ЗАКОНОМЕРНОСТИ В РАЗВИТИИ КОЛЛЕКТИВНОГО ИММУНИТЕТА К SARS-CoV-2 В ХОДЕ ПАНДЕМИИ COVID-19

Попова А.Ю.[1], Смирнов В.С.[2], Егорова С.А.[2], Дрозд И.В.[2], Миличкина А.М.[2], Дашкевич А.М.[3], Нурматов З.Ш.[4], Мелик-Андреасян Г.Г.[5], Рузиев М.М.[6], Тотолян Арег А.[2, 7]

[1] Федеральная служба по надзору в сфере защиты прав потребителей и благополучия человека, Москва, Россия
[2] ФБУН «Санкт-Петербургский научно-исследовательский институт эпидемиологии и микробиологии имени Пастера», Санкт-Петербург, Россия
[3] Республиканский центр гигиены, эпидемиологии и общественного здоровья, г. Минск, Республика Беларусь
[4] Национальный институт общественного здоровья Министерства здравоохранения Кыргызской Республики, г. Бишкек, Кыргызская Республика
[5] Национальный центр по контролю и профилактике заболеваний Министерства здравоохранения Республики Армения, г. Ереван, Республика Армения
[6] ГУ «Таджикский научно-исследовательский институт профилактической медицины» Министерства здравоохранения и социальной защиты населения Республики Таджикистан, г. Душанбе, Республика Таджикистан
[7] ФГБОУ ВО «Первый Санкт-Петербургский государственный медицинский университет имени академика И.П. Павлова» Министерства здравоохранения РФ, Санкт-Петербург, Россия

Резюме. Продолжающаяся на протяжении последних 3 лет пандемия коронавирусной болезни (COVID-19) вызвала пристальное внимание к проблеме популяционного иммунитета, под которым понимается «устойчивость к распространению инфекционного заболевания в популяции». Коллективный иммунитет формируется как в результате заболевания (при естественном распространении возбудителя в популяции восприимчивых индивидуумов), так и в результате применения специфических вакцин. В ходе пандемии COVID-19 реализовались оба варианта формирования популяционного иммунитета. В первую волну происходило естественное формирование невосприимчивости населения к вирусу после перенесенного заболевания COVID-19, обусловленного пандемическим распространением SARS-CoV-2. Начиная с декабря 2020 года в США, Великобритании, Китае, России и ряде других стран началось широкое применение специфических вакцин против SARS-CoV-2. Это запустило процесс формирования поствакцинального популяционного иммунитета, специфичность которого зависит от вида используемой вакцины. В настоящее время в тех странах, где широко проводится вакцинация и ревакцинации переболевших популяционный иммунитет является гибридным.

Адрес для переписки:

Попова Анна Юрьевна
Федеральная служба по надзору в сфере защиты прав потребителей и благополучия человека
127994, Россия, Москва, Вадковский пер., 18, стр. 5 и 7.
Тел.: 8 (499) 973-26-90.
E-mail: depart@gsen.ru

Address for correspondence:

Anna Yu. Popova
Federal Service for Supervision of Consumer Rights Protection and Human Welfare
18 Vadkovsky Lane, Bldg 5 and 7
Moscow
127994 Russian Federation
Phone: +7 (499) 973-26-90.
E-mail: depart@gsen.ru

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Принимая во внимание относительно сходный волнообразный характер эпидемического процесса COVID-19, обусловленный сменой геновариантов возбудителя во всех странах, а также развернутой программой массовой вакцинации населения, можно сделать некоторые выводы об общей для всех стран тенденции формирования популяционного иммунитета в ходе пандемии.

В начале пандемии, в 2020 году, серопревалентность населения в целом не превышала 20%, при этом наибольшие показатели серопревалентности отмечали в детской возрастной группе; выявлялись выраженные территориальные различия, наибольшие показатели отмечали в группе медицинских работников. Популяционный иммунитет развивался вследствие перенесенного заболевания и у большинства серопозитивных волонтеров был представлен антителами к обоим антигенам.

В разгар пандемии, летом 2021 года, серопревалентность населения достигла 50%. Это было обусловлено как значительным числом переболевших лиц, так и началом компании массовой вакцинации населения. Во всех странах практически нивелировались специфические различия в серопревалентности населения (территориальные, возрастные и профессиональные). В этот период наиболее явно можно отметить формирование гибридного иммунитета – увеличилась доля лиц, имеющих антитела только к RBD (вследствие вакцинации векторными вакцинами).

Позднее массовая вакцинация, а также вовлечение большей части населения в эпидемический процесс из-за появления высоко контагиозного штамма «Омикрон», подняли уровень популяционного иммунитета до 80-90%. Это привело к резкому снижению заболеваемости COVID-19 во второй половине 2022 года во всех странах, участвующих в исследовании. На поздних сроках пандемии (2022-2023 годы) практически у 90% серопозитивных волонтеров гуморальный иммунитет являлся гибридным и был представлен антителами к обоим антигенам (Nc+RBD).

Ключевые слова: коллективный иммунитет, популяционный иммунитет, COVID-19, пандемия, вакцинальный иммунитет, эпидемиология

PATTERNS IN THE DEVELOPMENT OF COLLECTIVE IMMUNITY TO SARS-CoV-2 DURING THE COVID-19 PANDEMIC

Popova A.Yu.[a], Smirnov V.S.[b], Egorova S.A.[b], Drozd I.V.[b], Milichkina A.M.[b], Dashkevich A.M.[c], Nurmatov Z.S.[d], Melik-Andreasyan G.G.[e], Ruziev M.M.[f], Totolian Areg A.[b, g]

[a] *Federal Service for Supervision of Consumer Rights Protection and Human Welfare, Moscow, Russian Federation*
[b] *Saint Petersburg Pasteur Institute, St. Petersburg, Russian Federation*
[c] *Republican Center for Hygiene, Epidemiology and Public Health, Minsk, Republic of Belarus*
[d] *National Institute of Public Health, Bishkek, Kyrgyz Republic*
[e] *National Center for Disease Control and Prevention, Yerevan, Republic of Armenia*
[f] *Tajik Research Institute of Preventive Medicine, Dushanbe, Republic of Tajikistan*
[g] *First St. Petersburg State I. Pavlov Medical University, St. Petersburg, Russian Federation*

Abstract. The ongoing coronavirus disease (COVID-19) pandemic over the past three years has caused close attention to the problem of herd immunity, which is understood as: "resistance to the spread of a contagious disease within a population or herd". Collective immunity is formed both as a result of infection (natural spread of the pathogen in a population of susceptible individuals) and as a result of the use of specific vaccines. During the COVID-19 pandemic, both mechanisms for the formation of collective immunity were realized. In the first wave, there was a natural formation of collective immunity to the virus following recoveries from COVID-19 caused by pandemic spread of SARS-CoV-2. Starting from December 2020, the widespread use of specific vaccines against SARS-CoV-2 began in the USA, Great Britain, China, Russia, and a number of other countries. This launched the process of post-vaccination collective immunity formation; its features have depended on the vaccine types implemented. Currently, in those countries where vaccination and re-vaccination of recovered patients is widely carried out, immunity is "hybrid" in nature.

Several commonalities should be noted in the pandemic experience: a somewhat regular, periodic (wave-like) nature of the COVID-19 epidemic process; changes in pathogen genetics in variants in all countries; and expansive mass vaccination programs in many populations. From these, we can draw some conclusions about the general trend for all countries in the formation of collective immunity during the pandemic:

At the beginning of the pandemic in 2020, overall population seroprevalence did not exceed 20%. Other findings were: the highest seroprevalence rates were noted in the children's age group; pronounced regional

differences were revealed; and the highest indicators were noted among medical workers. Collective immunity developed as a result of infection or illness, and in the majority of seropositive volunteers, it was represented by antibodies to both antigens.

At the height of the pandemic in the summer of 2021, population seroprevalence reached 50%. This was due to both a significant number of convalescents and the start of mass vaccination campaigns. In all countries, specific differences in seroprevalence (by age, region, profession) leveled out, leading to more uniformity. During this period, the formation of "hybrid" immunity is clearly prominent, and the proportion of individuals with antibodies to RBD alone increased (due to vaccination with vector vaccines).

Later, mass vaccination, as well as involvement of most of the population in the epidemic process due to the emergence of the highly contagious Omicron strain, raised the level of collective immunity to 80-90%. This led to a sharp decrease in COVID-19 incidence in the second half of 2022 in all countries participating in the study. In the later stages of the pandemic (2022-2023), almost 90% of seropositive volunteers had hybrid immunity, reflected as antibodies to both antigens (Nc, RBD).

Keywords: collective immunity, herd immunity, COVID-19, pandemic,vaccine-induced immunity, public health

Introduction

The ongoing coronavirus disease (COVID-19) pandemic over the past three years has caused close attention to the problem of herd immunity, which is understood as: "resistance to the spread of a contagious disease within a population or herd" [16]. Collective immunity is formed both as a result of infection (natural spread of the pathogen in a population of susceptible individuals) and as a result of the use of specific vaccines. During the COVID-19 pandemic, both mechanisms for the formation of collective immunity were realized. In the first wave, there was a natural formation of collective immunity to the virus following recoveries from COVID-19 caused by pandemic spread of SARS-CoV-2. Starting from December 2020, the widespread use of specific vaccines against SARS-CoV-2 began in the USA, Great Britain, China, Russia, and a number of other countries. This launched the process of post-vaccination collective immunity formation; its features have depended on the vaccine types implemented. Currently, in those countries where vaccination and re-vaccination of recovered patients is widely carried out, immunity is "hybrid" in nature [2]. In the recent time period with epidemic increases in case numbers alongside a lack of effective specific COVID-19 treatments, collective immunity has served as the only tool for controlling and managing the epidemic.

Materials and methods

At the beginning of the local epidemic in May 2020, Rospotrebnadzor developed a multi-stage program for seromonitoring of the population's immunity to SARS-CoV-2. It was implemented in 2020-2021 in Russia [5, 7, 14]. Since 2021-2023, neighboring countries have participated in a partnership program (Armenia, Belarus, Kyrgyzstan, Tajikistan) [6, 10, 11, 12]. The program has included the formation of volunteer cohorts, the volume and structure of which has made it possible to obtain representative data for the populations in the study region (countries) by age and professional group. Volunteers included in the cohort were divided into seven age groups (years old): 1-17, 18-29, 30-39, 40-49, 50-59, 60-69, and ≥ 70.

Due to their high representation during infectious and post-vaccination processes, two SARS-CoV-2 antigens are especially relevant to analytical methods: nucleocapsid (Nc) and S protein receptor-binding domain (RBD). Depending on vaccine design, antibodies to one, or both, antigens are formed. The presence of serum antibodies as a result of a previous infection makes it possible to use seromonitoring to detect not only clinical, but also subclinical cases of infection that would otherwise go unnoticed.

Levels of IgG antibodies (anti-Nc, anti-RBD) in volunteers were quantified by enzyme immunoassay using Russian assay systems: "Reagent set for enzyme immunoassay quantitative determination of human IgG Abs to SARS-CoV-2 N protein (N-Cov-2-IgG PS)" (Saint Petersburg Pasteur Institute) and "SARS-CoV-2-ELISA-IgG-screen" (LabPack). All studies were carried out according to a single algorithm, which included the use of cloud service (internet) technology to form a cohort of volunteers, collect test results, and assist analysis [8].

In Russia, the study by Rospotrebnadzor involved eight research institutes and twenty regional departments (centers of hygiene and epidemiology, etc.). It involved volunteers from 26 regions (located in all of the country's federal districts), whose population accounted for 54.7% of the total national population. Along with megacities featuring high populations and density (such as Moscow and St. Petersburg), regions with populations below 800,000 (Murmansk and Amur regions, the Republic of Crimea) and low population density (Krasnoyarsk region 1.21 km^{-2}) also took part. The total number of volunteers was 74,158 people and was representative of the total Russian population. The study was conducted in 2020-2021 in 5 stages, with an interval of 3-9 months (Figure 1) [5, 7, 14]. In Armenia, Belarus, Kyrgyzstan and Tajikistan, 32,128 volunteers were examined for population dynamics in 2021-2023; from 2 to 4 stages were carried out in each country (Figure 2).

The multi-stage studies, wherein the levels of Abs to various SARS-CoV-2 antigens were assessed at

26 regions of Russian Federation **238 646 volunteers are examined**

	I step: 06-09.2020	II step: 09-10.2020	III step: 12.2020	IV step: 03.2021	V step: 08-09.2021
Number of volunteers	74 244	50 055	43 326	37 158	33 863
Seroprevalence to SARS-CoV-2	4.3 – 50.2%	5.1 – 51.6%	21.2 – 74.8%	25.0 – 87.1%	25.2-72.6%

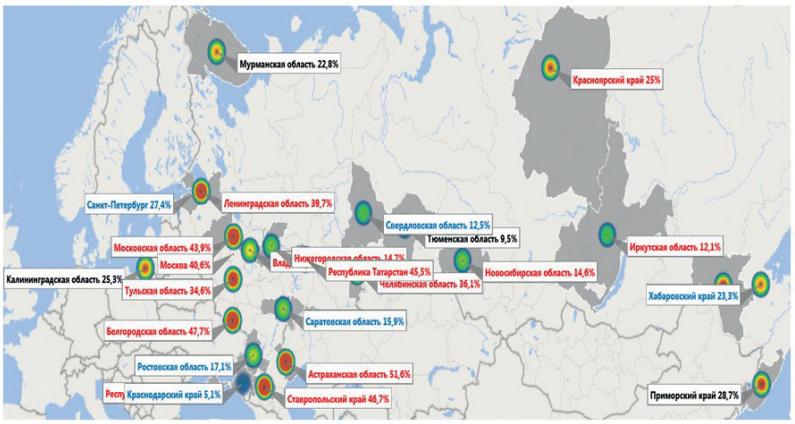

Figure 1. Russian regions included in the study of SARS-CoV-2 collective immunity, 2020-2021. The seroprevalence values presented on the map correspond to the first stage of the study

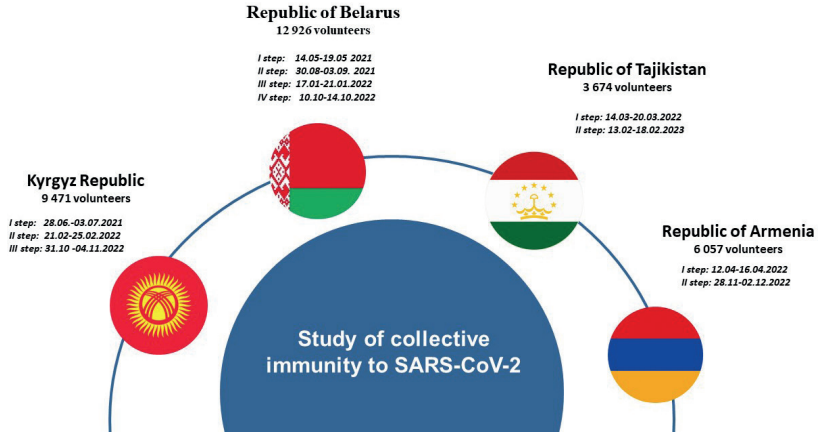

Figure 2. Neighboring countries included in the study of SARS-CoV-2 collective immunity, 2021-2023

different periods of the pandemic, made it possible to identify some patterns in the formation of collective immunity to coronavirus infection, common to populations of all countries included in the study.

Results and discussion

At the beginning of the pandemic in 2020 (stages 1-2 of the study in Russia), seroprevalence in the population varied significantly by region of the country. Average SARS-CoV-2 seroprevalence in the summer of 2020 was 18.0% (95% CI: 10.0-23.9), while the range of variation across regions exceeded 10-fold. The highest seropositivity levels were found in the Kaliningrad (50.2%; 95% CI: 48.4-52.0%) and Amur regions (45.4%; 95% CI: 43.6-47.2). The lowest were seen in the Republic of Crimea (4.3%; 95% CI: 3.6-5.1) and the Krasnodar region (8.0%; 95% CI: 7.1-9.0). No correlations were found between seroprevalence and local morbidity; nor between seroprevalence and local population density.

For the first half of 2020, overall seroprevalence in Russia could be considered low, which posed a certain threat of a further increase in incidence. This is exactly what has been happening everywhere since mid-October 2020 [https://coronavirus-monitor.ru]. Subsequently (2020-2021), following increased COVID-19 incidence, seroprevalence in the Russian population steadily increased, exceeding 70% in December 2021. At the same time, fluctuations in indicators across Russian regions gradually leveled off [5, 7, 14].

At the beginning of the pandemic (summer-autumn 2020), there were age differences in seroprevalence almost throughout Russia. Despite the fact that the number of children with COVID-19 was small, the seroprevalence of SARS-CoV-2 Abs in children was higher than the average value for the entire cohort or the value in adults [9]. One of the most likely reasons for this phenomenon could be a high frequency of asymptomatic or mildly-symptomatic infections in the children's age group. Such infections may have

proceeded under the guise of a common cold without serious clinical manifestations, yet accompanied by serological changes.

Thus, in the process of seromonitoring conducted in 2020-2021, among seropositive children, the proportion of individuals with asymptomatic infection exceeded 90% [9]. In addition, age-related reduced ACE-2 receptor density, and cross-immunity to closely related seasonal coronaviruses, may have markedly reduced susceptibility to SARS-CoV-2 [1, 3]. It has also been hypothesized that in children, mesenchymal stem cells may be a factor in limiting the virus in the body [13]. Such cells can suppress the pathological activation of immune responses (manifested in severe cases as a "cytokine storm") and also promote the regeneration of affected tissues. Mild and asymptomatic forms of infection led to the fact that children were less likely to come to the attention of a doctor, yet remaining a source of pathogen transmission. By March 2021, age-specific seroprevalence differences in the Russian population had completely evened out.

In a later period of pandemic development (spring 2021 – spring 2023), countries adjacent to Russia joined the study: the Republic of Belarus, the Kyrgyz Republic, the Republic of Tajikistan and the Republic of Armenia. By the time the studies began in these countries, significant portions of the population had already experienced infection in a manifest or asymptomatic form. Therefore, like Russia during this period, some statistically significant differences (by age, profession, region) in population seroprevalence were no longer identified in these countries. This is likely the result of the preceding epidemic phases (rising, intense) as well as the vaccination campaign initiated mid-2021 [6, 10, 11, 12].

In general, in those countries where the study began in 2020-2021 (Russian Federation, Republic of Belarus, Kyrgyz Republic), there was a steady upward trend in the level of collective immunity (percentage seropositive individuals) during the pandemic. In countries that joined the study at the height of the pandemic in 2022 (Republic of Tajikistan, Republic of Armenia), already in the first stage of the study, population seroprevalence was almost absolute (approaching 100%), both due to high incidence and high vaccination coverage (more than 70% of the population). This situation continued in 2023 (Figure 3, see 2nd page of cover).

Vaccines proposed for vaccination against SARS-CoV-2 can be divided into two main groups according to their antigenic composition and, accordingly, antibody types elicited. The first group induce the production of antibodies to RBD alone: vector vaccines (AstraZeneca, Sputnik V, Sputnik Light); and mRNA vaccines (Moderna, Pfizer). The second group includes vaccines that generate a response to both Nc and RBD antigens (whole-virion preparations Sinopharm/BIBP, CoronaVac, CoviVac). In Russia and Belarus, the Sputnik vector vaccines (Sputnik V, Sputnik Light) were most widely used. Until recently, they have accounted for up to 80% of vaccinations. To a much lesser extent, the EpiVacCorona peptide vaccine and the CoviVac whole-virion vaccine have been used [15]. In Russia, total vaccination coverage of the population by April 19, 2023 reached 61.4%. In Belarus, coverage had reached almost 70% by May 2022. In Kyrgyzstan, more than 30% of the population had been vaccinated by the end of 2022, with more than 70% of volunteers receiving the Sinopharm/BIBP whole-virion vaccine. In Armenia and Tajikistan, all volunteers who participated in the study were vaccinated by the beginning of 2023. In Armenia, vector and whole-virion vaccines were used equally. In Tajikistan, up to 70% were vaccinated with vector vaccines.

By design, specific vaccines induce the production of antibodies to various SARS-CoV-2 antigens in various ways. With this in mind, it is possible to draw certain conclusions about the nature and structure of collective immunity. At the beginning of the pandemic (summer/autumn of 2020 in the absence of specific prophylaxis), the structure of collective immunity was represented approximately evenly by individuals with: antibodies to Nc alone; or antibodies to both antigens (Nc, RBD) as a result of a previous SARS-CoV-2 infection (Figure 4).

With the start of vaccination of the population in 2021, and in the context of a slight decrease in COVID-19 incidence, there was a shift in the structure of seropositivity towards an increase in the proportion of people who had anti-RBD antibodies only. Given the specificity of vector vaccines (mainly used in Russia and Belarus), the presence of antibodies to RBD antigen alone, to a large extent although not exclusively, indicated post-vaccination immunity. It is obvious that, at that time, it was possible to say with a high degree of certainty that: collective immunity was hybrid in nature; and in half of the seropositive volunteers, it was due to vaccination (Figure 4).

Vaccination against coronavirus (both primary and booster) launched in the first half of 2021 and actively carried out in all countries, as well as genetic changes in the pathogen (such as the highly contagious Omicron variant), undoubtedly became the main reasons for rising collective immunity, reaching 80-90%. In 2022 and 2023, more than 80% of seropositive volunteers had humoral immunity with antibodies to both antigens (Nc, RBD). Obviously, in the late stages of a pandemic, under conditions of high incidence of a highly transmissible strain and high vaccination coverage, collective immunity is going to be "hybrid". Considering the variety of vaccines obtained from various platforms (vector, mRNA, whole-virion), as well as vaccination schedules including booster re-vaccination, it is currently difficult to quantify the exact contribution of vaccination to 'hybrid' immunity, although its valuable contribution is undisputed [6, 10, 11, 12].

The current pandemic has shown that a characteristic feature of COVID-19 is a large number of asymptomatic forms. The manifestations of this

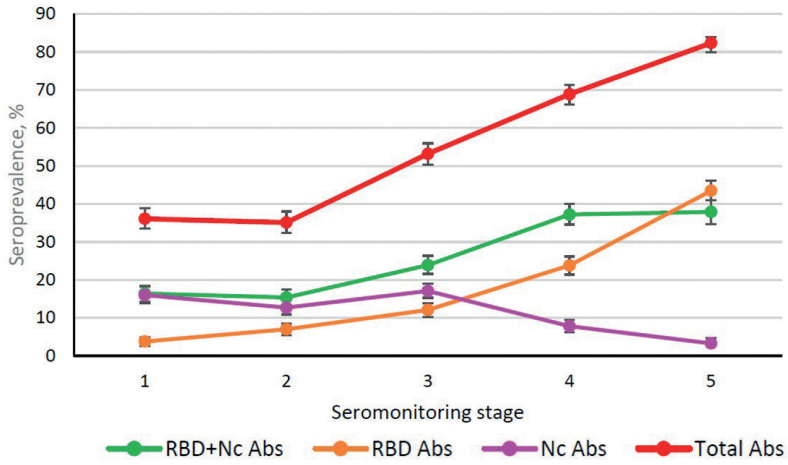

Figure 4. Seroprevalence dynamics from August 2020 (point 1) to September 2021 (point 5) [14]

Note. The status of antibodies to various SARS-CoV-2 antigens and their combinations are shown: "RBD+Nc Abs", double-positive volunteers with both Abs; "RBD Abs", those with only RBD Abs; "Nc Abs", those with only Nc Abs; "Total Abs", total number of seropositive volunteers (RBD+Nc, RBD, Nc) relative to all examined; vertical black lines, 95% CI.

phenomenon can be various, and the very definition of "asymptomatic" needs to be clarified. One possible form may be termed "carrier", in which only viral RNA is detected in blood by PCR in the absence of any other symptoms. In this regard, it can be expected that the host organism will respond to the circulation of viral RNA with an immune response in one form or another. The results obtained fully confirmed this assumption. The study included asymptomatic volunteers who did not have any experienced symptoms of overt COVID-19 in their anamnesis. According to available data, the share of asymptomatic forms of infection, both in the early period and during development of the pandemic, reached very high levels: in Russia (2020) 93.5%; in Belarus (2021) up to 50%; in Kyrgyzstan (2021) up to 70%; in Armenia (2022) 75.0%; and in Tajikistan (2022) above 90%. Moreover, the highest rates of asymptomatic cases in all countries were noted among children [5, 6, 7, 10, 11, 12, 14].

Conclusion

Several commonalities should be noted in the pandemic experience: a somewhat regular, periodic (wave-like) nature of the COVID-19 epidemic process; changes in pathogen genetics in variants in all countries; and expansive mass vaccination programs in many populations. From these, we can draw some conclusions about the general trend for all countries in the formation of collective immunity during the pandemic:

1. At the beginning of the pandemic in 2020, overall population seroprevalence did not exceed 20%. Other findings were: the highest seroprevalence rates were noted in the children's age group; pronounced regional differences were revealed; and the highest indicators were noted among medical workers. Collective immunity developed as a result of infection or illness, and in the majority of seropositive volunteers, it was represented by antibodies to both antigens.

2. At the height of the pandemic in the summer of 2021, population seroprevalence reached 50%. This was due to both a significant number of convalescents and the start of mass vaccination campaigns. In all countries, specific differences in seroprevalence (by age, region, profession) leveled out, leading to more uniformity. During this period, the formation of 'hybrid' immunity is clearly prominent, and the proportion of individuals with antibodies to RBD alone increased (due to vaccination with vector vaccines).

3. Later, mass vaccination, as well as involvement of most of the population in the epidemic process due to the emergence of the highly contagious Omicron strain, raised the level of collective immunity to 80-90%. This led to a sharp decrease in COVID-19 incidence in the second half of 2022 in all countries participating in the study. In the later stages of the pandemic (2022-2023), almost 90% of seropositive volunteers had hybrid immunity, reflected as antibodies to both antigens (Nc, RBD).

In summarizing the presented data, we can agree with existing opinions about the leading role of collective immunity in the course and outcome of the coronavirus epidemic. The combination of "post-infectious immunity", the natural immune response to pathogen contact, and 'artificial immunity', formed as a result of vaccine usage, together form a hybrid immunity that can serve as a major factor in ending the global COVID-19 pandemic.

The data obtained in our study are consistent with other authors [4] and indicate that achieving a 70% level of collective immunity may be sufficient to prevent severe COVID-19 and stop the transmission of SARS-CoV-2 strains with low or moderate transmissibility. However, in order to stop the spread of Omicron strains, or other new highly transmissible SARS-CoV-2 variants, the level of collective immunity must reach 90%. In addition, any vaccines used must be as effective as possible in preventing infection with highly transmissible strains.

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Авторы:

Попова А.Ю. *— д.м.н., профессор, руководитель Федеральной службы по надзору в сфере защиты прав потребителей и благополучия человека, Москва, Россия*

Смирнов В.С. *— д.м.н., профессор, ведущий научный сотрудник лаборатории молекулярной иммунологии ФБУН «Санкт-Петербургский НИИ эпидемиологии и микробиологии имени Пастера», Санкт-Петербург, Россия*

Егорова С.А. *— д.м.н., заместитель директора по инновационной работе, ФБУН «Санкт-Петербургский НИИ эпидемиологии и микробиологии имени Пастера», Санкт-Петербург, Россия*

Дрозд И.В. *— к.б.н., заведующая Центральной клинико-диагностической лабораторией ФБУН «Санкт-Петербургский НИИ эпидемиологии и микробиологии имени Пастера», Санкт-Петербург, Россия*

Миличкина А.М. *— к.м.н., главный врач медицинского центра ФБУН «Санкт-Петербургский НИИ эпидемиологии и микробиологии имени Пастера», Санкт-Петербург, Россия*

Дашкевич А.М. *— заместитель главного врача по эпидемиологии Республиканского центра гигиены, эпидемиологии и общественного здоровья, г. Минск, Республика Беларусь*

Нурматов З.Ш. *— д.м.н., руководитель Республиканского научно-практического центра по контролю вирусных инфекций Национального института общественного здоровья Министерства здравоохранения Кыргызской Республики, г. Бишкек, Кыргызская Республика*

Мелик-Андреасян Г.Г. *— д.м.н., профессор, заместитель директора по научной работе филиала «Референс Лабораторный Центр» Национального центра по контролю и профилактике заболеваний Министерства здравоохранения Республики Армения, г. Ереван, Республика Армения*

Рузиев М.М. *— д.м.н., директор ГУ «Таджикский научно-исследовательский институт профилактической медицины» Министерства здравоохранения и социальной защиты населения Республики Таджикистан, г. Душанбе, Республика Таджикистан*

Тотолян Арег А. *— д.м.н., профессор, академик РАН, заведующий лабораторией молекулярной иммунологии, директор ФБУН «Санкт-Петербургский НИИ эпидемиологии и микробиологии имени Пастера»; заведующий кафедрой иммунологии ФГБОУ ВО «Первый Санкт-Петербургский государственный медицинский университет имени академика И.П. Павлова» Министерства здравоохранения РФ, Санкт-Петербург, Россия*

Authors:

Popova A.Yu., *PhD, MD (Medicine), Professor, Head, Federal Service for Supervision of Consumer Rights Protection and Human Welfare, Moscow, Russian Federation*

Smirnov V.S., *PhD, MD (Medicine), Professor. Leading Research Associate, Laboratory of Molecular Immunology, Saint Petersburg Pasteur Institute, St. Petersburg, Russian Federation*

Egorova S.A., *PhD, MD (Medicine), Deputy Director for Innovation, Saint Petersburg Pasteur Institute, St. Petersburg, Russian Federation*

Drozd I.V., *PhD (Biology), Head, Central Clinical Diagnostic Laboratory, Saint Petersburg Pasteur Institute, St. Petersburg, Russian Federation*

Milichkina A.M., *PhD (Medicine), Head Physician, Medical Center, Saint Petersburg Pasteur Institute, St. Petersburg, Russian Federation*

Dashkevich A.M., *Deputy Chief Physician for Epidemiology, Republican Center for Hygiene, Epidemiology and Public Health, Minsk, Republic of Belarus*

Nurmatov Z.S., *PhD, MD (Medicine), Head, Republican Scientific and Practical Center for the Control of Viral Infections, National Institute of Public Health, Bishkek, Kyrgyz Republic*

Melik-Andreasyan G.G., *PhD, MD (Medicine), Professor, Deputy Director for Science, "Reference Laboratory Center" Branch, National Center for Disease Control and Prevention, Yerevan, Republic of Armenia*

Ruziev M.M., *PhD, MD (Medicine), Professor, Director, Tajik Research Institute of Preventive Medicine, Dushanbe, Republic of Tajikistan*

Totolian Areg A., *PhD, MD (Medicine), Professor, Full Member, Russian Academy of Sciences, Head, Laboratory of Molecular Immunology, Director, Saint Petersburg Pasteur Institute; Head, Department of Immunology, First St. Petersburg State I. Pavlov Medical University, St. Petersburg, Russian Federation*

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