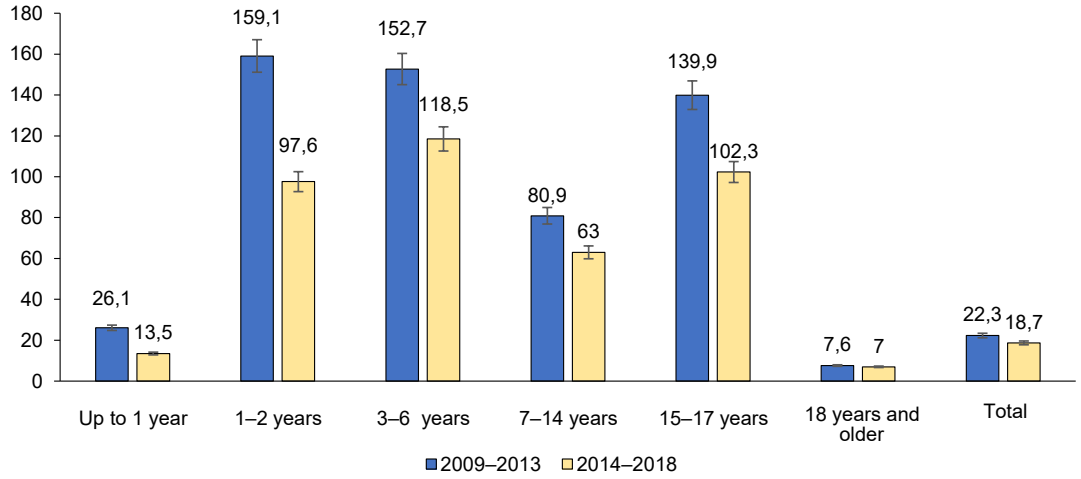

Fig. 3. Multiannual average rates of IM incidence during 2009–2013 and 2014–2018 in Moscow per 100,000 population.

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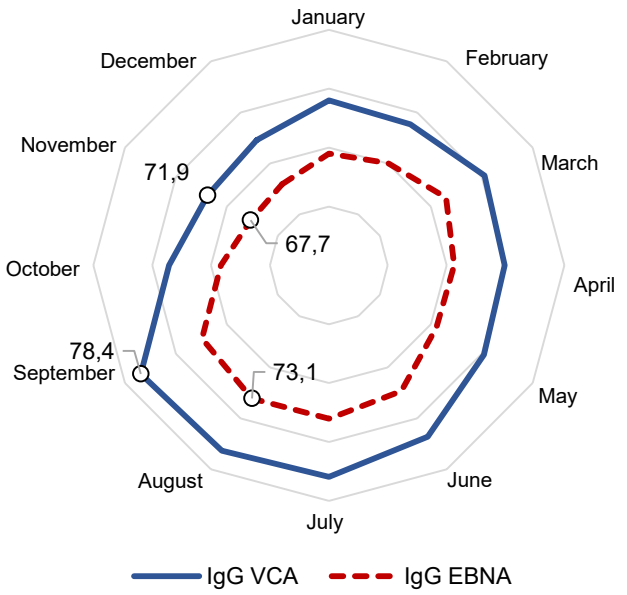

Рис. 4. Внутригодовая динамика серопревалентности IgG VCA и IgG EBNA в Москве в 2014–2020 гг. (%).

Fig. 4. Intra-annual dynamics of VCA IgG and EBNA IgG seroprevalence in Moscow during 2014–2020 (%).

92.0%); $p < 0.05$. Note that the VCA IgG seroprevalence tended to increase with the age of the examined, reaching its highest rates in the age group of 60-year-olds and older. At the same time, the similar EBNA IgG seroprevalence rate was the highest in the age group of 40–59-year-olds, while demonstrating a significant decrease among people of the older age (**Table 1**).

The VCA IgG and EBNA IgG seroprevalence was significantly higher in the group of women than among men ($p < 0.05$; Table 1). The statistical differences between rates recorded for women and men for each marker were found in the group of 0–17-year-olds, while the gender-related differences in VCA IgG rates were also significant in the age group of 18–39-year-olds ($p < 0.05$).

The analysis of detection rate markers of active EBV infection among residents of Moscow showed that during 2011–2020, VCA IgM antibodies were detected in 16.5% of the examined (95% CI 16.3–16.7), EA IgG – in 17.8% (95% CI 17.5–18.1), being significantly higher ($p < 0.05$) than the similar rates for VCA IgM. In the meantime, the total number of people tested for EA IgG (82,556 people) was twice as small as the number of people tested for VCA IgM (161,285 people).

The viral DNA in blood was detected significantly ($p < 0.05$) more rarely than other markers of active EBV infection – 4.2% (95% CI 4.0–4.4). The viral genetic material was detected significantly ($p < 0.05$) more frequently in saliva (35.5%; 95% CI 34.7–36.3) than in blood and significantly more frequently than serological markers of active EBV infection.

The year-to-year dynamics analysis showed that the changes in the detection rate for VCA IgM per 100 examined people and the changes in the IM incidence rates (2011–2020) were not synchronous ($r = 0.32$ – weak direct insignificant correlation). At the same time, the IM incidence rates and the detection rates for EA IgG during 2011–2020 and for EBV DNA in blood and saliva during 2014–2020 demonstrated a significant, strong direct correlation ($r = 0.85$; 0.73 and 0.89, respectively).

The inverse strong, significant correlation was found between the month-to-month changes in the IM incidence rates and the detection rates for VCA IgM, EA IgG and EBV DNA in saliva per 100 examined people ($r = –0.74$; $r = –0.84$ and $r = –0.83$, respectively). The direct moderate, insignificant correlation was revealed by the comparison between the incidence rates and the detection rates for EBV DNA in blood ($r = 0.6$).

In total, the detection rates for VCA IgM, EBV DNA in blood and saliva per 100 examined people

Table 1. Overall VCA IgG and EBNA IgG seroprevalence rates among men and women from different age groups residing in Moscow during 2014–2020, % (95% CI)

Age, years	Marker	Men	Women	Total contingent
0–17	IgG VCA	53,4% (52,9–54,0)	56,2% (55,6–56,7)	54,9% (54,5–55,3)
	IgG EBNA	47,3% (46,8–47,9)	51,3% (50,7–51,8)	48,8% (48,5–49,2)
18–39	IgG VCA	93,7% (93,3–94,2)	95,7% (95,4–95,9)	95,0% (94,8–95,2)
	IgG EBNA	91,6% (90,1–93,1)	93,0% (92,7–93,3)	92,6% (92,3–92,9)
40–59	IgG VCA	96,6% (96,1–97,0)	96,9% (96,6–97,2)	96,8% (96,5–97,1)
	IgG EBNA	94,0% (93,4–94,6)	92,7% (92,2–93,1)	93,2% (92,9–93,5)
≥60	IgG VCA	96,4% (95,4–97,4)	97,3% (96,7–97,9)	97,0% (96,5–97,5)
	IgG EBNA	92,6% (91,2–94,0)	91,7% (90,7–92,7)	92,0% (91,2–92,8)
Total	IgG VCA	68,7% (67, 5–69,9)	79,9% (79,6–80,2)	74,9% (74,7–75,1)
	IgG EBNA	63,9% (63,5–64,3)	75,6% (75,3–75,9)	70,4% (70,2–70,7)

were significantly lower in the group of women than in the group of men (**Table. 2**). Conversely, EA IgG were detected significantly more frequently among women generally and separately in each age group ($p < 0.05$).

Interestingly, the detection rates for VCA IgM among the total examined population tended to decrease with the age of the examined. The opposite trend was demonstrated by the detection rates for EA IgG: the lowest rates were recorded in the age group of 0–17-year-olds; the highest rates were recorded for 60-year-olds and older people (the differences between the rates were statistically significant in all age groups; $p < 0.05$). EBV DNA in blood was detected significantly more frequently among children aged 0–17 years compared to the other age groups ($p < 0.05$), which, in their turn, did not demonstrate significant differences ($p > 0.05$). Conversely, the detection rates for EBV DNA in saliva were the lowest in the age group of 0–17-year-olds ($p < 0.05$).

Discussion

The study revealed multiannual and intra-annual cyclicity of IM incidence in Moscow.

The earlier studies of multiannual changes in the above incidence in Moscow during 2000–2016 [17], in the Perm Territory during 2006–2015 [18], and in Saratov during 1996–2009 [14] did not reveal any cyclical patterns, which can be explained by IM diagnostic recording errors [23, 24] as well as by the time span selected for the analysis. In our study, we found that the interval between two peaks (troughs) in IM incidence was quite long, lasting for 9–11 years, and, as such, was not identifiable during few years of monitoring. It should be noted that the occurrence of multiannual incidence cycles (long and short) was identified for a number of infections [25], including those of herpesviral etiology [26]. For example, in the Republic of Belarus, chickenpox is characterized by repetitive incidence peaks with an interval of 32 years for longer cycles, and 3 to 9 years for shorter cycles [27]. Further monitoring of the IM incidence dynamics in Moscow may help identify not only short (from 9 to 11 years) cycles, but also longer ones.

IM seasonal patterns have received limited scientific attention. Increased incidence rates during autumn-winter-spring months were studied in Nizhny

Table 2. Detection rates for markers of active EBV infection among men and women from different age groups residing in Moscow during 2011–2020, per 100 examined people (95% CI)

Age, years	Marker	Men	Women	Total contingent
0–17	IgM VCA	21,0 (20,7–21,3)	24,6 (24,2–25,0)	22,6 (22,3–22,9)
	IgG EA	15,3 (14,9–15,7)	17,0 (16,5–17,5)	16,1 (15,8–16,4)
	EBV DNA in the blood	6,6 (6,0–7,2)	7,5 (6,8–8,2)	7,0 (6,5–7,5)
	EBV DNA in saliva	31,4 (29,9–32,9)	30,4 (28,8–32,0)	30,9 (29,8–32,0)
18–39	IgM VCA	11,3 (10,8–11,8)	10,7 (10,4–11,0)	10,8 (10,5–11,1)
	IgG EA	16,8 (16,0–17,6)	19,3 (18,7–19,9)	18,5 (18,0–19,0)
	EBV DNA in the blood	2,0 (1,4–2,6)	1,0 (0,7–1,3)	1,4 (1,1–1,7)
	EBV DNA in saliva	44,7 (42,1–47,3)	36,2 (34,4–38,0)	39,1 (37,6–40,6)
40–59	IgM VCA	5,0 (4,5–5,5)	6,5 (6,1–5,9)	6,0 (5,7–6,3)
	IgG EA	16,7 (15,5–17,9)	23,9 (22,8–25,0)	21,2 (20,4–22,0)
	EBV DNA in the blood	1,4 (0,7–2,1)	0,7 (0,4–1,0)	1,0 (0,7–1,3)
	EBV DNA in saliva	48,9 (45,2–52,6)	36,5 (33,9–39,1)	40,8 (38,7–42,9)
≥60	IgM VCA	5,6 (4,4–6,8)	4,2 (3,5–4,9)	4,7 (4,1–5,3)
	IgG EA	22,5 (19,6–25,4)	28,9 (26,8–31,0)	26,8 (25,0–28,6)
	EBV DNA in the blood	1,5 (0,2–2,8)	2,1 (0,9–3,3)	1,9 (1,0–2,8)
	EBV DNA in saliva	50,0 (42,3–57,7)	43,5 (38,6–48,4)	45,4 (41,2–49,6)
Total	IgM VCA	17,1 (16,8–17,4)	16,1 (15,9–16,3)	16,5 (16,3–16,7)
	IgG EA	15,9 (15,5–16,3)	19,3 (19,0–19,6)	17,8 (17,5–18,1)
	EBV DNA in the blood	4,8 (4,4–5,2)	3,8 (3,5–4,1)	4,2 (4,0–4,4)
	EBV DNA in saliva	37,2 (36,0–38,4)	34,2 (33,1–35,3)	35,5 (34,7–36,3)

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Novgorod and St. Petersburg [28, 29]; spring seasonal patterns were reported in Norway and Italy [30]. Russian researchers have found the inverse correlation between the intra-annual changes in the incidence and the changes in the outside air temperature [28]. The seasonal upswing in IM incidence in Moscow during the cold period of the year had been described by the authors of this study for the period of 2014-2018 [23, 24]. This study covers a larger time span (2014–2020); the obtained results re-confirm the marked increase in the IM incidence from October to April, with the highest rates recorded in November.

The typical IM incidence risk groups described by other authors [14, 18, 20, 21] were also identified during this study. For example, in age groups of 1–2, 3–6, 7–14, and 15–17-year-olds, the incidence was significantly higher than among people over 18 years and infants under 1 year. Furthermore, it was the incidence among the child population that had a critical effect on the overall peaks and troughs in the incidence, while the multiannual average incidence rates among the adult population, which were relatively high (2009–2013) and low (2014–2018), did not demonstrate significant differences. This can be explained by the fact that people over 18 years are tested positive not for primary acute EBV infection, but for reactivation of chronic infections [31], which does not follow the general patterns of epidemic prevalence and requires separate recording and tracking.

This study is distinct in its parallel analysis of IM incidence rates among the Moscow population and the test results from a significant sample proportion of the Moscow population tested for presence of EBV infection markers within a specific period of time.

Thus, for the first time in many years, using the sample of more than 100,000 people, we assessed the prevalence of EBV infection markers among the total population of Moscow, the year-to-year and month-to-month changes in the detection rates and their relationship with IM incidence rates, the higher occurrence frequency of reactivated EBV infection among women, and the age-related specifics of detection of active EBV infection markers. Previously, seroprevalence had been estimated for the limited groups of people who, as a rule, had concomitant diseases, and the studied groups included not more than 200 people in total [21, 32, 33]. There had been assumptions about higher prevalence of EBV infection among women, though, due to small-size samples of the examined population, no significant differences had been found [34, 35]. During this study, we found that women had higher VCA IgG and EBNA IgG detection rates; they also demonstrated significantly higher detection rates for EA IgG, which is, primarily, a reactivation marker.

The results indicating the age-related change in detection rates for markers of active EBV infection and the fact of underestimating the role of EA IgG in the diagnosis of EBV infection, especially among the adult population, are of practical significance. At significantly higher detection rates for EA IgG ($p < 0.05$), the tests for presence of this marker were conducted twice as rarely as the tests for VCA IgM, which is, first of all, a marker of acute primary infection and is quite rarely detected during reactivation [36]. In our study, it is confirmed by the absence of direct correlation between the multiannual IM incidence rates and the VCA IgM detection rates as well as by the existing strong direct correlation between the above incidence rates and the detection rates for IgG EA. The strong inverse correlation between the intra-annual IM incidence rates and the EA IgG detection rates is explained by the fact that this marker is produced a month after the previous active EBV infection and remains in blood for 3 to 4 months. Since EBV infection, due to the diversity of clinical symptoms, may be difficult to diagnose, especially in adult patients [37], EA IgG is an indispensable marker, and tests for its presence are critical for identification of the etiology of the pathological process. Therefore, to improve the quality of diagnostics of EBV infection and the accurateness of the diagnosis, it is important to provide additional training to healthcare workers and include subject-related courses in continuous medical education [38].

Conclusions

The comprehensive approach used for studying of EBV infection in Moscow helped identify the following epidemiological patterns:

- prevalence of chronic EBV infection markers among the Moscow population is 74.9% for VCA IgG and 70.4% for EBNA IgG ($p < 0.05$);
- multiannual dynamics of IM incidence is characterized by the periodic occurrence every 9 to 11 years and has strong direct significant correlations with the detection rates for markers of active EBV infection (EA IgG – $r = 0.85$, EBV DNA in blood – $r = 0.73$, and EBV DNA in saliva – $r = 0.89$);
- intra-annual dynamics of IM incidence is characterized by a seasonal upswing during the cold period of the year, with the highest rates in October, November or February, and a marked decrease in the VCA IgG and EBNA IgG seroprevalence (significant, strong inverse correlation: $r = –0.8$ and $r = –0.77$, respectively);
- the risk groups for IM (primary infection) incidence include children aged 1–17 years, which can be seen from significantly lower, compared to adults, detection rates for markers of chronic EBV infection (VCA IgG and EBNA IgG) and higher rates for VCA IgM and EBV DNA in blood;
- the contribution of adult population to the epidemic process is formed through reactivation of

chronic EBV infection, demonstrating a significant decrease in the detection rates for markers of acute primary infection (IgM VCA and EBV DNA in blood) along with a significant increase in the detection rates for IgG EA, EBV DNA in saliva as well as for IgG VCA and IgG EBNA with aging of the examined;

- women are infected with EBV at the earlier age and have reactivation of chronic infection more frequently than men, as demonstrated by significantly higher detection rates for VCA IgG and EBNA IgG in the group of 0–17-year-olds and IgG EA in all age groups ($p < 0.05$);
- EA IgG, being a marker of active EBV infection, indicates, first of all, the existence of reactivation, as it is significantly more often detected among the adult population; when used in laboratory practice, it will be a powerful tool for improving etiological explanation of pathological conditions associated with EBV infection.

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