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SARS-CoV-2 COLLECTIVE IMMUNITY AMONG THE POPULATION OF THE REPUBLIC OF ARMENIA

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Abstract. *Background.* The COVID-19 pandemic has become a substantial global health crisis, unparalleled in world history. Infection dynamics can have specific characteristics in different countries due to social, economic, climatic, or geographic factors. Aim: to study features of SARS-CoV-2 collective immunity among the Armenian population. *Materials and methods.* A cross-sectional, randomized study of collective immunity was carried out according to a program developed by Rospotrebnadzor and the St. Petersburg Pasteur Institute, taking into account WHO recommendations. The study was approved by the ethics committees of the National Center for Infectious Diseases (Armenia) and the St. Petersburg Pasteur Institute (Russia). A volunteer cohort was formed (N = 6057), randomized by age and region. The study's analysis included: shares and distributions of antibodies (Abs) to nucleocapsid (Nc) antigen (Ag) and receptor binding domain (RBD) S-1 Ag in the cohort; and quantitative determination of these Abs by ELISA. During the survey, a history of vaccination was indicated by 4395 people. *Results.* Overall seropositivity formed in the whole cohort (by April 14, 2022) was 98.6% (95% CI: 98.1–98.7). It did not depend on age, place of residence, or occupation. When quantifying Nc and RBD Abs, the proportions of volunteers with Nc Ab levels of 1–17 BAU/ml and RBD Ab levels of 22.6–220 BAU/ml were the smallest, amounting to 6.9% (95% CI: 6.2–7.5) and 20.4% (95% CI: 19.4–21.4), respectively. With increasing serum concentrations (Nc > 667 BAU/ml, RBD > 450 BAU/ml), the proportions of individuals with the corresponding levels were 20.2% for Nc (95% CI: 19.2–21.3) and 54.2% for RBD (95% CI: 52.9–55.5). Vaccination coverage was 72.6% (95% CI: 71.5–73.7). The most frequently used were Sinopharm/BIBP (32.4%), AZD1222 (22.3%), and Gam-COVID-Vac (21%). The remaining vaccines (CoronaVac, mRNA-1273, BNT162b2, CoviVac) were used by 24.3% of vaccinated individuals. When summing vaccines by platform, it was found that: vector vaccines were used in 40.34% (95% CI: 33.57–42.39) of cases; whole-virion vaccines were used in 26.83% (95% CI: 24.76–32.20); and mRNA vaccines were used in 6.33% (95% CI: 4.84–8.91). *Conclusion.* The epidemic situation in Armenia by April 2022 was characterized by a high level of collective immunity, independent of age or regional factors. Vector and whole-virion vaccines have been used most widely.

Key words: *SARS-CoV-2, COVID-19, Republic of Armenia, volunteers, herd immunity, population, vaccination.*

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КОЛЛЕКТИВНЫЙ ИММУНИТЕТ К SARS-CoV-2 НАСЕЛЕНИЯ РЕСПУБЛИКИ АРМЕНИЯ

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Резюме. *Введение.* Пандемия COVID-19 стала серьезным глобальным кризисом в области здравоохранения, не имеющим аналогов в мировой истории. Динамика инфекции может иметь специфические особенности в разных странах в силу социальных, экономических, климатических или географических факторов. Цель: изучить особенности коллективного иммунитета против SARS-CoV-2 среди населения Армении. *Материалы и методы.* Поперечное рандомизированное исследование коллективного иммунитета проводили по программе, разработанной Роспотребнадзором и Санкт-Петербургским институтом Пастера с учетом рекомендаций ВОЗ. Исследование одобрено этическими комитетами Национального центра инфекционных болезней (Армения) и Санкт-Петербургского института Пастера (Россия). Была сформирована когорта добровольцев (N = 6057), рандомизированная по возрасту и региону. Анализ исследования включал: доли и распределение антител (АТ) к нуклеокапсиду (Nc), антигену (Ag) и рецепторсвязывающему домену (RBD) S-1 Ag в когорте; и количественное определение этих антител с помощью ELISA. В ходе опроса в анамнезе прививки указали 4395 человек. *Результаты.* Общая серопозитивность, сформированная во всей когорте (к 14 апреля 2022 г.), составила 98,6% (95% ДИ: 98,1–98,7). Оно не зависело от возраста, места жительства или рода занятий. При количественном определении антител Nc и RBD доля добровольцев с уровнями антител Nc 1–17 BAU/мл и уровнями антител RBD 22,6–220 BAU/мл была наименьшей и составила 6,9% (95% ДИ: 6,2–7,5). и 20,4% (95% ДИ: 19,4–21,4) соответственно. При повышении концентрации в сыворотке (Nc > 667 BAU/мл, RBD > 450 BAU/мл) доля лиц с соответствующими уровнями составляла 20,2% для Nc (95% ДИ: 19,2–21,3) и 54,2% для RBD (95% ДИ: 52,9–55,5). Охват вакцинацией составил 72,6% (95% ДИ: 71,5–73,7). Наиболее часто использовались Sinopharm/BIBP (32,4%), AZD1222 (22,3%) и Gam-COVID-Vac (21%). Остальные вакцины (CoronaVac, mRNA-1273, BNT162b2, CoviVac) использовали 24,3% привитых. При суммировании вакцин по платформам установлено, что: векторные вакцины применялись в 40,34% (95% ДИ: 33,57–42,39) случаев; цельновирионные вакцины использовались в 26,83% (95% ДИ: 24,76–32,20); мРНК-вакцины использовались в 6,33% (95% ДИ: 4,84–8,91). *Вывод.* Эпидемическая ситуация в Армении к апрелю 2022 г. характеризовалась высоким уровнем коллективного иммунитета, не зависящим от возрастных и региональных факторов. Наибольшее распространение получили векторные и цельновирионные вакцины.

Ключевые слова: *SARS-CoV-2, COVID-19, Республика Армения, волонтеры, коллективный иммунитет, население, вакцинация.*

Introduction

The main feature of the COVID-19 pandemic has been the global spread of infection in an unprecedentedly short period of time in almost all countries of the world [19]. As those authors rightly point out, «The global crisis provoked by the coronavirus pandemic has no analogues in modern history.» As of 12/04/2022, 503 million cases have been registered globally (63 117 per 1 million pop.). Six million people died from COVID-19, or 1.23% of the total number of patients [3, 12]. Unfortunately, a universal COVID-19 treatment has not yet been created [21, 26]. Development of new drugs and re-purposing of existing ones frequently has been ineffective for various reasons [10]. In this context, the unprecedentedly rapid development and implementation of the SARS-CoV-2 vaccine family became the most important step in the fight against the COVID-19 pandemic [5].

The initial hopes placed on vaccination were largely justified. Israel can serve as an example. It was possible to reduce incidence by more than 150-fold as a result of mass immunization with the BNT162b2 (mRNA) vaccine from 24/01 to 3/04/2021 [7]. Unfortunately, mutational processes, alongside the emergence of new viral variants with potential to overcome existing adaptive immunity, significantly reduced the initial effect [24, 25]. COVID-19 prevalence in the Republic of Armenia (RA) was about 141 thousand cases per 1 million population as of April 2022. This is slightly higher than in neighboring Azerbaijan (75 thousand per million) and Iran (82 thousand per million), but significantly lower than in Georgia (444 thousand per million) and Turkey (170 thousand per million) [3, 6, 12]. Epidemic process dynamics in the RA were characterized by five waves (Fig. 1).

The first wave, the peak of which was recorded on June 22, 2020, was caused by the B4 strain (Fig. 1). The second wave, with a maximum on October 28, 2020, was the result of circulation of the B.1.1 virus. The third wave's emergence could be associated with the circulation of B.1.1.7 and the rise in morbidity following the appearance of B.1.617.2. The fourth wave was caused mainly by the B.1.617.2 viral variant. Finally, the fifth wave was the result of the global spread of the B1.1.529 lineage [8, 11].

As in other countries, it was expected that specific vaccines against SARS-CoV-2 would become an important factor in controlling the pandemic. Scheduled vaccination began on 31/03/2021, when 565 people were first vaccinated with the 1st dose of vaccine. By June 20, 2021, 11 784 people had completed vaccination. Booster re-vaccination began on December 26, 2021 (Fig. 2).

The rate of vaccination subsequently slowed, and by 22/05/2022 the total number of vaccinated individuals in the RA was 1.1 million (38.1% of the total population). This value was, of course, insufficient to completely stop the pandemic [18]. However, another 422 900 people with adaptive immunity to SARS-CoV-2 following manifest COVID-19 illness should be added to the calculation [6, 12]. After a simple summation, we find that at least 51% of the population had real adaptive immunity as of April 22, 2022. Obviously, this number does not include individuals with asymptomatic infection. Therefore, the total percentage with immunity in the population may be much higher.

The purpose of the study was to analyze the level and structure of collective immunity among the Armenian population which had formed by the 16th month of the COVID-19 pandemic.

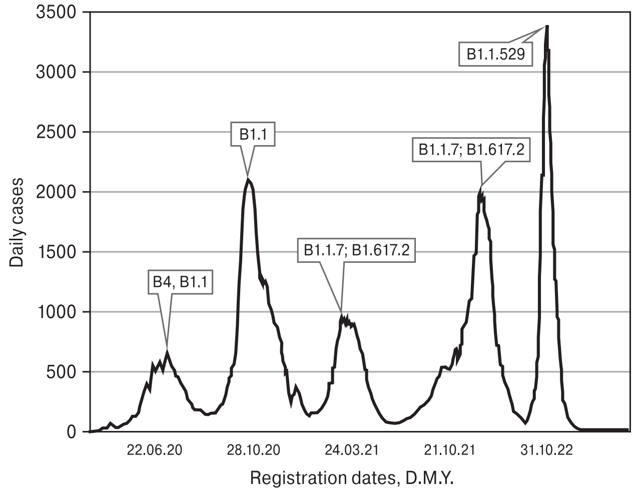


Figure 1. Incidence dynamics in the Armenian population for the entire observation period until April 14 2022

Note. The x-axis shows time with peak registrations (day.month.year) [17]. The y-axis shows the number of new cases registered daily. Frames show SARS-CoV-2 variants circulating during each wave.

Materials and methods

The study was organized and conducted as part of scientific cooperation activities between countries of Eastern Europe, Transcaucasia, and Central Asia to assess population immunity to novel coronavirus infection in accordance with: Rospotrebnadzor order "Procedure for the Implementation of the Decree of the Government of the Russian Federation" (No. 1658-r, 18.06.2021) on the one hand; and order of the Ministry of Health (No. 380-A, 31.01.2022), Republic of Armenia, on the other.

Design and organization of the study

A cross-sectional, randomized cohort study of herd immunity was carried out according to a program developed by the Federal Service for Supervision of Consumer Rights Protection and Human Welfare with the participation of the Saint Petersburg Pasteur Institute, taking into account WHO recommendations [15, 16]. A cloud service (internet server) was initially developed to facilitate formation of a representative sample of volunteers, organization of sampling, and quick analysis of results. Three days before study initiation, a wide explanatory campaign

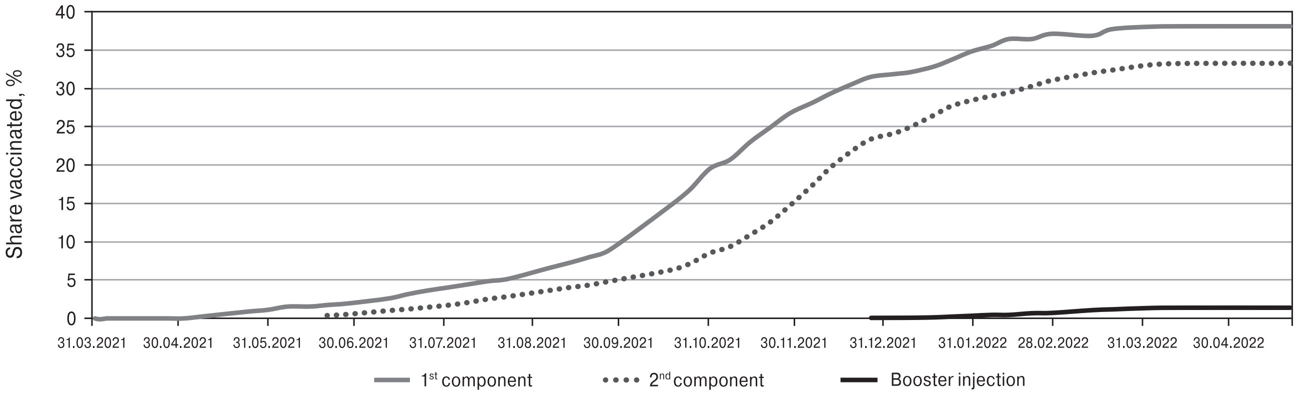


Figure 2. Dynamics of COVID-19 vaccination in Armenia [6]

Note. Seven-day moving averages are shown. 1st component — the proportion of residents who received the 1st vaccine component; 2nd component — the proportion who received the 2nd component (complete primary vaccination); booster — the proportion who received a booster dose of vaccine (re-vaccination). X-axis: date of registration (1 division = 1 month).

was conducted (TV, media, social networks) about the start of free testing for the presence of SARS-CoV-2 antibodies, including an internet link for completing a survey.

Those who expressed a desire to participate followed the link, filled out a questionnaire (Table 1S), and sent it to the cloud service. Received questionnaires were analyzed by the server for compliance with study inclusion criteria. If the candidate matched the requirements, he/she received a letter to their indicated e-mail address with a unique ID number and an invitation to follow an internet link for choosing a convenient blood sampling point and time. Grounds for non-inclusion in the study were: a refusal of subsequent laboratory testing; or the presence of manifest COVID-19 at the moment of questionnaire completion.

The cloud resource summarized the number of participants by age and place of residence. Registration of incoming questionnaires was terminated when the maximum number of volunteers in each age group living in each region was reached. In this case, the person received a rejection letter. This approach made it possible to effectively randomize a cohort of volunteers by age and region.

Each volunteer, or their legal representative (as with children), was acquainted with the goals and conditions of the upcoming study and signed an informed consent. The study was organized in accordance with the provisions of the Declaration of Helsinki and approved by the Ethics Committee of the National Center for Infectious Diseases of the Armenian Ministry of Health (No. 01, dated February 17, 2022) and the local Ethics Committee of the St. Petersburg Pasteur Institute (protocol No. 64, dated May 26, 2020). The algorithm of the study is shown in the flowchart below (Fig. 3). As shown, the survey is a continuous process from research design to final report preparation.

General characteristics of the volunteer cohort

The study was carried out in Yerevan and all Armenian regions. Blood samples were collected for five days from April 12–16, 2022. In accord-

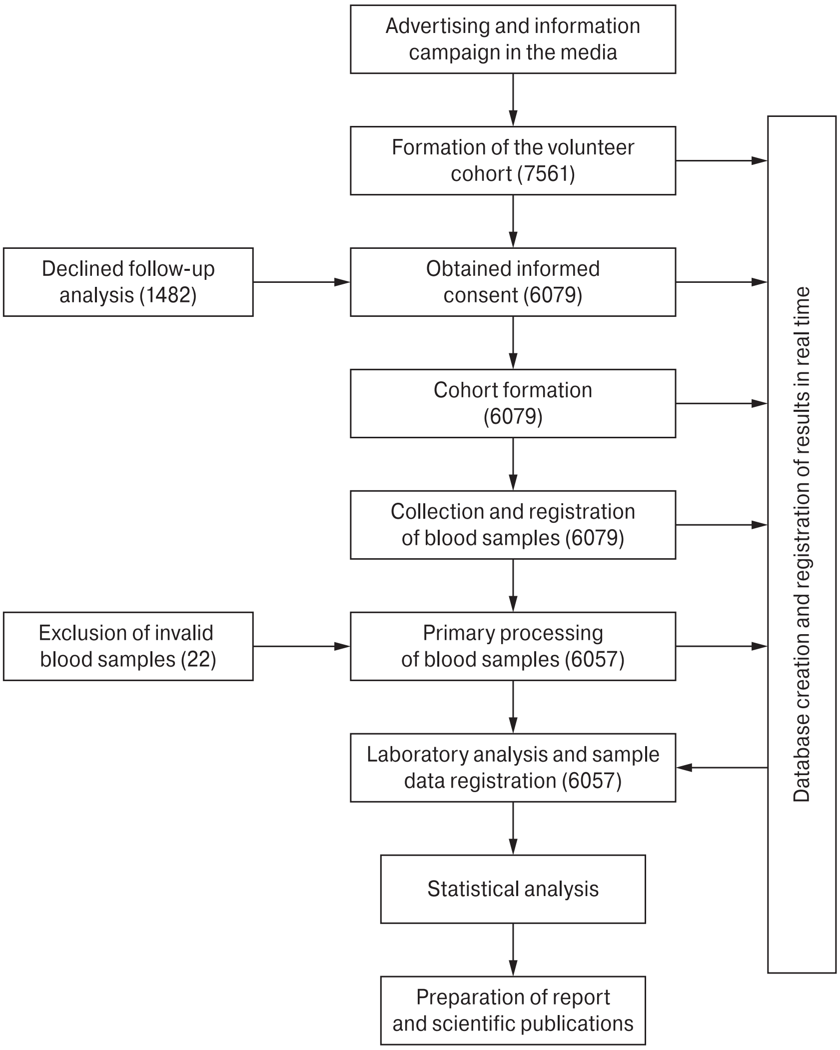


Figure 3. Algorithm for organization and conduct of the study of SARS-CoV-2 collective immunity in the Republic of Armenia

ance with the de Moivre—Laplace limit theorem [2], a cohort of 6079 volunteers was formed. After exclusion of invalid samples, 6057 people were included in the analyzed cohort. Volunteer distribution by age group turned out to be relatively homogeneous, both in terms of absolute value and share of representation (Table 1).

The number of volunteers who took part in the study represented 0.2% (95% CI: 0.20—0.21) of the country's population. Volunteers were distributed almost evenly across all regions (Table 2). As expected, the largest number of volunteers was recruited in Yerevan city (the capital). However, given the actual number of city residents, volunteer representation did not differ from that in other regions. Share representation (averaged) ranged from 0.18—0.22%, without significant differences in general for the RA. Regarding regional distribution, most volunteers lived in Yerevan city. The least were from Vayots Dzor Province, featuring the smallest population (Table 2).

As in other studies [13, 14], women participated more actively than men. The ratio (men, women) was 1399 (23.1%; 95% CI: 22.1—24.2) and 4655 (76.9%; 95% CI: 75.8—77.0), respectively. Among volunteers, 1750 people (28.9%; 95% CI: 27.8—30.1) had an official COVID-19 diagnosis (through a medical institution). The cohort included twelve occupational groups, the unemployed, pensioners, children (preschool, school age), and students (Table 2S). The most represented group was healthcare workers; their share in the surveyed cohort was 36.6% (95% CI: 35.4—37.8). The least volunteers (< 1.0%) were registered among transportation and agricultural workers, military personnel, and IT workers.

Table 1. Age structure of the volunteer cohort analyzed

Age group in years	Analyzed volunteers	
	Individuals	Percentage of entire cohort
1–17	670	11.07
1–6	71	1.19
7–13	225	3.73
14–17	374	6.19
18–29	702	11.60
30–39	962	15.89
40–49	954	15.78
50–59	973	16.11
60–69	972	16.06
70+	821	13.60
Total	6054	100

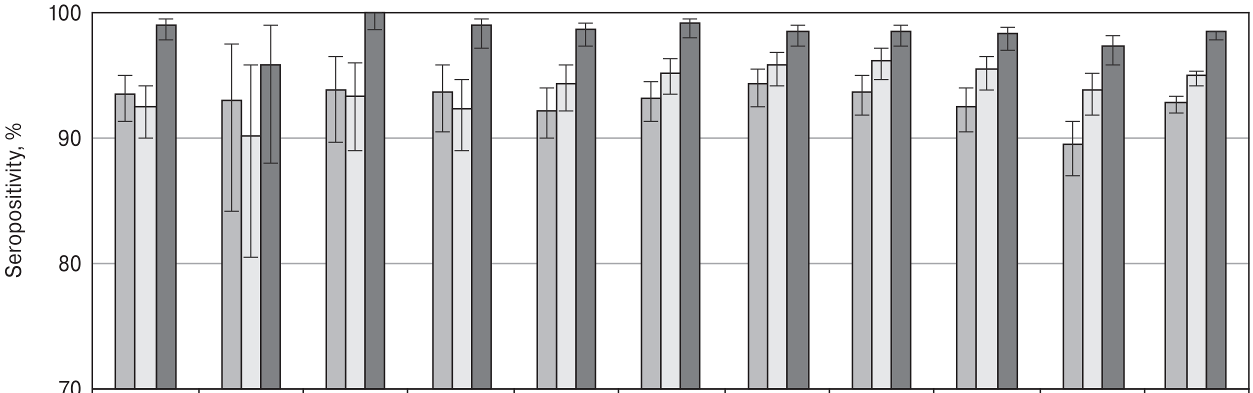
Organization of laboratory research

At the appointed time, the volunteer visited the blood collection point, where a medical officer took a blood sample from a peripheral vein (3 ml into vacutainers containing EDTA). After centrifugation, plasma was separated from cellular elements, transferred into plastic test tubes, and stored until analysis (≤ 24 hrs) at 4°C. COVID-19 recovery or SARS-CoV-2 vaccination results in the formation of various Abs. Antibodies to Nc and S protein receptor binding domain (RBD) feature prominently due to their high representation during infectious or post-vaccination processes. Thus, assessment of humoral immunity in the Armenian population included determination of Nc and RBD specific antibodies. The pooled proportion of volunteers who had any form of positive antibody status (Nc+, RBD+, Nc+RBD+) was termed complete seropositivity (CS). Antibody content (Nc, RBD) was quantified by ELISA using the appropriate test systems as described previously [16, 20]. Analytical results were expressed generally for groups (share seropositive) or quantitatively (BAU/ml). Received data, without any processing, was immediately transferred to the cloud service.

Table 2. Volunteer numbers and representation of different Armenian regions

District	Population			Examined, people		
	Urban	Rural	Total	Number	Share% (95% CI)	
					of overall number	of regional pop.
Yerevan city*	1 096 100	0	1 096 100	2407	39.7 (38.5–41.0)	0.22 (0.21–0.23)
Aragatsotn	26 400	97 800	124 200	218	3.6 (3.2–4.1)	0.18 (0.15–0.2)
Ararat	71 800	184 800	256 600	409	6.8 (6.1–7.4)	0.16 (0.14–0.18)
Armavir	82 500	181 700	264 200	527	8.7 (8.0–9.4)	0.20 (0.18–0.22)
Gegharkunik	66 000	161 000	227 000	491	8.1 (7.4–8.8)	0.22 (0.20–0.24)
Lori	124 800	87 100	211 900	458	7.6 (6.9–8.3)	0.22 (0.20–0.24)
Kotayk	136 700	114 700	251 400	542	9.0 (8.2–9.7)	0.22 (0.20–0.23)
Shirak	134 500	95 900	230 400	458	7.6 (6.9–8.3)	0.20 (0.18–0.22)
Tavush	50 100	69 800	119 900	229	3.8 (3.3–4.3)	0.19 (0.17–0.22)
Syunik	91 100	44 000	135 100	236	3.9 (3.4–4.4)	0.18 (0.15–0.20)
Vayots Dzor	16 700	31 100	47 800	82	1.4 (1.1–1.7)	0.17 (0.14–0.21)
Overall	1 896 700	1 067 900	2 964 600	6057	2.0 (2.0–2.1)	0.20 (0.20–0.21)

Note. *Yerevan city was considered like a district.



	1–17	1–6	7–13	14–17	18–29	30–39	40–49	50–59	60–69	70+	Overall
Nc Ab	93.5	93	93.8	93.6	92.2	93.1	94.3	93.7	92.5	89.4	92.8
RBD Ab	92.4	90.1	93.3	92.3	94.3	95.1	95.8	96.2	95.5	93.8	94.9
CS	99	95.8	100	98.9	98.6	99.1	98.5	98.5	98.3	97.3	98.4

Figure 4. Volunteer seroprevalence by age group
Note. Nc Ab — the share of volunteers with Nc Abs; RBD Ab — the share with RBD Abs; CS (complete seropositivity) — the share who have Abs to Nc or RBD (jointly or separately). Black vertical lines are confidence intervals. The x-axis shows age interval (years).

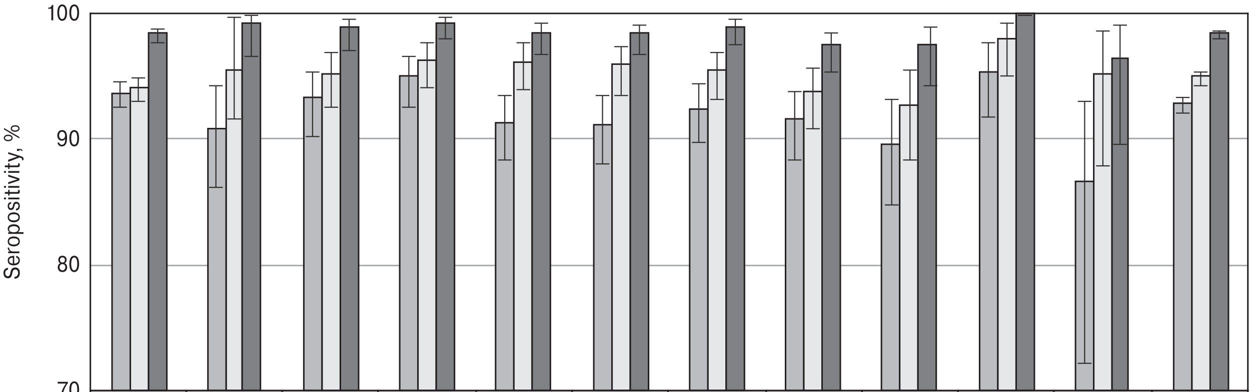
Statistical analysis

Statistical analysis was carried out using functions in Microsoft Excel 2010. Mean values and confidence intervals of shares were calculated by the method of A. Wald and J. Wolfowitz [23] with the correction of A. Agresti and B.A. Coull [1]. The significance of differences in proportions was calculated by z-test using a special calculator [20]. For other statistical calculations not mentioned, Statistica 13 (StatSoft) was used. Unless otherwise indicated, $p \leq 0.05$ was used as the statistical threshold of significance for differences. Graphics were made in Microsoft Excel 2010 or Statistica 13.

Results

Volunteer seroprevalence by age group

Seropositivity in the volunteer cohort formed by the 16th month of the COVID-19 pandemic turned out to be quite high, significantly exceeding initial forecasts. Complete seropositivity (presence of either Ab, jointly or separately) for the cohort as a whole was 98.4% (95% CI: 98.1–98.7). Its level was approximately the same regardless of age interval (Fig. 4). Antibodies were absent in 94 volunteers (1.6%; 95% CI: 1.3–1.9). Nucleocapsid Ab seroprevalence (92.8%; 95% CI 92.1–93.4) was significantly lower



	Yerevan city	Aragatsotn region	Ararat region	Armavir region	Gegharkunik region	Lori region	Kotayk region	Shirak region	Tavush region	Syunik region	Vayots Dzor region	Overall
Nc Ab	93.6	90.8	93.2	94.9	91.2	91.1	92.4	91.5	89.5	95.3	86.6	92.8
RBD Ab	94.1	95.4	95.1	96.2	96.1	95.9	95.4	93.7	92.6	97.9	95.1	94.9
CS	98.3	99.1	98.8	99.2	98.4	98.3	98.9	97.4	97.4	100	96.3	98.4

Figure 5. Volunteer seroprevalence by region of residence
Note. Nc Ab — the share of volunteers with Nc Abs; RBD Ab — the share with RBD Abs; CS (complete seropositivity) — the share who have Abs to Nc or RBD (jointly or separately). Black vertical lines are confidence intervals. Armenian regions are shown on the x-axis. Yerevan city was considered like a district.

than RBD Ab seroprevalence (94.9%; 95% CI 94.3–95.4) in the cohort ($p < 0.01$).

When analyzing volunteers by age, there were no significant differences in CS. The share of volunteers with Nc Abs exceeded 90% in all age groups, but was significantly lower than the proportion of CS ($p < 0.01$) in all groups except for children aged 1–6 years old (Fig. 4). RBD seropositivity did not differ from Nc, but was again significantly lower than CS. Thus, the obtained data convincingly show that collective immunity exceeded 90% in all age groups. This would logically be expected to precede a sharp decrease in incidence, which was indeed confirmed by monitoring studies in April 2022 (Fig. 1).

In terms of gender, the cohort consisted of 23.1% males and 76.9% females. At serological examination, SARS-CoV-2 Ab status values in men were: 97.4% CS (95% CI: 96.5–98.2); 90.6% with Nc (95% CI: 89.0–92.1); and 91.9% with RBD Abs (90.4–93.2). Seropositivity in women was significantly higher than in men: 98.7% CS (95% CI: 98.4–99.0); 93.4% with Nc (95% CI: 92.7–94.1); and 95.8% with RBD Abs (95% CI: 95.2–96.3).

Volunteer seroprevalence by region of residence and professional activity

Considering the high level of collective immunity among volunteers in all age categories, it could be expected that the region of residence in Armenia (the smallest nation in the Transcaucasus, 29 743 km^2) would not have a significant impact on seroprevalence. The results, with some reservation, confirm these assumptions. Thus, CS in general for the RA was 98.4% (95% CI: 98.1–98.7). The lowest seroprevalence was noted in Vayots Dzor Province (96.3%; 95% CI: 89.7–99.2). The highest was in Syunik Province (100%; 95% CI: 98.7–100). Seroprevalence

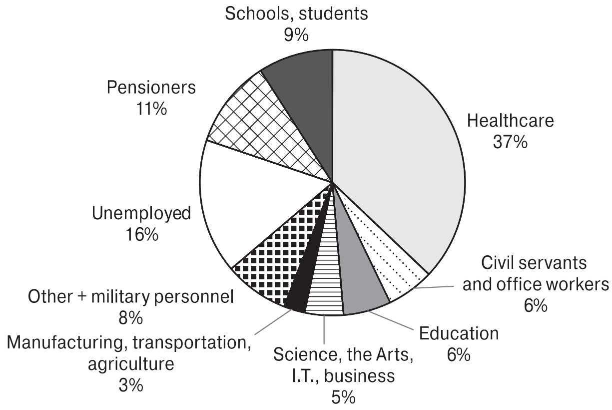
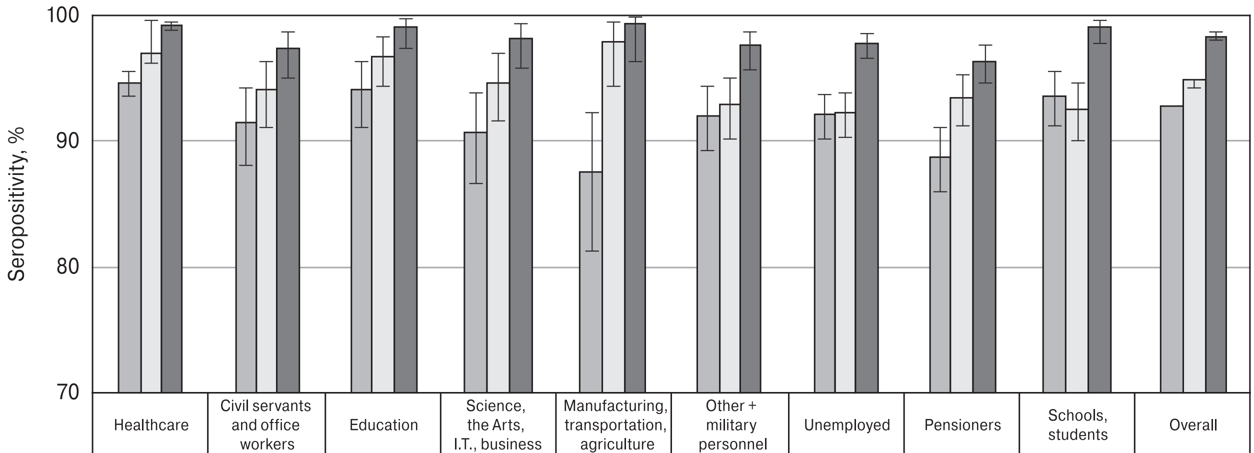


Figure 6. Distribution of the volunteer cohort by occupation with grouping
Note. Shares within frames are rounded to integer values.

distributions in other areas varied by 6–7%, without statistical significance at $p < 0.05$ (Fig. 5).

Occupation can be a significant factor determining SARS-CoV-2 infection risk and seroprevalence. The distribution of volunteers by occupation turned out to be very heterogeneous. The best represented groups were healthcare workers (36.6%; 95% CI: 35.4–37.8), unemployed (16.2%; 95% CI: 15.3–17.2), and pensioners (10.6%; 95% CI: 9.9–11.4%). Representative share for other fields ranged from 0.4–0.5% (agriculture, transportation, military, IT) to 5.7% (education). Since sample sizes in some professional categories turned out to be insufficiently representative, the data for a number of groups were combined, taking into account similar working conditions (Fig. 6).

Hence, the following combined groups were formed: 'civil servants and office workers'; 'workers in science, the Arts, IT-specialists, and business';



	Healthcare	Civil servants and office workers	Education	Science, the Arts, I.T., business	Manufacturing, transportation, agriculture	Other + military personnel	Unemployed	Pensioners	Schools, students	Overall
Nc Ab	94.7	91.6	94.2	90.8	87.6	92.1	92.2	88.8	93.7	92.8
RBD Ab	97.1	94.2	96.8	94.7	98	93	92.3	93.5	92.6	94.9
CS	99.3	97.4	99.1	98.2	99.4	97.7	97.9	96.4	99.1	98.4

Figure 7. Volunteer seroprevalence by field of activity
Note. Nc Ab — the share of volunteers with Nc Abs; RBD Ab — the share with RBD Abs; CS (complete seropositivity) — the share who have Abs to Nc or RBD (jointly or separately). Black vertical lines indicate confidence intervals.

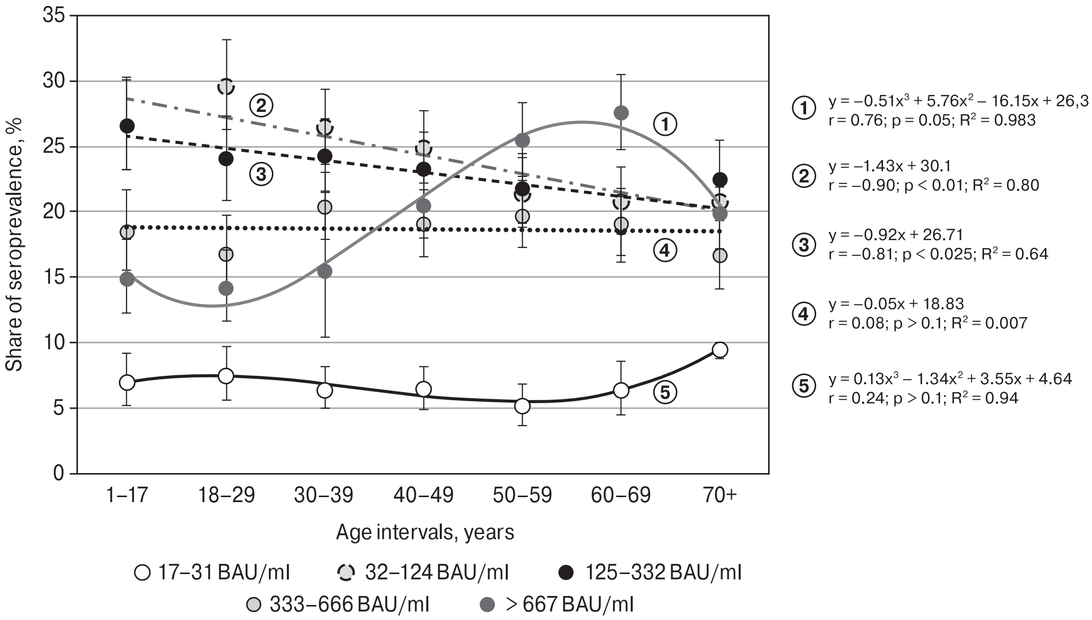


Figure 8. Nc antibody serological intervals plotted by age group

Note. Plasma Ab ranges are expressed in BAU/ml. Colored curves are trend lines for each Ab range. Regressions, rank correlation coefficients, p-values, and coefficients of determination are given (highlighted in the color of the corresponding range). Vertical black lines are 95% confidence intervals.

‘workers in manufacturing, transportation, and agriculture’; and ‘schoolchildren and students’. In the adjusted groups, the state of collective immunity was assessed by serological levels (Nc, RBD, CS) (Fig. 7).

Complete seropositivity among healthcare workers (99.3%; 95% CI: 98.9–99.6) was significantly higher, and among pensioners (96.4%; 95% CI: 94.7–97.7) significantly lower, than the cohort average ($p < 0.05$). Regarding Nc Ab status, the lowest seroprevalence values were observed in the groups ‘manufacturing, agriculture, transportation’ (87.6%; 95% CI: 81.3–92.4) and pensioners (88.8%; 95% CI: 86.1–91.1). The differences were significant ($p < 0.05$) relative to cohort Nc seropositivity (92.8%; 95% CI: 92.1–93.4). Unlike other professional groups, Nc seroprevalence in the group ‘schoolchildren and students’ (93.7%; 95% CI: 91.3–95.6) exceeded RBD seroprevalence (92.6%; 95% CI: 90.1–94.7), although insignificantly. This coincided with similar data seen in the children’s group with age analysis (Fig. 3). When determining RBD seroprevalence levels, no significant differences were found between professional groups.

Thus, analysis of the structure of SARS-CoV-2 collective immunity among Armenian volunteers showed humoral responses in at least 90% regardless of age, place of residence, or occupation. However, this inevitably raises the question of the quantitative distribution of SARS-CoV-2 Abs.

Quantitative analysis of IgG antibodies to Nc and RBD by age

When assessing the quantitative content of Nc Abs, it was found that only a small proportion of seropositive volunteers had very low Ab levels, 17–31 BAU/ml, regardless of age (Fig. 8, Table 3S). The regression curve in this group was described by a 3rd degree polynomial of the form $y = 0.13x^3 - 0.34x^2 + 3.55x + 4.64$. A slightly higher proportion seropositive in the age group of 18–29 years, and slightly lower among those aged 50–59 years, was not significant.

The largest share of seropositive individuals had Nc Abs in the range 32–124 BAU/ml. The age distribution had a descending character described by a linear regression of the form $y = -1.43x + 30.1$ The equation correctly described the real distribution with a coefficient of determination R = 0.80. In other words, higher Nc Ab titers were accompanied by: an increase in the proportion of seropositive individuals aged 1–17 years, which amounted to 26.6% (95% CI: 23.3–30.1); and a decrease in the 70+ group to 20.8% (95% CI: 18.1–23.8). The differences were not statistically significant. However, the trend was statistically significant with a rank correlation coefficient of –0.90 at $p < 0.01$.

Higher Nc Ab levels in the range 125–332 BAU/ml did not change the form of the regression dependence, but led to a slight decrease in the equation’s coefficient: $y = -0.92x + 26.1$. The regression line became flatter, the slope decreased to –1.0, and the coefficient of determination became 0.64. The rank correlation coefficient was –0.81 ($p < 0.025$).

In volunteers with Nc Ab levels in the range 333–666 BAU/ml, the shares of seropositivity were distributed almost evenly across all age groups. The regression was a horizontal line ($tg\alpha = -0.2$), described by the equation $y = -0.05x + 18.83$. Coefficients of rank correlation and determination varied within 0.08 and 0.007, respectively ($p > 0.1$).

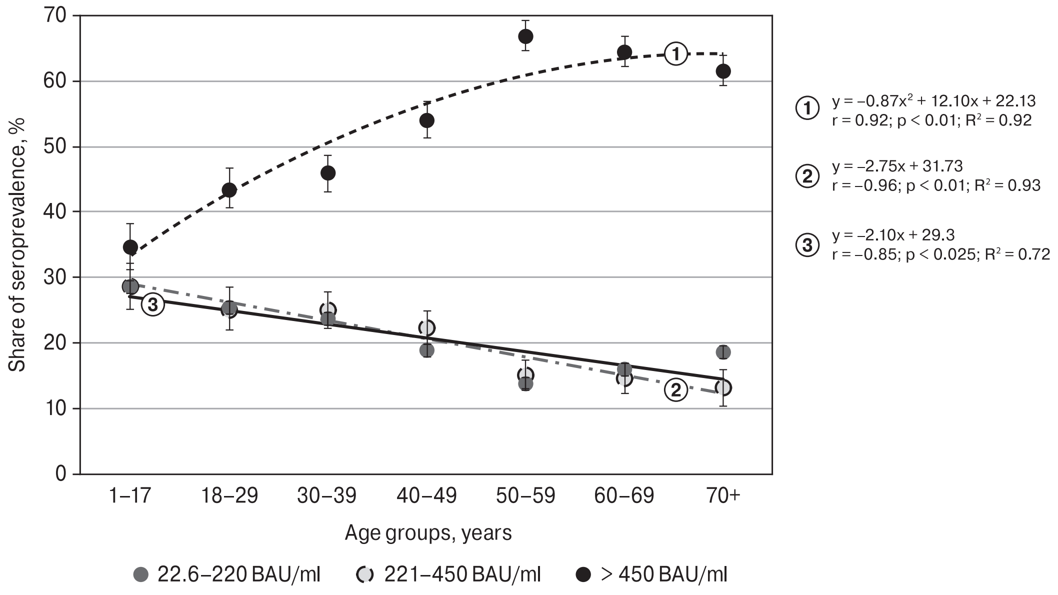


Figure 9. RBD antibody serological intervals plotted by age group

Note. Plasma Ab ranges are expressed in BAU/ml. Colored curves are trend lines for each Ab range. Regressions, rank correlation coefficients, p-values, and coefficients of determination are given (highlighted in the color of the corresponding range). Vertical black lines are 95% confidence intervals.

Upon reaching the maximum Nc Ab level (> 667 BAU/ml), the trend line for interage distribution of seropositivity transformed into an s-shaped 3rd degree polynomial curve described by the equation: $y = 0.51x^3 + 5.76x^2 - 16.15x + 26.30$. Several regions were clearly distinguishable on the regression curve: a depression among volunteers aged 18–29 years; a significant increase in the proportion of seropositive individuals aged 50 to 69 years; followed by a downward trend in the group 70+ years old (Fig. 8, Table 3S). The rank correlation was 0.76 ($p \cong 0.05$), and the determination coefficient was 0.98.

During analysis, seroprevalence distribution features were noted depending on age and plasma RBD concentration (Fig. 9, Table 4S). The minimum share of seropositivity was noted among individuals with RBD Abs in the range of 22.6–220 BAU/ml. The relationship between volunteer age and RBD seropositivity was described by the linear regression equation $y = -2.10x + 29.30$, with a determination coefficient $R^2 = 0.72$. As with Nc, the largest proportion of seropositive individuals with this RBD Ab level was found in the age group 1–17 years old (28.8%; 95% CI: 25.4–32.4). This proportion continuously decreased with increasing age, with an angular coefficient of 1.7. In the 50–59 age group, it reached 14.0% (95% CI: 11.9–16.3). By 70+ years, it increased by 6% to 20.4% (95% CI: 19.4–21.4; $p < 0.05$). The noted decrease was not accidental; the rank correlation coefficient was –0.85 ($p < 0.025$).

A similar relationship was found in the group of individuals with RBD Ab levels of 220–450 BAU/ml. Only the numerical values of the coefficients a and b changed. The coefficient of determination increased to 0.93, and the value of the rank correlation coefficient became –0.96 ($p < 0.001$). The main trend remained unchanged: a decrease in the proportion of seropositive individuals on the x-axis (ages from 1–17 to 70+), with a slope equal to –2.95. The correlation coefficient for these groups was –0.96 ($p < 0.01$).

Achievement of maximum RBD Ab levels (> 450 BAU/ml) was accompanied by a trend change from negative to positive. The linear regression was transformed into a 2nd order polynomial ($y = -0.87x^2 + 18.10x + 22.13$), while the coefficient of determination increased to 0.92. The observed change in the regression curve was also not random; the rank correlation coefficient was 0.92 ($p < 0.01$).

Analysis of RBD Ab levels showed (Fig. 9) that, in 34.8–66.9% of seropositive volunteers of different ages, levels exceeded 450 BAU/ml (the upper threshold of the test system). Among persons from 1 to 39years of age, the proportion of individuals with maximum RBD Ab levels was significantly below

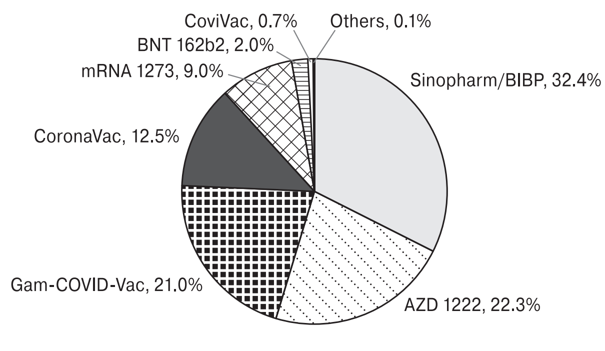


Figure 10. Vaccine usage structure in Armenia by share

Note. Others — the volunteer could not recall the name of the vaccine received.

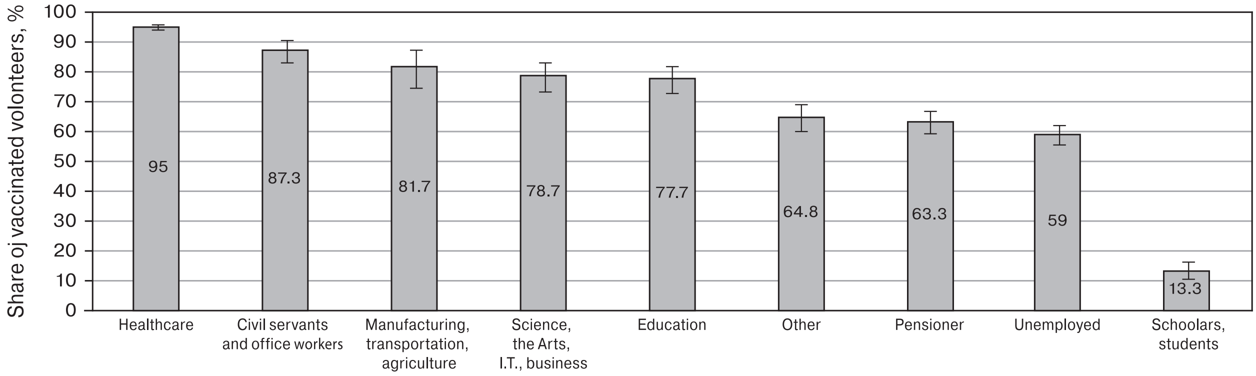


Figure 11. Vaccination coverage by professional group

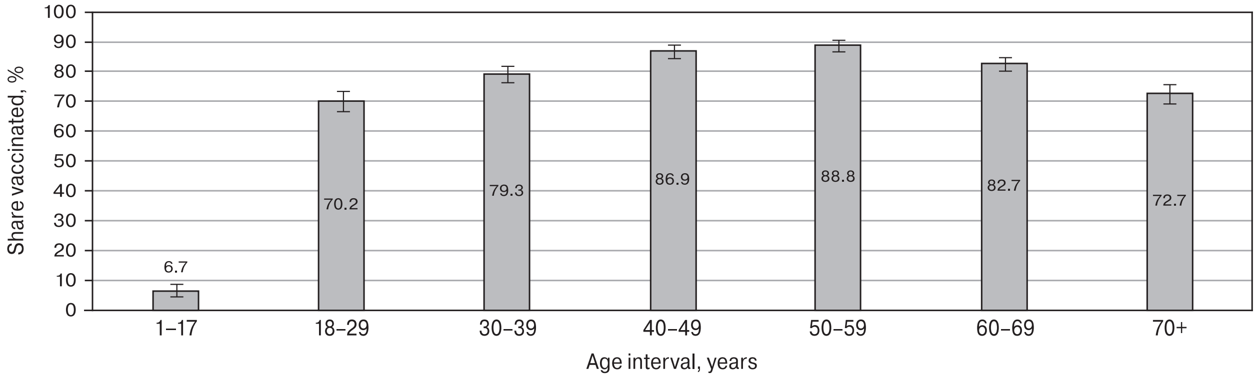


Figure 12. Vaccination coverage by age group

the cohort mean of 54.2% (95% CI: 52.9–55.5) at $p < 0.05$. In groups older than 40 years, the proportion of individuals with high RBD Ab levels (220–450 BAU/ml) was significantly higher than among volunteers aged 1 to 39 years ($p < 0.05$–0.001). A question arises: Do RBD Ab levels in older individuals (40–69 y.o.) reflect increased intensity of immunity formed in response to more frequent contact with the pathogenic agent? This cannot be ruled out, but the question requires a special study.

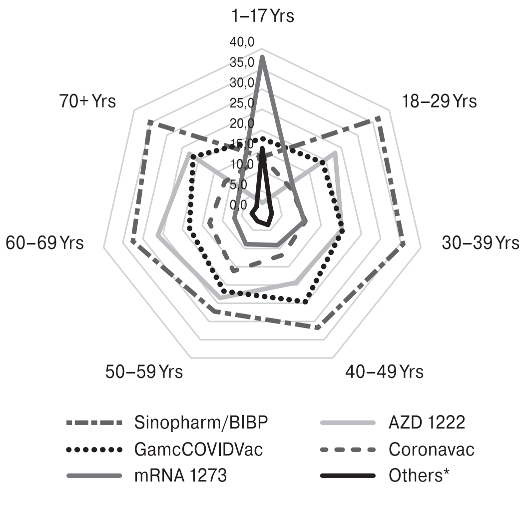


Figure 13. Distribution of the main vaccine types by age

Note. The group 'Other' combines the shares of individuals vaccinated with vaccines not shown (BNT162b2, mRNA-1273, EpiVacCorona, CoviVac, unknown).

Vaccination of volunteers

Vaccination of Armenian residents was carried out with a wide range of eight vaccines (Fig. 10). The Sinopharm/BIBP (inactivated whole-virion) vaccine was used most frequently, accounting for 32.4% (95% CI: 31.1–33.8). AZD1222 vaccine (22.3%) occupied 2nd place (10% lower usage). Gam-COVID-Vac was used slightly less frequently (21.0%). In total, these represented 75.7% of vaccinations (Fig. 10). The remaining vaccines accounted for 24.3%.

According to official data, about 38.1% of residents were vaccinated (Fig. 2) as a result of the vaccination campaign in the RA (as of April 2022). In the study cohort, the proportion vaccinated exceeded 70%. This is primarily due to the greater involvement of medical workers in the study, whose proportion in the cohort exceeded 30.0%. A second factor that likely influenced the high vaccination coverage in the cohort could be a greater interest in participation among vaccinated individuals wishing to clarify the status of their post-vaccination immunity. Such a pattern was noted in the surveyed cohort, where the share of fully vaccinated medical workers was 95.0% (95% CI: 94.1–95.9); this was significantly higher than in other professional groups ($p < 0.01$). Second place in terms of immunization coverage

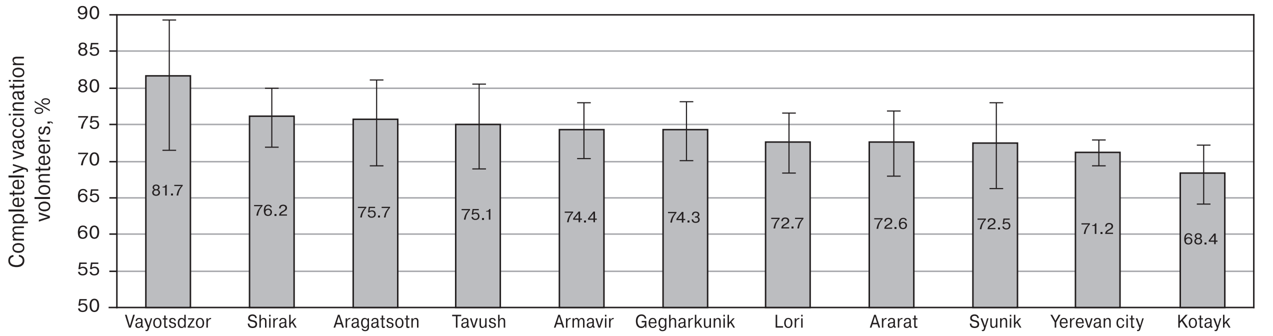


Figure 14. Share of completely vaccinated volunteers by region (as of 16/04/2022)
Note. The x-axis indicates region. Yerevan was considered like a region.

were civil service and office workers, among whom 87.3% (95% CI: 83.3–90.6) indicated a history of vaccination in the questionnaire (Fig. 11).

Among other active, working-age population groups, there was a slightly lower predisposition to vaccination among those from industrial enterprises (manufacturing, transportation, agriculture) to education workers. Lower vaccination coverage, reaching significance, was noted among pensioners and the unemployed ($p < 0.01$). Unsurprisingly, the lowest vaccination coverage was found among schoolchildren and students, 13.3% (95% CI: 10.6–16.5). This can apparently be explained by a certain prejudice against SARS-CoV-2 vaccination of children or adolescents in some strata of society. When assessing the age distribution of those vaccinated (Fig. 12), clear differences in vaccination level were seen. This partially explains the quantitative distribution of RBD Abs shown in Figure 9.

In the study cohort, the total vaccinated were 4395, or 72.6% (95% CI: 71.5–73.7). In the children's group, this indicator was expectedly the lowest, 6.7% (95% CI: 4.9–8.9). Among adults, it increased to 80.8% (95% CI: 79.7–81.8). Maximum vaccination coverage values were noted in the groups 40–49 y.o. (86.9%; 95% CI: 84.6–89.0) and 50–59 y.o. (88.8%; 95% CI: 86.7–90.7). Values were somewhat less among 18–29 y.o. (70.2%; 95% CI 66.7–73.6) and volunteers over 70 (72.7%; 95% CI: 69.5–75.7). The differences were significant ($p < 0.05$). With regard to specific vaccine types, the Chinese Sinopharm/BIBP inactivated vaccine was most frequently indicated by volunteers (Fig. 13). The majority of adult volunteers received this vaccine (32.6%; 95% CI: 31.2–34.0). Sinopharm was administered to children only in selected cases (13.3%; 95% CI: 5.1–26.8).

The AZD1222 vaccine and the Gam-COVID-Vac family of vaccines (Sputnik V, Sputnik Light) were less actively used. Total vaccination coverage with vector vaccines was equal to, or in some cases slightly more than, that of inactivated vaccines. The mRNA-1273 vaccine was used least often. However, it was used in 37.8% (95% CI: 23.8–53.5) of child vaccinations (Fig. 13).

Analysis of volunteer vaccination by Armenian region did not reveal significant differences (Fig. 14). Slightly higher values were noted in the Vayots Dzor region; the lowest were in the Kotayk region. Regional differences did not reach statistical significance.

When assessing the regional distribution of vaccines by platform type (inactivated whole-virion, vector, mRNA), the picture changed markedly (Fig. 15).

The distribution of volunteers receiving whole-virion preparations showed that inactivated vaccines prevailed in two of the eleven regions: Yerevan (the capital) and the Tavush region. In Yerevan, this predominance turned out to be significant ($p < 0.01$). In the rest of Armenia, vector vaccines were more popular, accounting for 40.34% (95% CI: 35.55–45.27) of the total vaccinated population. It should be noted that in 6 out of 11 regions, vector vaccines significantly prevailed over whole-virion types ($p < 0.05$). As for mRNA vaccines, their share was only 8.31% (95% CI: 5.83–11.42), hardly enough to have any significant impact on the level of post-vaccination immunity.

When summarizing the results, it can be seen that vaccination coverage turned out to be relatively uniform in terms of age, regional, and occupational

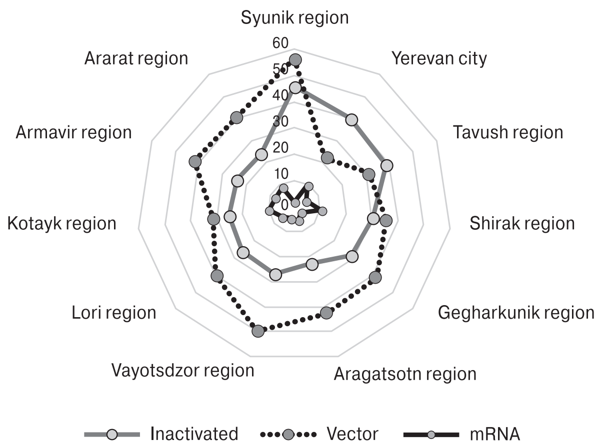


Figure 15. Regional distribution of vaccine usage (%) by production platform

characteristics. Among medical workers, however, the share vaccinated was significantly higher. When grouping vaccines by platform, vector vaccine predominance was noted in nine out of eleven Armenian regions. Yerevan and, to a lesser extent, Tavush region, were exceptions wherein inactivated whole-virion vaccines dominated.

Structure of post-vaccination specific humoral immunity

The results obtained, especially distributions with vaccines combined into separate platform categories, raised the inevitable question: Does the structure of elicited specific humoral immunity depend on platform (inactivated whole-virion, vector, mRNA)? The question stems foremost from the antigenic structure of the specific preparations. Inactivated whole-virion vaccines contain the entire spectrum of SARS-CoV-2 antigens, whereas vector and, especially, mRNA preparations contain only spike protein components or even RBD antigens [22]. With this in mind, we analyzed the structure of humoral immunity formed in response to usage of each vaccine type.

Table 3. Structure of SARS-CoV-2 Ab seroprevalence among volunteers immunized with inactivated whole-virion vaccines (Sinopharm/BIBP, CoronaVac, CoviVac; n = 2004)

	Number Nc+ % (95% CI)	Number Nc– % (95% CI)	Total % (95% CI)
RBD+	1886 94.1% (93.0–95.1)	55 2.7% (2.1–3.6)	1941 96.9% (96.0–97.6)
RBD–	39 2.0% (1.4–2.6)	24 1.2% (0.8–1.8)	63 3.1% (2.4–4.0)
Total	1925 96.1% (95.1–96.9)	79 3.9% (3.1–4.9)	2004 100%

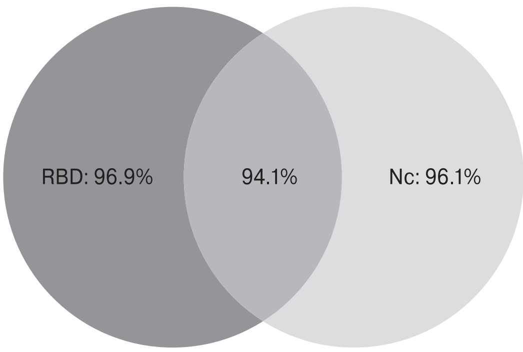


Figure 16. Structure of seropositivity (RBD, Nc) following completion of immunization with inactivated vaccines

Note. Right and left circles represent individuals seropositive for the Nc or RBD antigens, respectively. The central zone represents double-positive individuals (positive for both antigens).

As expected, the effect of the inactivated Sinopharm/BIBP vaccine containing all viral antigens was formation of a complete immune response (Table 3).

The vast majority of volunteers responded to vaccination with the formation of a full-fledged humoral immune response. Of the total cohort who completed immunization with inactivated whole-virion vaccines, the proportion Nc seronegative was 3.9% (95% CI: 3.1–4.9). Only 1.2% (95% CI: 0.8–1.8) of volunteers did not develop specific Abs upon immunization. Assessment of response distribution (shares of individuals positive for one or both antigens) indicates formation of a full-fledged immune response in the overwhelming number of vaccinated (Fig. 16).

A different predisposition of volunteers to vaccination was revealed with the vector vaccines AZD1222 and Gam-COVID-Vac. Their total share was 43.3% (95% CI: 41.8–44.8) (Table 4).

In response to the use of vector vaccines, the proportion Nc seropositive volunteers decreased significantly, while the proportion Nc seronegative increased significantly ($p < 0.001$, both cases).

Table 4. Structure of seropositivity among volunteers (n = 1902) immunized with the vector vaccines AZD1222 or Gam-COVID-Vac (Sputnik V, Sputnik Light)

	Number Nc+ % (95% CI)	Number Nc– % (95% CI)	Total % (95% CI)
RBD+	1675 88.1% (86.5–89.5)	161 8.5% (7.2–9.8)	1836 96.5% (95.6–97.3)
RBD–	42 2.2% (1.6–3.0)	24 1.3% (0.8–1.9	66 3.5% (2.7–4.4)
Total	1717 90.3% (88.8–91.6)	185 9.7% (8.4–11.1)	1902 100%

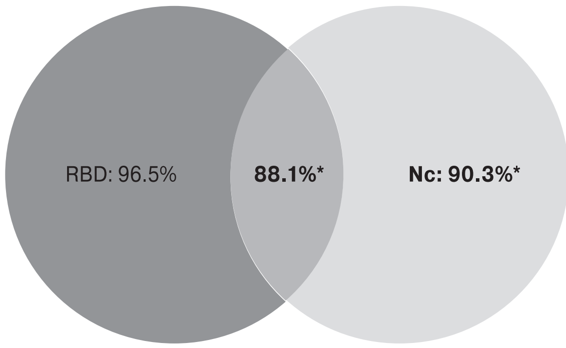


Figure 17. Structure of seropositivity (RBD, Nc) following completion of immunization with vector vaccines

Note. Right and left circles represent individuals seropositive for the Nc or RBD antigens, respectively. The central zone represents double-positive individuals (positive for both antigens). An asterisk indicates significantly lower compared to results with inactivated vaccines (Fig. 16).

Simultaneously with the decrease in the share Nc+, the percentage of double-seropositive (Nc+RBD+) volunteers decreased significantly ($p < 0.001$). The share of RBD+ practically did not change. This structure is likely due to the presence of only RBD antigen in the vector preparations. This is clearly seen when comparing Figures 16 and 17.

The proportion of volunteers immunized with mRNA vaccines was the smallest, amounting to only 11.1% (95% CI: 10.0–12.0) (Table 5).

The immune response to mRNA vaccines was characterized by a further decrease in the proportion of Nc+RBD+ double-seropositive volunteers (Table 5). Indeed, in response to whole-virion vaccines, 94.1% (95% CI: 93.0–95.1) of individuals were double-seropositive. After immunization with mRNA vaccines, it decreased to 86.3% (95% CI: 83.0–89.3) at $p < 0.0001$. This is foremost due to a significant decrease in the proportion of people with an Nc antigen response ($p < 0.0001$). This is expected since mRNA vaccines contain only mRNA encoding spike protein antigens [22]. Naturally, there were no grounds to expect a decreased RBD antigen response (Fig. 18).

The data presented in this section confirm the current view that the antigenic composition of any vaccine is a determining factor in its effectiveness. Thus, the maximum immune response in our studies was obtained in response to whole-virion inactivated vaccines, in contrast to vector and, especially, mRNA preparations.

Discussion

The conducted cross-sectional, randomized study showed that by mid-April 2022, the total SARS-CoV-2 seroprevalence in the Armenian population included in the study reached 98.4% (95% CI 98.1–98.7). This significantly exceeds the previously postulated threshold beyond which epidemic spread of a pathogenic virus stops [18, 22]. As expected, statistics provided by global sources show that after 15/04/2022, COVID-19 incidence in the RA decreased to almost zero, manifesting only in the form of individual sporadic cases in the subsequent period [3, 6, 12, 17].

Seropositivity values for individual Abs in men were: 92.8% to Nc (95% CI: 92.1–93.4) and 94.9% to RBD (95% CI: 94.3–95.4). Seropositivity among women was significantly higher than in men: Nc Abs — 93.4% (95% CI: 92.7–94.1) and RBD Abs — 95.8% (95% CI: 95.2–96.3). At the time of the study, there were no differences among volunteers by age or occupational status. Seroprevalence structures (Nc, RBD) also did not show any significant differences among volunteers by region of residence (Fig. 19, see cover II).

When assessing quantitative plasma Ab content, it was found that among Nc+ volunteers, Ab levels below 17 BAU/ml were found in less than 10% of individuals. The remaining volunteers were evenly distributed over different serological intervals in almost all age groups. In volunteers of different ages, RBD Ab levels exceeded 450 BAU/ml (the upper sensitivity threshold of the test system) in 35–67% of cases. In the group older than 40 years, the proportion of such persons was significantly higher than among persons from 1 to 39 years old (Fig. 8, 9).

It can be assumed that such a high level of collective immunity is determined by several significant factors. Firstly, 422 900 people (22.3% of the population) fell ill with overt COVID-19 during the pandemic [3, 6, 12]. Secondly, active vaccination played a role, thanks to which the total number immunized in the RA amounted to 1.1 million individuals or 38.1% of the population. In total, this amounted to 60.5%, enough to significantly impede the epidemic process [9, 18].

In the study cohort of adult volunteers, the proportion vaccinated was 80.8% (95% CI 79.7–81.8). The maximum vaccination coverage was observed among persons 40–49 years old (86.9%; 95% CI:

Table 5. Structure of seropositivity among volunteers (n = 485) immunized with the mRNA vaccines mRNA–1273 or BNT162b2

	Number Nc+ % (95% CI)	Number Nc– % (95% CI)	Total % (95% CI)
RBD+	419 86.3% (83.0–89.3)	47 9.7% (7.2–12.6)	466 96.1% (93.9–97.6)
RBD–	15 3.1% (1.7–5.1)	4 0.8% (0.2–2.1)	19 3.9% (2.4–6.1)
Total	434 89.5% (86.4–92.1)	51 10.5% (7.9–13.6)	485 100%

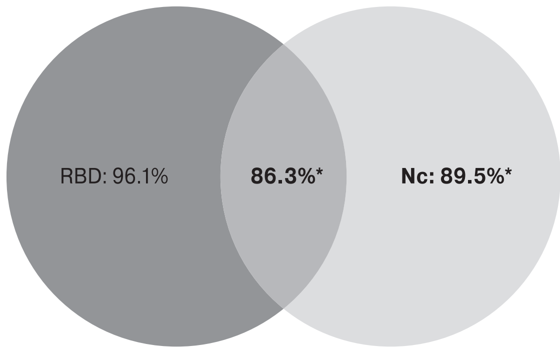


Figure 18. Structure of seropositivity (RBD, Nc) following completion of immunization with mRNA vaccines

Note. Right and left circles represent individuals seropositive for the Nc or RBD antigens, respectively. The central zone represents double-positive individuals (positive for both antigens). An asterisk indicates significantly lower compared to results with inactivated vaccines (Fig. 16).

84.6–89.0) and 50–59 years old (88.8%; 95% CI: 86.7–90.7). The minimums were among those 18–29 years old (70.2%; 95% CI: 66.7–73.6) and those 70+ (72.7%; 95% CI: 69.5–75.7) (Fig. 11). Among occupational groups, healthcare workers were almost completely vaccinated (95.0%; 95% CI: 94.1–95.9) (Fig. 12).

The whole-virion, inactivated Sinopharm/BIBP vaccine prevailed in the structure of vaccines used, with a share of 32.4%. CoronaVac and CoviVac were used less frequently (12.5% and 0.7%, respectively). In total, these designs amounted to 45.6%. In second place were the vector vaccines AZD1222 and Gam-COVID-Vac (Sputnik V, Sputnik Light), together accounting for 41.3%. Vaccines on the mRNA platform (mRNA-1273, BNT162b2) were used for immunization in 11% of cases. Whole-virion inactivated vaccines and vector vaccines were used for immunization mainly in the adult population, while the mRNA-1273 vaccine was more often used in children (Fig. 13).

All vaccines used were characterized by high efficiency in relation to the production of RBD Abs, 96.6% (95% CI: 96.1–97.1). Nucleocapsid Ab seroprevalence depended on the type of vaccine received. This indicator was higher with whole-virion vaccines (96.0%; 95% CI: 95.1–96.8), compared to vector vaccines (90.2%; 95% CI: 88.9–91.5), mRNA vaccines (89.5%; 95% CI: 86.4–92.1), or unvaccinated volunteers (90.2%; 95% CI: 88.7–91.6). The presence of Nc Abs in individuals immunized with vector or mRNA vaccines indicates that about 90.0% of such volunteers had likely experienced COVID-19 or perhaps asymptomatic infection.

The results show that the adaptive humoral immunity of volunteers, formed in response to the use of various vaccines of different origin, had a number of differences. After completion of full immunization, inactivated vaccine usage resulted in the largest proportion of double-seropositive individuals compared with other preparations (differences significant, $p < 0.001$). The lowest proportion of double-seropositive individuals was noted with usage of the mRNA-1273 preparation. This is likely related to a lower share of Nc+ individuals, which was significantly different when using vector or mRNA vaccines versus inactivated whole-virion preparations. It should also be noted that the vaccines used generated the same proportions of RBD seropositive. The reason for the noted features seems to be that inactivated vaccines contain the maximum set of viral antigens by design, unlike vector or especially mRNA preparations [22].

Conclusion

The results obtained indicate that the collective immunity of the Armenian population was close to 100% at the time of the study. There were no strong correlations with volunteer age, occupational status, or regional affiliation. Seropositivity was a hybrid phenomenon resulting from both a high number of convalescents and high vaccination coverage [4]. In almost 90.0% of volunteers, serological status reflected the simultaneous presence of antibodies to both antigens (Nc, RBD). Double positive status was understandably highest in convalescents who had received whole-virion vaccines at some point. It can be stated that the population of the Republic has reached the maximum level of collective immunity, a necessary prerequisite for stopping the epidemic spread of COVID-19.

Limitations of the study

The authors would like to note several factors that could affect the representativeness of the sample or the analytical results. Despite the fact that the information campaign was carried out as widely as possible for the population (state television channels, news sites, Facebook), there is a problem of limited internet access for parts of the rural population. In addition, residents who are more responsible for their health and the health of their loved ones (primarily women and healthcare workers) are more likely to take part in studies of this kind. Healthcare workers feature heightened awareness due to frequent contacts with COVID-19 patients. Since the study included an assessment of post-vaccination immunity, vaccinated residents were also more interested in participating. As such, the volunteer cohort's vaccination coverage was likely significantly higher than the national average. These factors may have resulted in greater representation of women, healthcare workers, and vaccinated residents.

Supplementary materials

Table 1S. Volunteer Questionnaire; Table 2S. Distribution of volunteers by occupation; Table 3S. Age distribution of seropositive volunteers by quantitative Nc Ab content; Table 4S. Age distribution of seropositive volunteers by quantitative RBD Ab content; Table 5S. Age distributions for the main vaccine types used. Tables are available at: http://dx.doi.org/10.15789/2220-7619-SCI-2450.

Author contributions

AYP, AVV — research planning and direction; AAT, NGB, RAA, SAE — research planning and coordination; AAM, GGM — organization of laboratory research; IVD, GOP, ASK — collection and sorting of laboratory samples; TVA, OVZ, OAP, AVG, APR — sorting and laboratory testing of samples; VAI — primary processing and analysis of results; VSS — statistical analysis of the results and preparation of the manuscript; AAT, SAE — approval of the manuscript; ESR — translation into English and editing.

Data availability statement

The authors confirm that the data supporting the findings of this study are available within the article and/or its Supplementary Materials.

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Conflicts of interest

The authors declare no conflict of interest.

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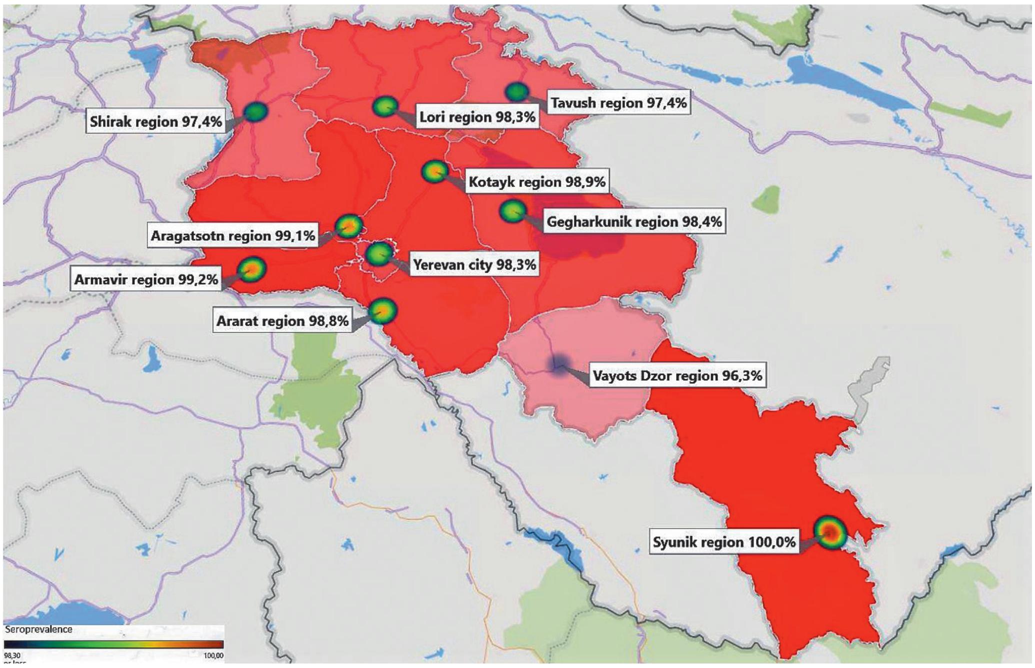

Figure 18. Heat map of the regional distribution of SARS-CoV-2 seroprevalence

Note. White boxes indicate seroprevalence levels (%). The color intensities of regions correspond to the percentage of seropositive individuals. The scale is shown in the lower left corner.