EVALUATION OF POPULATION-LEVEL IMMUNITY TO SARS-COV-2 ACROSS BULGARIA (END OF 2023)

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ABSTRACT

Background: The COVID-19 pandemic in Bulgaria was characterized by a high mortality rate and vaccination efforts yielded suboptimal results. Understanding population immunity is important as new SARS-CoV-2 variants continue to emerge. This study aimed to assess the seroprevalence of SARS-CoV-2 antibodies in the general population of Bulgaria and examine demographic variations in antibody presence.

Materials and methods: In December 2023, 1895 serum samples were randomly collected from healthy individuals across all 28 provinces. Samples were tested for SARS-CoV-2 spike protein-specific IgG antibodies using ELISA method. A subset of the positive samples was subsequently tested for neutralizing antibodies. Seroprevalence was analyzed by sex, age group, and geographic region. Statistical analyses were conducted using SPSS v.26.

Results: Overall seroprevalence was 91.9%, with similar rates between males (91.6%) and females (92.0%). Seroprevalence was highest in the 18-39 age group (95.1%) and lowest in those over 65 (89.3%). Regional seroprevalence ranged from 80.0% to 98.3%. Among samples tested for presence of neutralizing antibodies, 90.5% were positive, indicating effective immune response.

Conclusions: The high seroprevalence suggests widespread prior exposure to SARS-CoV-2 and/or vaccination among the Bulgarian population. The strong presence of neutralizing antibodies might provide potential protection against severe disease. Targeted interventions towards older age groups could be appropriate in order to sustain immunity as COVID-19 remains a public health concern.

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INTRODUCTION

The coronavirus disease 19 (COVID-19) pandemic began in early 2020 and was caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (1). In Bulgaria, the government quickly implemented various public health measures in order to control the spread of the virus including lockdowns, social distancing, and mass testing (2-6). A major breakthrough in the fight against the virus was the rapid development and implementation of vaccines, with the vaccination campaign in Bulgaria beginning at the end of 2020 (7).

Despite the introduced public health measures, Bulgaria's pandemic response was hindered by a combination of public misinformation and noncompliance, healthcare system weaknesses, vaccine hesitancy, and instability (8-11). These factors resulted in Bulgaria having one of the highest COVID-19 death rates and one of the lowest vaccination rates in Europe (12-15).

However, the true extent of the virus's spread, particularly among individuals who may have had mild or no symptoms, remains unclear. Seroprevalence studies are an important epidemiological tool in the efforts to understand the spread of the virus. These studies can be helpful in evaluating the actual exposure to the virus and they are also crucial for assessing the overall immunity of the population, whether acquired through natural infection or vaccination. This is especially important in the setting of low vaccination coverage and rising portion of vulnerable population in regards to respiratory diseases in the country.

The aim of this study is to estimate the proportion of the population that has developed antibodies against

SARS-CoV-2 and to identify demographic variations in seroprevalence across Bulgaria. By testing for specific IgG antibodies against the spike protein, both naturally acquired and vaccine-induced antibodies can be detected. Further testing for SARS-CoV-2 neutralizing antibodies helps in the assessment of the functional immunity in seropositive individuals. The seroprevalence data obtained can provide insight about the current state of immunity in the general population and guide strategies to mitigate future outbreaks.

MATERIALS AND METHODS

Serum samples (n=1895) were randomly collected from healthy citizens over 18 years of age from all 28 administrative Bulgarian provinces. Samples were collected in December 2023 by polyclinic laboratories from individuals visiting for routine health screenings. Information on the sex and age of participants was recorded. The study included 778 males and 1114 females and the mean age of participants was 54.79 (SD±17.20) years. For analysis of the results, participants were divided into three age groups: 18-39 (n=407), 40-64 (n=868), and over 65 years of age (n=620).

All samples were tested for specific IgG antibodies against the Spike (S) protein of SARS-CoV-2. Positive samples from nine provinces chosen at random (Burgas, Haskovo, Kardzhali, Pernik, Silistra, Sofia-region, Targovishte, Yambol and Vidin), were additionally tested for specific SARS-CoV-2 neutralizing antibodies. Both tests were conducted utilizing ELISA techniques with commercially available kits, according to the manufacturer's instructions. Screening for IgG antibodies was performed with Anti-SARS-CoV-2 ELISA (EI 2606-9601 G), Euroimmun, Germany, and neutralizing antibodies were tested with cPass SARS-CoV-2 Neutralizing antibody detection kit (L00847), GenScript, China.

The results for specific IgG antibodies were calculated semiquantitatively as a ratio between the extinction of the tested sample and the extinction of the calibrator. The interpretation of the results was as follows: positive, if the ratio was ≥1.1, and negative, if the ratio was <1.1. A ratio ≥ 0.8 to < 1.1 was interpreted as borderline. The presence of neutralizing antibodies was evaluated qualitatively as the result of signal inhibition (in percentages, %). Calculations were performed using the following formula: % Signal inhibition = 1-(OD of sample/OD value of Negative control) x 100, OD=optical density. Following the manufacturer's instructions, a cut off value of 30% was applied, with results considered negative when signal inhibition was <30% and positive when signal inhibition was ≥ 30%.

The statistical analyses were performed with IBM SPSS Statistics v.26. The Analysis of Variants (ANOVA) method was used to compare differences between the groups. A p-value <0.05 was considered statistically significant.

Ethical approval for this study was obtained from the Institutional review board at NCIPD (approval number 5/17.10.2023).

RESULTS

Presence of specific anti-SARS-CoV-2 IgG antibodies

Table 1. SARS-CoV-2 seropositivity among the Bulgarian population by December 2023.

		Tested samples, n	Positive and borderline, n (%)	95% CI	p
Age, years					
	18-39	407	**387 (95.1%)**	92.8-97.1	-
	40-65	868	**800 (92.1%)**	90.2-93.8	ns
	over 65	620	**554 (89.3%)**	86.5-91.5	0.003
Sex					
	male	778	**713 (91.6%)**	90.1-93.9	-
	female	1117	**1028 (92.0%)**	90.4-93.6	ns
Total		**1895**	**1741 (91.9%)**	**90.7-93.2**	

CI=Confidence Interval

Table 2. COVID-19 prevalence in Bulgaria (December 2023).

Province	Tested samples, n	Positive samples, n	Seroprevalence, %	95% CI
Overall	**1895**	**1741**	**91.9%**	**90.7-93.2**
Blagoevgrad	63	61	96.8%	92.3-99.9
Burgas	96	92	95.8%	92.1-99.9
Dobrich	60	55	91.7%	85.1-98.8
Gabrovo	95	88	92.6%	87.9-98.1
Haskovo	100	91	91.0%	85.3-96.6
Kardzhali	65	61	93.8%	88.2-99.8
Kyustendil	50	42	84.0%	73.8-94.1
Lovech	60	59	98.3%	94.4-99.9
Montana	60	53	88.3%	79.8-96.2
Pazardzhik	100	93	93.0%	88.0-98.0
Pernik	70	56	80.0%	70.6-89.3
Pleven	60	58	96.7%	91.0-100
Plovdiv	70	65	92.9%	87.0-98.9
Razgrad	60	58	96.7%	91.0-100
Ruse	60	51	85.0%	76.0-94.0
Shumen	82	77	93.9%	88.7-99.1
Silistra	60	54	90.0%	82.4-97.6
Sliven	60	58	96.7%	92.3-100
Smolyan	60	59	98.3%	94.4-100
Sofia	60	55	91.7%	85.1-98.9
Sofia-region	80	69	86.3%	78.4-93.6
Stara Zagora	60	54	90.0%	82.4-97.6
Targovishte	80	76	95.0%	90.2-99.8
Varna	60	55	91.7%	85.1-98.9
Veliko Tarnovo	64	56	87.5%	78.8-95.2
Vidin	40	38	95.0%	88.2-99.9
Vratsa	60	58	96.7%	91.0-100
Yambol	60	49	81.7%	72.3-91.7

CI=Confidence Interval

was detected in 91.9% (1741/1895) of the tested population. Of those, 89.5% (1697/1741) were positive and 2.4% (44/1741) – borderline. No specific antibodies were detected in 8.1% (154/1895) of participants. Results are presented in Table 1.

The seroprevalence among male and female participants was similar, with 91.6% (713/778) of males and 92.0% (1028/1117) of females testing positive or borderline for anti-SARS-CoV-2 antibodies. A slight decline in seropositivity was observed across the three age groups: 95.1% (387/407) in the 18-39 age group; 92.1% (800/868) in the 40-64 age group and 89.3% (554/620) among participants aged 65 years and older. Statistically significant differences were found between the first and the third group (p=0.003).

The COVID-19 seroprevalence across the Bulgarian provinces ranged from 80.0% to 98.3%. The lowest seroprevalence rates (<85%) were detected in Pernik, Yambol, Kyustendil and Ruse. The highest seroprevalence rates (>95%) were found in Burgas, Pleven, Razgrad, Sliven, Vratsa, Blagoevgrad, Lovech and Smolyan. Details for each province are given in Table 2.

We further tested for presence of virus neutralizing antibodies in 571 of the positive samples from

Table 3. SARS-CoV-2 virus neutralizing antibodies in samples, positive for presence of specific anti-S IgG antibodies.

		Tested samples, n	Positive, n (%)	95% CI
Age, years				
	18-39	126	**115 (91.3%)**	87.3-96.7
	40-65	262	**241 (92.0%)**	88.7-95.3
	over 65	183	**161 (88.0%)**	83.3-92.7
Sex				
	male	231	**209 (90.4%)**	86.1-93.9
	female	340	**308 (90.5%)**	86.8-93.2
Total		**571**	**517 (90.5%)**	**87.5-92.5**

randomly selected provinces and confirmed neutralization activity in 90.5% (517/571). The demographic patterns were parallel to those for the specific anti-spike IgG antibodies: similar results were seen between males and females, while across the age groups, the same tendency for decline of the immune response with age was observed (Table 3). However, no significant differences were found between the age groups.

DISCUSSION

In this study, an overall 91.9% seroprevalence rate of SARS-CoV-2 at the end of 2023 was found across the general population of Bulgaria with high prevalence rates observed in all provinces. These results suggest that a significant proportion of the Bulgarian population has either been exposed to the virus and/or has been vaccinated. Taking into consideration the relatively low vaccination rate in the country, with only about 30-31% of the total population having completed the primary vaccination series (16), this finding is probably a reflection of a widespread natural infection. A high proportion (90.5%) of the samples tested for neutralizing antibodies against SARS-CoV-2 were positive, meaning that the antibodies present are effective in preventing cell attachment and replication of the virus. Therefore, despite the challenges faced during the vaccination campaign, a high level of antibody presence in the population has been achieved, which might provide some protection against severe outcomes in cases of reinfection (17-20).

No significant differences were found between male and female participants which echoes findings from previous studies (21-23). In general, the differences in antibody prevalence by sex observed in the literature have not been consistent (24, 25) and systematic and meta-analysis studies have established that sex is not significantly associated with presence of anti-SARS-CoV-2 antibodies (26, 27).

The relatively lower seroprevalence rate observed in the older population (>65 years) might be due to different factors, including a weaker immune system and fewer social interactions in high-risk settings. This result suggests that additional immunization efforts in this demographic group could be beneficial for maintaining effective protection against the virus. On the other hand, the relatively higher prevalence in the 18-39 and 40-65 age groups may be attributed to the fact that these individuals are more likely to be socioeconomically and socially active. While similar findings have been observed in previous studies (27, 28) other reports have found that higher seroprevalence rates were associated with older age (24,29,30). However, most of those studies were conducted in 2020 and 2021 when older individuals were more likely to have been recently exposed to the virus or vaccinated and their antibody levels had not started to wane yet. It should also be taken into consideration that older individuals were often prioritised during the early stages of COVID-19 vaccination campaigns in many countries.

Many studies have been conducted on the durability of antibody response against SARS-CoV-2, mostly concluding that antibodies remain detectable at least 3-6 months after infection (20,31,32). Some studies

have found that anti-SARS-CoV-2 IgG antibodies could remain positive over 1 year in convalescent individuals (33-35). In Bulgaria, the last significant COVID-19 peak was seen at the end of 2022 and the beginning of 2023 (36). Afterwards, with the declining number of cases, COVID-19 started fading from media and social consciousness, and thus, testing and vaccination rates significantly decreased. Despite that, new SARS-CoV-2 variants continued to emerge and circulate among the population, including the EG.5 descendant lineage of XBB.1.9.2 and BA.2.86 (37, 38). In this study, samples were collected at the end of 2023, but it is difficult to say whether the observed results could be attributed to a robust long-lasting immunity or were due to new cases passing undetected throughout the year. One of the limitations of our study is the lack of epidemiologic data regarding past infections and immunizations of the participants. Another limitation of the study is the lack of longitudinal follow-up which hinders the deeper understanding of the duration and stability of SARS-CoV-2 specific immunity.

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