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Original article

ANTI-SARS-COV-2 ANTIBODIES IN MACEDONIAN HEALTHCARE WORKERS: AN INTERIM ANALYSIS

Tosheska-Trajkovska Katerina[1], Babacic Haris[2], Toseska-Spasova Natasa[3], Kostovska Irena[1], Bogdanska Jasna[1], Labudovikj Danica[1], Cekovska Svetlana[1], Brezovska Julijana[1], Ampova Hristina[1], Emin Melda[1], Stanojevska-Petrusevska Elena[1], Topuzovska Sonja[1]

[1]Department of Medical and Experimental Biochemistry, Faculty of Medicine, Ss. Cyril and Methodius University in Skopje, R.N. Macedonia
[2]Karolinska Institute, Stockholm, Sweden
[3]Department of Orthodontics, Faculty of Dentistry, Ss. Cyril and Methodius University, Skopje, R.N. Macedonia
e-mail: *katerina.tosheska.trajkovska@medf.ukim.edu.mk*

Abstract

Introduction. The spectrum of COVID-19 in adults ranges from asymptomatic infection to mild respiratory tract symptoms to severe pneumonia with acute respiratory distress syndrome (ARDS) and multiorgan dysfunction.

Healthcare workers (HCWs) are exposed to the virus at a greater extent than society as a whole and may be considered at an elevated risk of infection.

The aim of the study was to estimate the seroprevalence of SARS-CoV-2 antibodies among HCWs all over the territory of North Macedonia.

Material and methods. In this interim analysis, we included 2,334 healthcare workers (HCW), who were tested for serum IgM and IgG antibodies to SARS-CoV-2 virus during the period from 28/05/2020 to 20/08/2020.

Chemiluminescent (CLIA) analytical system was used for detection of anti SARS CoV-2 IgM and IgG antibodies.

Results. A total of 195 HCWs, out of 2,334, tested positive for either IgM or IgG anti-SARS-CoV-2 serum antibodies (IgM/G+). Of these, 167 individuals tested positive for IgM antibodies (IgM+) and 54 tested positive for IgG antibodies (IgG+). Based on these data, the cumulative incidence of anti-SARS-CoV-2 antibodies in HCWs during the period from 28/05/2020 to 20/08/2020 was estimated at 8.355% (95% CI = 7.279-9.57%).

Conclusions. HCWs represent a population at high risk of contracting COVID-19. To decrease the risk of SARS-CoV-2 infection, absolute adherence to infection preventive measures is needed: proper use of face masks at all times in the workplace, avoiding of overcrowding in different working spaces, and keeping a recommended distance in meetings, clinical handouts and work meals. Early identification and isolation of infected HCWs is highly recommended.

Keywords: SARS-CoV-2, COVID-19, healthcare workers, IgM, IgG antibodies

Introduction

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is responsible for coronavirus disease-2019 (COVID-19). Coronaviruses are important human and animal pathogens. At the end of 2019, a novel coronavirus was identified as the cause of atypical pneumonia cases in Wuhan, a city within the Hubei Province of China. It rapidly spread, resulting in an epidemic throughout China, followed by an increasing number of cases in other countries throughout the globe. The World Health Organization (WHO) declared COVID-19 to be a pandemic on March 11, 2021. Quarantine measures, including closed borders and "lock-down" in many countries, were instituted in January 2020 to prevent spread of the virus.

The first laboratory confirmed case of COVID-19 infection in the Republic of North Macedonia was observed in February 2020, escalating to 152,367 cases and 4,855 deaths as of 30 April 2021.

COVID-19 is a health emergency, with enormous impact on society, global health care systems and the affected individuals. The spectrum of symptomatic infection ranges from mild to critical. One of the most feared complications is acute respiratory distress syndrome (ARDS), due to its high mortality and can manifest shortly after the onset of dyspnea. But, there are cases when many patients can be asymptomatic, which increases the uncertainty of the diagnostic work-up[1]. The timely diagnosis of COVID-19 infection is the cornerstone of appropriate treatment of patients and it is important for limiting further spread of the virus, because particularly asymptomatic or mildly symptomatic subjects may be responsible for virus transmission[2]. The incubation period from the time of exposure until the onset of symptoms is four to five days on average, but could also be as long as 14 days. So, testing assumes critical relevance for ensuring a good response to COVID-19 outbreak. The gold standard for the diagnosis of SARS-CoV-2 infection is (real time) reverse transcriptase polymerase chain reaction (rRT-PCR)[3-5].

Detection of specific antibodies, particularly anti-SARS-CoV-2 IgM and IgG, should be used as an additional method for diagnosis of the disease, especially in patients who present late, or who have negative PCR results but characteristic symptoms of COVID-19. However, the timing of requests for serological assays and the interpretation of antibody results are pre-requisites of crucial importance in their efficacy[6].

Serological population-based studies provide a useful tool in the estimation of the number of individuals who have been infected with the SARS-CoV-2 virus. Healthcare workers (HCWs) are exposed to the virus at a greater extent than others within the society and they are at higher risk of infection[7].

Little is, however, known about the occupational risk of HCWs to SARS-CoV-2 infection, but the few emerging studies report relatively low seroprevalences, ranging from 1.6% to 11.0% [8-10].

The aim of the study was to estimate the seroprevalence of SARS-CoV-2 antibodies among HCWs all over the territory of North Macedonia.

Material and methods

In this interim analysis, we included 2,334 healthcare workers (HCWs), who were tested for serum IgM and IgG antibodies to the SARS-CoV-2 virus. The process of collecting data on the remaining HCWs is ongoing.

The serum samples included in this analysis were collected during the period from 28/05/2020 to 20/08/2020, by sequential sampling, with HCWs voluntarily requesting a test. The HCWs from 13 cities of North Macedonia signed up for testing: Valandovo, Bitola, Prilep, Makedonski Brod, Gevgelija, Radovish, Negotino, Kumanovo, Kichevo, Veles, Sveti Nikole, Shtip, and Skopje. Almost half of the samples (n = 1,155; 49.49%) were collected in Skopje, the capital of the country. The sampling occurred in primary, secondary, and tertiary health care facilities.

The MAGLUMI™ 800 (New Industries Biomedical Engineering Co., Ltd [Snibe], Shenzhen, China) is a chemiluminescent analytical system (CLIA), featuring high throughput (up to 100 tests/h). According to the manufacturer the 2019-nCoV IgM and 2019-nCoV IgG cut-off is 1.0 AU/mL and the calculated sensitivities of IgM and IgG were 78.65% and 91.21%, respectively, while specificities of IgM and IgG were 97.50% and 97.3%, respectively.

Results

The HCWs were grouped in four categories according to their workplace: medical doctor/physician/dentist (n = 770, 33%), medical nurse/technician or laboratory technician (n = 978, 42%), administrator (n = 297, 13%), and cleaning personal/courier/driver (n = 286, 12%).

Most of the HCWs were women (n = 1,676, 71.87%), and 656 were men (28.13%), with 2 missing values. Information of age was available for 2,332 HCWs. The mean age of the subjects was 45.23 years old (median: 46, SD[1]: 11.31), ranging from 19 to 70 years old. For age-specific estimates of incidence, subjects were categorised in age groups: 19-29 (n = 258, 11.12%), 30-39 (n =504, 21.72%), 40-49 (n = 622, 26.81%), 50-59 (n = 672, 28.97%), and 60+ years old (n = 264, 11.38%). Workplace information was available for almost all HCWs, with only 2 missing values.

A total of 195 HCWs, out of 2,334, tested positive for either IgM or IgG anti-SARS-CoV-2 serum antibodies (IgM/G+). Of these, 167 individuals tested positive for IgM antibodies (IgM+) and 54 tested positive for IgG antibodies (IgG+). This indicates that most of the HCWs requested a test early on during the development of coronavirus disease 19 (COVID-19).

Based on these data, the cumulative incidence of anti-SARS-CoV-2 antibodies in HCWs during the period from 28/05/2020 to 20/08/2020, is estimated at 8.355% (95% CI[2] = 7.279-9.57%).

Stratifying for sex, women had a slightly higher cumulative incidence of 8.532% (95% CI = 7.260-9.998%) compared to the incidence in men, estimated at 7.923% (95% CI = 6.029-10.332). However, the findings were not statistically significant ($p = 0.678$, Fisher's test).

Stratifying for age groups, a trend of minor increase in incidence was observed with the increasing age (Figure 1), but this was not true for the age group of 30-39 years old, which had a similar incidence as the oldest age group (60+). However, the 95% CI overlap, showed that there was no difference in incidence in difference age groups. Cumulative incidence per workplace is presented in Figure 2.

[1] SD = standard deviation
[2] CI = confidence intervals

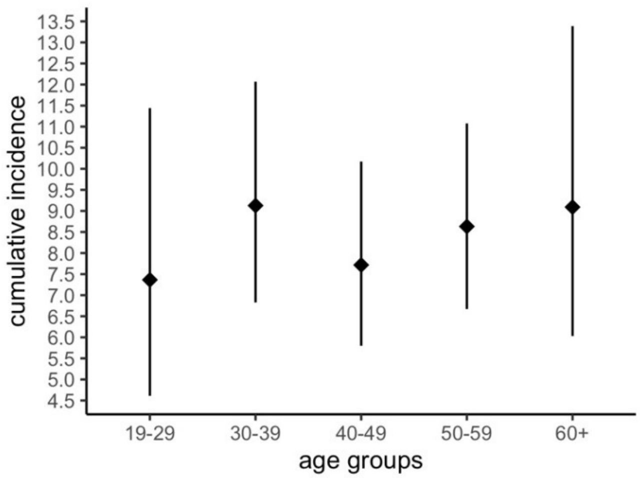

Fig. 1. Cumulative incidence per age groups. The dots represent the estimated incidence during the period 28/05/2020 – 20/08/2020. The lines represent the 95% CI, i.e., the interval in which the true value of the estimate might be.

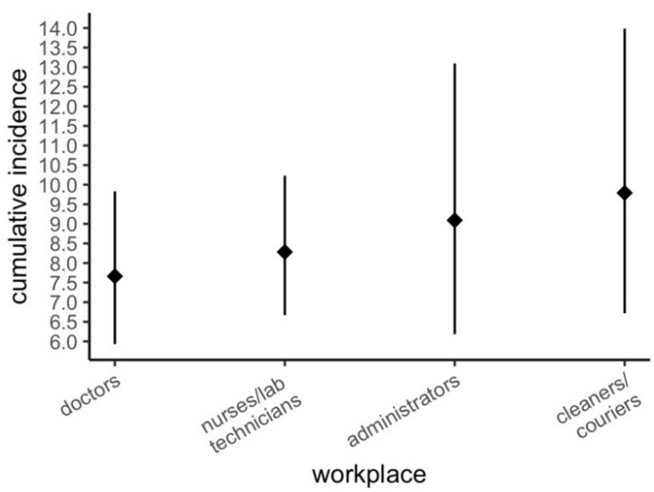

Fig. 2. Cumulative incidence per workplace. The dots represent the estimated incidence during the period 28/05/2020 – 20/08/2020.The lines represent the 95% CI, i.e., the interval in which the true value of the estimate might be.

Based on the estimates of positive predictive value (PPV) and negative predictive value (NPV), Table 1 shows a number of false positives and false negatives, and suggests a corrected incidence estimate at 8.654% (95% CI: 7.561-9.887%).

Table 1. Contingency tables estimating the false positives and false negatives, i.e., how many individuals would have been positive of those who did not have the disease, and how many individuals who had the disease tested negative.

COVID-19			
TEST	**Present**	**Absent**	**Total**
Positive	150	45	195
Negative	52	2087	2139
Total	202	2132	2334

Discussion

Surveillance of infectious diseases is a critical public health need and estimation of overall prevalence and incidence of new infections is of imminent importance in this process.

There is a high variability in the seroprevalence of SARS-CoV-2 antibodies in the population-based studies in the USA, ranging from 1.1% to 14.4%[7-11]. On the other hand, studies in Europe[12-14] and China[15] show different seroprevalence in the general population, ranging from 0.23% to 10.9%. In studies conducted in North America seroprevalence was 12.7% compared to studies conducted in Europe (8.5%), Africa (8.2%) and Asia (4%)[16].

Sahu *et al.*[17] found that the proportion of HCWs who were SARS-CoV2 positive was lower in China (4.2%) compared to USA (17.8%) and Europe (9%). Due to previous infections with SARS virus, HCWs in China were prepared for new infection and readily implemented preventive measures against infection and appropriate use of personal protective equipment. On the contrary, during the first months of the COVID-19 pandemic the knowledge in USA and Europe was limited and HCWs were unprepared to handle the situation.

In the study of Rudberg *et al.*[18] 2,149 healthcare workers were recruited between April 14th and May 8th 2020 and the seroprevalence of IgG antibodies against SARS-CoV-2 was 19.1%.

Our study showed that the cumulative incidence of anti-SARS-CoV-2 antibodies in HCWs, during the period from 28/05/2020 to 20/08/2020, is estimated at 8.355% (95% CI = 7.279-9.57%).

Based on the estimates of positive predictive value (PPV) and negative predictive value (NPV) from Plebani *et al.*[19] we found a similar number of false positives and false negatives that suggests a corrected incidence estimated at 8.654%. Taking a conservative approach in correcting the values based on estimates of sensitivity and specificity of Plebani *et al.*[19], gives a similar incidence estimate of 8.783% (95% CI: 7.681-10.023%).

The estimates of antibody incidence and prevalence are always affected by the performance of an assay, i.e., the sensitivity and specificity. Recently, a large study on 3,000 HCWs in Veneto, Italy, has also validated the performance of the SNIBE chemiluminescence method for measuring anti-SARS-CoV-2 antibodies, reporting a high accuracy of 97%, with sensitivity of 73% and specificity of 98%[19].

Several studies emphasized the risk of occupational transmission of SARS-CoV-2 among HCWs[20-25]. The risk for transmission of the virus is bidirectional: working with infected patients represents a high risk for HCWs, and, in the opposite direction, infected HCWs could transmit the infection to patients, other HCWs, family members and the community. Clinical meetings and shared use of small work spaces are potential places for transmission between HCWs. Infected and ill HCWs could cause problems due to understaffing in the health system, too.

Interesting enough, in our study the incidence seemed lower among medical HCWs compared to the non-medical staff of administrators, cleaners, couriers, and drivers, albeit statistically not significant ($p = 0.662$). The difference can be driven by the smaller sample size among the non-medical staff, which tends to overestimate incidence. Still, the effect could be true because medical HCWs are better trained at protecting themselves and have better access to protective gear. Rigorous use of personal protective equipment and absolute adherence to all preventive measures are crucial to reduce nosocomial transmission of SARS-CoV-2[26-29].

According to Grant *et al.* seropositivity was lower among HCWs in ICUs[30]. There are several possible explanations of this finding, such as the proper use of the personal protective equipment for HCWs in ICUs and the fact that patients who require ICU admission are mostly admitted around day 10 of their illness[29,30], by which point the viral load is usually not very high[30].

Household contact with a suspected or confirmed case of COVID-19 is associated with a positive SARS-CoV-2 antibody test in HCWs[31-34]. As transmission in the community increases, the risk of SARS-CoV-2 exposure for HCWs is higher outside clinical setting.

Our study has several limitations. Seroprevalence is dynamic, and the data presented in this study represent the prevalence in May-August 2020. A new study will yield different results. Participation in the study was on voluntary basis, and a selection bias cannot be excluded.

Conclusion

We can conclude that HCWs represent a population at a high risk of contracting COVID-19. To decrease the risk of SARS-CoV-2 infection, early identification and isolation of infected HCWs is highly recommended. Absolute adherence to infection prevention is needed: proper use of face masks at all times in the workplace, avoiding of overcrowding in different working spaces, and keeping a recommended distance in meetings, clinical handouts and work meals.

From the lessons learned during the SARS-CoV-2 pandemic, we could try to provide a roadmap for the response to future outbreaks.

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