DOI 10.1007/s10517-022-05492-5

Peculiarities of Humoral Immunity Formation in Medical Institution Employees Recovered from or Vaccinated against COVID-19 in Irkutsk

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Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny*, Vol. 173, No. 1, pp. 66-70, January, 2022
Original article submitted November 26, 2021

We performed a seroepidemiological survey of the level and structure of population immunity to SARS-CoV-2 among employees of medical institution in the Irkutsk region during the COVID-19 pandemic. Seroprevalence assessment was organized from May 2020 to April 2021. The level of antibodies to SARS-CoV-2 was measured by ELISA. It was found that 139 (46%) of 299 examined workers were seropositive, including 50 (36%) vaccinated against COVID-19, 75 (54%) patients diagnosed with COVID-19, and 14 (10%) asymptomatic cases of SARS-CoV-2. The results obtained should be taken into account when predicting the dynamics of the epidemic process and organizing preventive (antiepidemic) measures, including vaccination.

Key Words: *humoral immunity; specific antibodies; COVID-19; SARS-CoV-2; seroprevalence*

The new COVID-19 infection has become not only the global health problem, but also the most serious challenge for the global community in the 21st century. Within 3 months since the first detection in China (Wuhan) in December 2019, the new coronavirus has rapidly spread around the world, and on March 11, 2020, the WHO declared COVID-19 a pandemic [1,7]. According to official data, as of April 2021, more than 136.6 million cases of COVID-19 infection and more than 2.9 million deaths were registered in the world [3,5]. In the Russian Federation, cases of COVID-19 have been registered since January 31, 2020. More than 4.6 million cases of SARS-CoV-2 infection have been laboratory confirmed in the Russian Federation in all regions of the country and more than 101,000 deaths from this disease have been registered at the moment of writing this article (April 2021) [3,5].

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The emergence and spread of COVID-19 have set the priority tasks for healthcare professionals to quickly diagnose and organize qualified medical care for patients, which can only be solved with a clear understanding of the features of the immunogenesis of a new coronavirus infection, in particular, the relationship between the severity of the disease and the kinetics of the antibody response. For example, a number of articles support the finding that people with more severe COVID-19 who needed care in intensive care units seroconverted earlier than those with milder disease [9,10]. A significant role in the pathogenesis of COVID-19 is played by the characteristics of the patient's immune system. It is known that an insufficiently rapid response of innate immunity to the introduction of the SARS-CoV-2 virus leads to its long-term persistence, which determines the abnormally long duration of the infectious process and the risk of dangerous mutations [2,4,8,12].

An important role in the fight against COVID-19 is assigned to the study of population immunity to SARS-CoV-2, in particular the dynamics of seropre-

valence and the formation of post-infection humoral immunity. This knowledge is necessary for developing programs and interpreting the results of seroepidemiological studies, scientific forecasting of the development of an epidemic situation, evaluating the effectiveness of vaccination, and planning the preventive and anti-epidemic measures [6,11].

Our aim was to study the dynamics of the formation of specific antibodies to the SARS-CoV-2 virus and the duration of their persistence in recovered and vaccinated subjects, healthcare institution workers in the Irkutsk region.

MATERIALS AND METHODS

The detection of specific antibodies to the SARS-Cov-2 virus was carried out in dynamics, during the epidemic outbreak in the Irkutsk region from May 2, 2020 to April 5, 2021, every 25-30 days in a healthcare institution in Irkutsk. In total, the study involved 299 volunteers (117 men and 182 women) aged 20-39 years (n=129), 40-59 years (n=104), and ⩾60 years (n=66). All surveyed subjects were divided into the following groups: patients with laboratory-confirmed COVID-19 (n=82) and asymptomatic course of the disease (n=14), vaccinated workers (n=60) with negative tests for SARS-CoV-2 virus RNA (PCR) and specific antibodies to the virus (ELISA) at the time of vaccination, and "conditionally healthy" subjects (n=143). The study followed the ethical principles of the Declaration of Helsinki of the World Medical Association. The study was approved by the Local Ethics Committee of the Irkutsk Antiplague Research Institute (Protocol No. 7, November 15, 2021).

Specific IgG were determined by ELISA using a commercial kit for the analysis of human serum or plasma for the presence of IgG antibodies to the nucleocapsid (N-protein SARS-CoV-2; State Research Center for Applied Microbiology and Biotechnology, Federal Service for Surveillance on Consumer Rights Protection and Human Wellbeing) and to surface S-glycoprotein of the virus (SARS-CoV-2-Ig G-ELISA-BEST; Vector-Best). In additionally, IgG antibodies to the receptor-binding domain of the surface glycoprotein S (spike) of the coronavirus were detected using SARS-CoV-2-RBD-ELISA-Gamaleya kits in the serum of volunteers vaccinated with Gam-COVID-Vac and IgG antibodies to coronavirus proteins were detected using SARS-CoV-2-IgG-Vector kits (State Research Center of Virology and Biotechnology VECTOR) in subjects vaccinated against COVID-19 with EpiVacCorona vaccine.

The measurements were performed on a Stat Fax 4200 semi-automatic analyzer of enzyme-linked immunosorbent reactions (Awareness Technology) by absorption at λ=450 nm; the results were considered positive at positivity index (PI)⩾1 (calculated according to instructions of kits manufacturers).

The study employed epidemiological (descriptive and analytical) and statistical methods. Statistical processing was performed using the methods of variation statistics (Microsoft Excel). The differences were significant at p<0.05.

RESULTS

In the surveyed group, 82 (27%) workers had COVID-19 until April 5, 2021, of them 68 (23%) subjects had manifest disease in the form of an acute respiratory infection or community-acquired pneumonia and 14 (5%) cases were asymptomatic. The first 4 cases of the disease, unrelated to each other, were registered in May, the maximum number of cases fell on October, and then, the number of cases decreased to single cases in February, which coincided with the dynamics of the epidemics in Irkutsk (Fig. 1).

Despite the fact that men had COVID-19 more often (29%) than women (27%), this difference was insignificant (p>0.05). The disease was significantly (p<0.01) more often diagnosed in groups ⩾60 years (39%) and 40-59 years (36%) than in the group 20-39 years (15%).

Of 299 examined workers, 139 (46%) were seropositive: 75 (54%) had verified COVID-19, 14 (10%) were asymptomatic, and 50 (36%) were vaccinated against COVID-19 (Fig. 2). A gradual increase in seroprevalence was revealed in the dynamics of the epidemic process: 1% (n=4) in June 2020, 2% (n=7) in September 2020, 13% (n=38) in January 2021, and 47% (n=139) in April 2021.

Among all participants with verified COVID-19 (n=82), 91% (n=75) were seropositive, which was

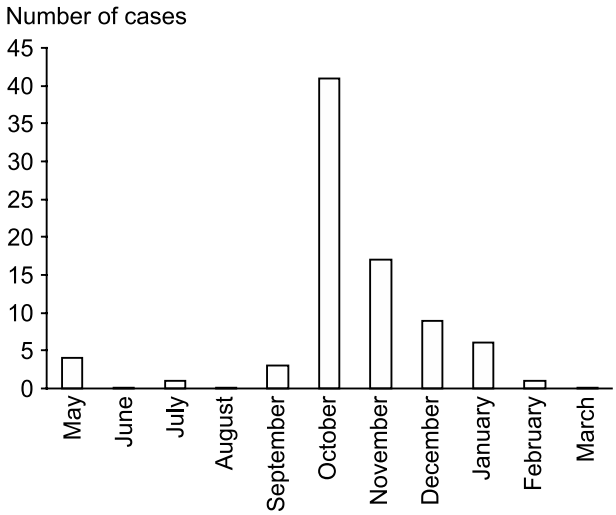

Fig. 1. Verified cases of COVID-19 from May 2, 2020 to April 5, 2021 among medical institution employees.

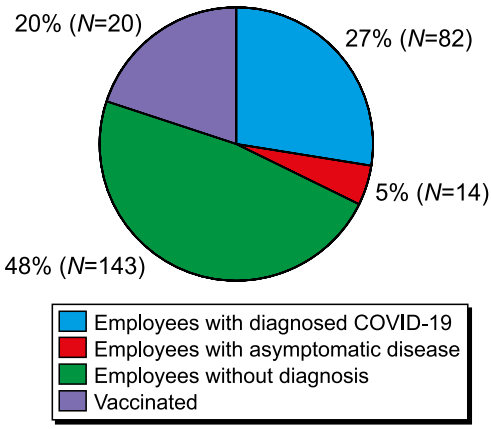

Fig. 2. Characteristics of the surveyed group of the medical institution employees.

significantly higher ($p<0.001$) than among workers with undetermined laboratory diagnosis.

Seroprevalence did not differ in men and women (91 and 92%, respectively). The age structure of seroprevalence was heterogeneous and varied from 89% (age group 20-39 years) to 96% (in the group ⩾60 years) (Table 1).

When assessing the time of the appearance of specific antibodies to the SARS-CoV-2 virus, we found that IgG were detected starting from the 6th day from the moment of diagnosis (Fig. 3). During the period from day 25 to 175 from the disease onset, the proportion of seropositive subjects was 70% (n=57). In some cases, the surveyed showed a decrease of the production of specific IgG to the SARS-CoV-2 nucleocapsid starting from day 150 after the diagnosis.

The number of volunteers diagnosed with COVID-19 who have specific IgG to the SARS-CoV-2 nucleocapsid during the observation period was 75 (92%), while 16 previously seropositive persons have registered the decline of PI below the reference value (PI<1.0) by April 2021. At the same time, IgG to the SARS-CoV-2 virus glycoprotein was detected in all seropositive volunteers at all follow-up periods. It was also noted that 7 subjects diagnosed with COVID-19 had no antibodies to SARS-CoV-2 nucleocapsid or glycoprotein.

IgM production in recovered workers was detected at the early stage (days 5-6) and persisted up to day 45 after diagnosis.

Analysis of personal data showed that 60 (20%) individuals of all surveyed were vaccinated against COVID-19 with Gam-COVID-Vac vaccine (n=11; 18%) or EpiVacCorona (n=49; 82%). The ratio of men and women among the vaccinated was 27 (45%) and 33 (55%), respectively.

A reaction to vaccination was noted in 24 (40%) individuals, including pain at the injection site (n=17; 71%), fever (n=4; 17%), weakness, symptoms of acute respiratory disease, and acute allergic reaction (n=1 for each complain; 4%).

The seroprevalence in age groups varied from 56% (⩾60 years) to 100% (20-39 years) (Table 1).

Among vaccinated workers, 50 (83%) individuals were seropositive, of these 11 (22%) workers were vaccinated with Gam-COVID-Vac vaccine and 39 (78%) workers were vaccinated with EpiVacCorona.

The research results showed that seroconversion among medical institution employees after vaccination with EpiVacCorona was recorded in 34 (69%) people, starting from days 42-44 after primary immunization (in case of Gam-COVID-Vac vaccine starting from day 45). It is important to note that specific IgG antibodies to the proteins of the SARS-CoV-2 coronavirus, and to the nucleocapsid and glycoprotein of the SARS-CoV-2 virus were not detected in 10 (20%) volunteers vaccinated with EpiVacCorona. At the same

TABLE 1. SARS-CoV-2 Seroprevalence in Medical Institution Employees Diagnosed with COVID-19 and Vaccinated against COVID-19

Age group	Number of participants		Seroprevalence index	
	abs.	%	abs.	%
Employees with diagnosed COVID-19				
20-39 years	19	23	17	89
40-59 years	37	45	33	89
≥60 years	26	32	25	96
Total	82	100	75	91.5
Employees vaccinated against COVID-19				
20-39 years	20	33	20	100
40-59 years	24	40	21	87
≥60 years	16	27	9	56

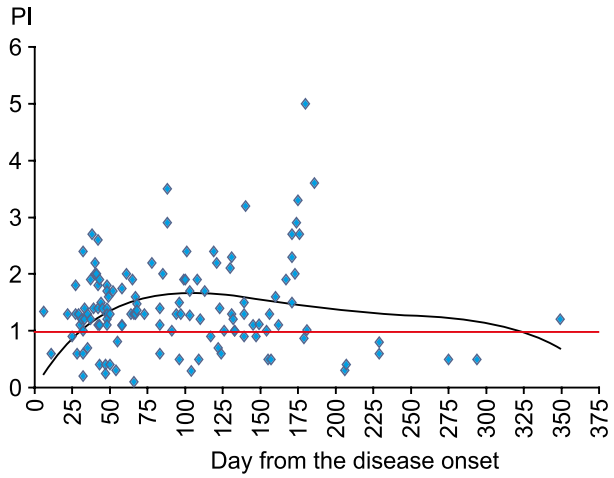

Fig. 3. Dynamics of detection of IgG antibodies in employees of a medical institution who had COVID-19. Dots correspond to individual serum samples, black curve is a polynomial curve of the mean values of the analyzed parameters, red line corresponds to PI=1.0.

time, all vaccinated with Gam-COVID-Vac had specific antibodies to the receptor-binding domain of the surface glycoprotein S of the SARS-CoV-2 coronavirus.

Thus, the epidemiological patterns of the spread of COVID-19 in a single group were characterized by an undulating course and a low intensity of the outbreak, with 27% of the group being involved in the epidemic process from May 2020 to March 2021. It is important to note that none of the study participants had repeated cases of the disease during the entire observation period despite the continuing unfavorable situation with COVID-19 in the Irkutsk region. And there were no cases of an unfavorable outcome of the disease. The level of herd immunity among volunteers of the institution during the development of the epidemic was characterized by an upward trend and at the time of the research (May 4, 2021) it was 46.5% (139/299). The current results of serological monitoring serve as a scientific basis for adjusting the list and scope of anti-epidemic (preventive) measures in a single team, in particular, for planning vaccination against COVID-19.

The authors of this article report no conflicts of interest.

The planning of the experiment, the analysis of the results, and the writing of the article were carried out by V. I. Dubrovina; setting reactions, accounting and analysis of the results, writing and design of the article — D. D. Bryukhova; setting reactions, accounting and analysis of the results — N. O. Kiseleva; analysis of the results, writing the article — M. V. Chesnokova; setting reactions, accounting and analysis of the results, design of the article — K. M. Korytov; setting reactions, accounting and analysis of the results — A. B. Pyatidesyatnikova; analysis of the results, design of the article — V. A. Vishnyakov; planning a scientific topic, designing the article — S. V. Balakhonov.

REFERENCES

1. Briko NI, Kagramanyan IN, Nikiforov VV, Suranova TG, Chernyavskaya OP, Polezhaeva NA. Pandemic COVID-19. Prevention measures in the russian federation. Epidemiol. Vaktsinoprof. 2020;19(2):4-12. doi: 10.31631/2073-3046-2020-l9-2-4-12. Russian.
2. Kostinov MP. Immunopathogenic properties of SARS-CoV-2 as a basis for the choice of pathogenetic therapy. Immunopatol. 2020;41(1):83-91. doi: 10.33029/0206-4952-2020-41-1-83-91. Russian.
3. Online data. Стопкоронавирус.рф — Official Internet-source for provision of information to the public concerning COVID-19. [URL: https://xn--80aesfpebagmfblc0a.xn--p1ai/information/].
4. Platonova TA, Golubkova AA, Karbovnichaya EA, Smirnova SS. Features of the formation of humoral immunity in individuals with various clinical manifestations of COVID-19. Epidemiol. Vaktsinoprof. 2021;20(1):20-25. doi: 10.31631/2073-3046-2021-20-1-20-25. Russian.
5. Comprehensive Coronavirus Statistics. CORONAVIRUS (COVID-19): Online Coronavirus Distribution Map.[URL: https://coronavirus-monitor.info/].
6. Popova AYu, Ezhlova EB, Mel'nikova AA, Balakhonov SV, Chesnokova MV, Dubrovina VI, Lyalina LV, Smirnov VS, Trukhina AG, Perezhogin AN, Pyatidesyatnikova AB, Bryukhova DD, Kiseleva NO, Gefan NG, Gavrilova OV, Gavrilova TA, Lomonosova VI, Totolyan AA. Experience in studying seroprevalence to SARS-CoV-2 virus in the population of the Irkutsk region during COVID-19 outbreak. Probl. Osobo Opasn. Infekt. 2020;(3):106-113. doi: 10.21055/0370-1069-2020-3-106-113. Russian.
7. Shchelkanov MYu, Kolobukhina LV, Burgasova OA, Kruzhkova IS, Maleev VV. COVID-19: etiology, clinical picture, treatment. Infekts. Immunitet. 2020;10(3):421-445. doi: 10.15789/2220-7619-CEC-1473. Russian.
8. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, Qiu Y, Wang J, Liu Y, Wei Y, Xia J, Yu T, Zhang X, Zhang L. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet. 2020;395:507-513. doi: 10.1016/S0140-6736(20)30211-7
9. Isho B, Abe KT, Zuo M, Jamal AJ, Rathod B, Wang JH, Li Z, Chao G, Rojas OL, Bang YM, Pu A, Christie-Holmes N, Gervais C, Ceccarelli D, Samavarchi-Tehrani P, Guvenc F, Budylowski P, Li A, Paterson A, Yue FY, Marin LM, Caldwell L, Wrana JL, Colwill K, Sicheri F, Mubareka S, Gray-Owen SD, Drews SJ, Siqueira WL, Barrios-Rodiles M, Ostrowski M, Rini JM, Durocher Y, McGeer AJ, Gommerman JL, Gingras AC. Persistence of serum and saliva antibody responses to SARS-CoV-2 spike antigens in COVID-19 patients. Sci. Immunol. 2020;5(52):eabe5511. doi: 10.1126/sciimmunol.abe5511
10. Iyer AS, Jones FK, Nodoushani A, Kelly M, Becker M, Slater D, Mills R, Teng E, Kamruzzaman M, Garcia-Beltran WF, Astudillo M, Yang D, Miller TE, Oliver E, Fischinger S, Atyeo C, Iafrate AJ, Calderwood SB, Lauer SA,

Yu J, Li Z, Feldman J, Hauser BM, Caradonna TM, Branda JA, Turbett SE, LaRocque RC, Mellon G, Barouch DH, Schmidt AG, Azman AS, Alter G, Ryan ET, Harris JB, Charles RC. Persistence and decay of human antibody responses to the receptor binding domain of SARS-CoV-2 spike protein in COVID-19 patients. Sci. Immunol. 2020;5(52):eabe0367. doi: 10.1126/sciimmunol.abe0367

11. Johansson MA, Quandelacy TM, Kada S, Prasad PV, Steele M, Brooks JT, Slayton RB, Biggerstaff M, Butler JC. SARS-CoV-2 Transmission From People Without COVID-19 Symptoms. JAMA Netw. Open. 2021;4(1):e2035057. doi: 10.1001/jamanetworkopen.2020.35057
12. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, Wang B, Xiang H, Cheng Z, Xiong Y, Zhao Y, Li Y, Wang X, Peng Z. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. JAMA. 2020;323(11):1061-1069. doi: 10.1001/jama.2020.1585