DARIA BURDALSKA[1], ADAM KONKA[1], SZYMON WOROSZYŁO[1], KLIWIA PIÓRKOWSKA[1], JOANNA ZEMBALA-JOHN[1,2,3], MARLENA GOLEC[1], MARTYNA FRONCZEK[1,4], RAFAŁ JAKUB BUŁDAK[1,5]

SARS-CoV-2 antibody screening in healthcare workers: lessons learned from the first months of COVID-19 outbreak in Europe. Significance of serology testing for effective pandemic management and reduction of the occupational risk

Abstract

Introduction. Detected in 2019 in Wuhan, China, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), causing a coronavirus disease 2019 (COVID-19), has changed almost all aspects of human lives. It has had an enormous impact on societies, economies and politics across the world. Nevertheless, first and foremost, it has led to a global health crisis on an unprecedented scale. Since the pandemic's beginning, one of the greatest global challenges has been to stop the spread of infection among healthcare workers (HCWs). As a front-line fighters, they are at higher risk of contracting SARS-CoV-2 than other professions.

Aim. The study aimed to determine the role of serological testing among HCWs by analyzing screening results for the presence of SARS-CoV-2 antibodies in this group in 12 European countries during the first wave of the pandemic.

Material and methods. Pubmed, MEDLINE, Web of Science, Google Scholar, and WHO COVID-19 databases were searched for studies on screening among HCWs using immunoassays or chemiluminescence assays for preventive purposes and determining the percentage of HCWs with acquired immunity to SARS-CoV-2. The number of 30 papers were selected. Immunoglobulin G (IgG) percentage was analyzed, and determination of immunoglobulin A (IgA) and immunoglobulin M (IgM) antibodies and their diagnostic usefulness.

Results. The screening results of HCWs were juxtaposed with epidemic situation of that time and public health measures in given country.

Conclusion. Introduction of routine serological testing of HCWs could be a valuable strategy to monitor the occupational risk in this group and effectiveness of local epidemic management strategies.

Keywords: SARS-CoV-2, COVID-19, serologic test, health personel, seroprevalence, IgG antibody.

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INTRODUCTION

At the end of 2019, the world has faced a formidable challenge due to the detecting in Wuhan, China, a new pathogen – severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), causing coronavirus disease 2019 (COVID-19) [1,2]. On March 11, 2020, three months after confirming the first official case, the World Health Organization (WHO) announced the COVID-19 outbreak as a pandemic. On that day there were 118 000 confirmed infections worldwide [3]. By June 9, 2020, number of global cases rose to 7 069 278, including 405 587 deaths, and in the European Economic area countries and United Kingdom 1 444 710 cases (20.00% of global cases), including 169 207 deaths (42.00% of all global deaths) were reported [4].

The COVID-19 outbreak has affected almost all aspects of human lives. On the micro-level, it has profoundly changed our behaviors and lifestyle. On the macro – it has had an enormous impact on societies, economies and politics. Nevertheless, first and foremost, it has led to a global health crisis on unprecedented scale. It has resulted in millions of lives lost, weakening public health, and pushing healthcare systems worldwide to the brink.

Since the pandemic's beginning, one of the greatest challenges for national governments has been to stop the spread of infection among healthcare workers (HCWs). They play a crucial role in response to the COVID-19, but, at the same time, as a front-line "coronafighters", they are at higher risk of contracting SARS-CoV-2 in comparison to other professions. Each HCW's absence weakens the healthcare system and may result in less effective treatment of COVID-19 and non-COVID-19 patients. A significant threat in uncontrolled virus spread poses asymptomatic SARS-CoV-2 infection [5]. This form of the disease is particularly dangerous when it refers to HCWs: it may lead to unconscious transmission of

[1] Silesian Park of Medical Technology Kardio-Med Silesia, Zabrze, Poland
[2] Chair and Department of Medicine and Environmental Epidemiology, Faculty of Medical Sciences in Zabrze, Medical University of Silesia in Katowice, Zabrze, Poland
[3] Silesian Center for Heart Diseases in Zabrze, Zabrze, Poland
[4] Department of Pharmacology, Faculty of Medical Sciences in Zabrze, Medical University of Silesia in Katowice, Zabrze, Poland
[5] Department of Clinical Biochemistry and Laboratory Diagnostics, Institute of Medical Sciences, University of Opole, Poland

the virus within medical facilities, among medical staff and from HCWs to patients, and - in a consequence – contribute to the dramatic collapse of the whole healthcare system. The studies on screening, conducted during the first wave, indicate that 15.60% of cases are asymptomatic, and almost 50.00% – asymptomatic in the early stage of infection [6]. HCWs' compliance with safety protocols and use of personal protective equipment (PPE) alone may be insufficient to eliminate the risk of contracting and transmitting COVID-19. Seroprevalence studies conducted in this group during the first months of the pandemic revealed specific anti-SARS-CoV-2 antibodies in up to 11.00% of HCWs [7]. Hence, widespread routine testing of HCWs is critical in identifying pre-symptomatic or asymptomatic cases and reducing the likelihood of COVID-19 transmission in this community.

AIM

The main aim of this study was to investigate data related to the determination of anti-SARS-CoV-2 antibodies among HCWs in selected European countries during the first months of the COVID-19 epidemic. Results of this work may contribute to designing an optimal epidemic management strategy for this group.

MATERIAL AND METHODS

Data source and search strategy

A literature search was conducted using Pubmed, MEDLINE, Web of Science, Google Scholar, and WHO COVID-19 databases, using keywords: health care workers, medical personnel, SARS-CoV-2, COVID-19, seroprevalence, antibody detection, immunoglobulin G (IgG) antibodies, seroconversion, anti-SARS-CoV-2 IgG, immune response SARS-CoV-2, antibody test, serological test. In addition, an advanced search builder was used to maximize the results: (SARS-CoV-2) AND (antibody screening) AND (healthcare professionals), (SARS-CoV-2) AND (HCWs) AND (antibody detection), (SARS-CoV-2) AND (antibody test) AND (HCWs). A detailed search strategy was presented in Figure 1.

Out of 683 publications found, 549 (80.40%) were considered irrelevant after the title and abstract screening. The exclusion criteria were: research conducted after August 31, 2020, and studies carried out in non-European populations. In addition, studies using rapid immunochromatographic cassette tests for COVID-19 diagnostics were removed (due to their low sensitivity and specificity coefficient). Initially, 134 (19.60%) articles were included. They described antibody testing results in professionally active HCWs, working in diverse establishments, performed using a serum antibody test (including enzymatic immunosorbent tests and chemiluminescent immunoassays). Eventually, 30 (22.40%) papers most relevant to the topic and conducted among HCWs working in hospitals in 12 selected European countries, were included, constituting 4.40% of all articles found.

The screening results were juxtaposed with the epidemic situation of that time in each country described. The COVID-19 data was obtained from the European Centers for Disease Control and Prevention (ECDC) website [8].

Diagnostic methods of SARS-CoV-2 detection

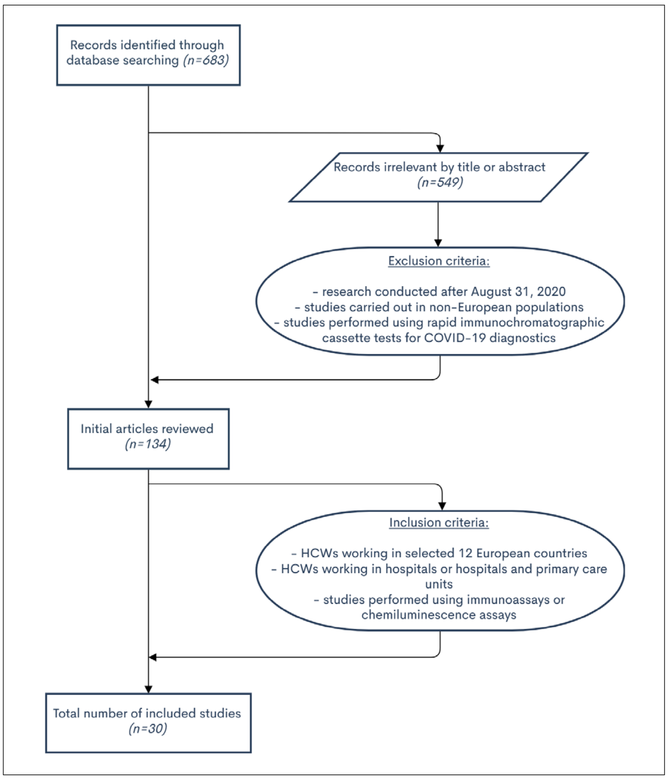

FIGURE 1. Search strategy of publications about antibody screening in healthcare workers.

Currently, three testing technologies are used to detect SARS-CoV-2 infection: molecular (e.g., Reverse Transcriptive – quantitative Polymerase Chain Reaction, RT-qPCR), antigen, and serological tests (e.g., ELISA). The first two allow detecting the presence of coronavirus in the organism, the latter – the presence of COVID-specific antibodies – a result of exposure to pathogen, infection or vaccination.

It must be stressed that those tests differ regarding, i.a., recommended application time and reliability (sensitivity and specificity). Sensitivity (true-positive rate) is the ability of the test to diagnose the disease correctly. Specificity is the ability of the test to detect people who are actually healthy [9].

$$Specificity\ (\%) = 100\ \frac{true\ negative}{true\ negative + false\ positive}$$

$$Sensitivity\ (\%) = 100\ \frac{true\ positive}{true\ positive + false\ negative}$$

Knowledge about the pros and cons of each test type, its specificity and sensitivity, seroconversion, application time, is crucial in proper diagnostics of COVID-19 and detection of state immunity (IgG) in convalescent cases [10]. Dependence between the infection stage and detection capability using different tests is shown in Figure 2.

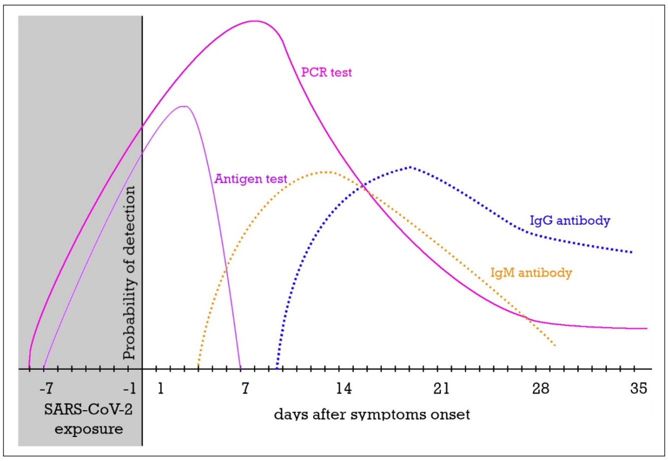

FIGURE 2. Probability of detection SARS-CoV-2 after symptoms onset by different methods [10].

From the symptom onset, the median for anti-SARS-CoV-2 seroconversion for IgA, IgM, and IgG antibodies is 11, 12, and 14 days, respectively [11]. Whereas, it is unclear whether combining detection of IgM/IgG and IgA is diagnostically useful. In a study by Bułdak et al., all IgM and IgA positive HCWs were tested for SARS-CoV-2 RNA by RT-qPCR. 100.00% of samples were negative; therefore, the diagnostic utility of IgA and IgM antibodies was not confirmed. It is worth noting that in abovementioned study, all positive IgM or IgA sera were collected from asymptomatic HCWs [12]. In other studies, the correlation between IgA serum concentration and severity of SARS-CoV-2 RNA positive was observed. Generally, the higher IgA titers, the more severe illness course [13,14].

On the other hand, Bułdak et al., in their work revealed no statistical significance between positive antibody outcomes and symptoms. To increase the credibility of the outcomes in this research and avoid potential "serological window", the blood was drawn twice [12]. It should be noted that in Bułdak et al.'s work, reagents were more immunogenic (S1 domain) than in study by Huang et. al. and Guo et. al (Nucleocapsid protein), thereby results obtained from tests with different epitopes with no equal immunogenicity shall not be compared [12,14,15].

The WHO and national guidelines recommend performing serological tests for specific purposes: to evaluate the concentration of antibodies in individuals donating plasma for therapeutic purposes (IgG antibodies specific to the SARS-CoV-2 virus S protein), to assess the immune response following vaccination in patients with immunodeficiency or during immunosuppressive treatment (IgG antibodies specific for SARS-CoV-2 S protein), for retrospective diagnostics of SARS-CoV-2 infections (to estimate the number or percentage of people exposed to the virus), as well as in the population studies. It is worth noting that a positive serological test result may indicate exposure to the coronavirus or vaccination and cannot be used to diagnose a current SARS-CoV-2 infection or infer contagiousness [16]. Whereas, it is not recommended to use qualitative, so-called rapid cassette (immunochromatographic) tests for detecting anti-SARS-CoV-2 antibodies due to limited usefulness, low diagnostic sensitivity and specificity, and high risk of false negative and false positive results [16].

RESULTS

Prevalence of antibodies against SARS-CoV-2 in European HCWs

This paper focuses on antibodies screening using immunoassays and/or chemiluminescence assays, performed during the months of COVID-19 pandemic in Europe among HCWs to prevent viral transmission in medical settings and define the percentage of HCWs with immunity to SARS-CoV-2. Studies included in this review are listed in Table 1.

Comparison of COVID-19 new daily cases and deaths per 100 000 individuals in chosen European countries is shown in Figure 3 and Figure 4. Based on the daily number of new confirmed infections per 100 000 inhabitants, selected countries were divided into 3 groups [4]:

- I: Sweden, Belgium, and Spain: 2.50-4.00 daily number of new confirmed infections per 100 000 inhabitants
- II: the United Kingdom, Italy, Switzerland: 2.00-2.50 daily number of new confirmed infections per 100 000 inhabitants
- III: France, Germany, Austria, Norway, Poland, Greece: <0-2.00 daily number of new confirmed infections per 100 000 inhabitants.

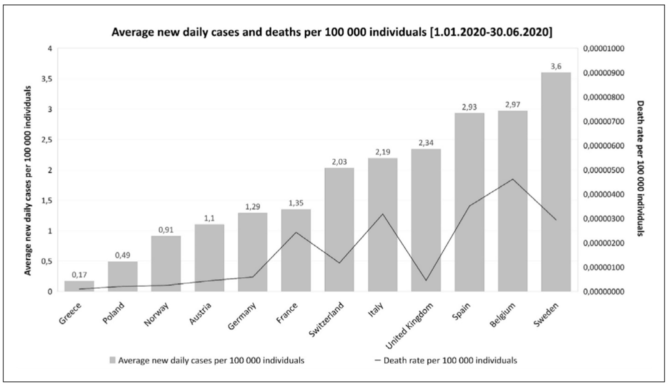

FIGURE 3. Average of new daily cases and deaths per 100 000 individuals in described European countries [4].

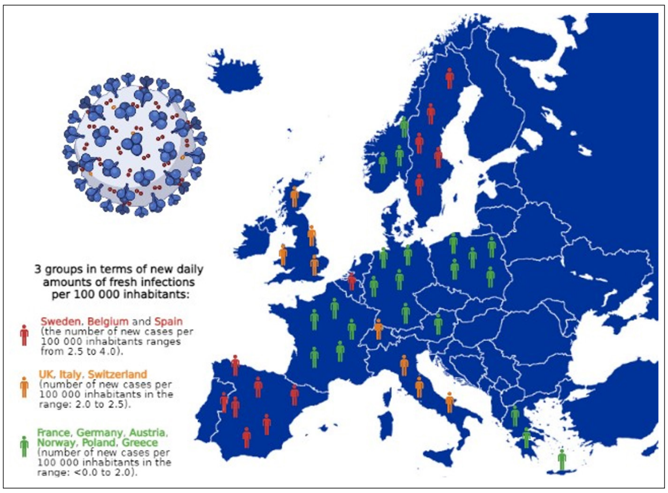

FIGURE 4. Daily amounts of fresh infection per 100 000 inhabitants during the first wave COVID-19 outbreak in Europe (selected countries). The countries most affected by the SARS-CoV-2 virus epidemic are marked in red, the countries that have coped better with suppressing the outbreak of infection are marked in orange. Countries with the lowest percentage of infections in the selected time period are marked in green.

Analysis of incidence and mortality data, presented in Figures 3, reveals great discrepancy in terms of seroprevalence rate and the number of daily new cases and deaths among selected countries.

One of the possible explanations of this phenomenon is different from country to country, number of tests performed and the rules for testing symptomatic/asymptomatic individuals. In addition, at the beginning of the pandemic, the RT-qPCR was considered qualitatively comparable to the antigen test, which could affect outcomes reliability.

Not without significance are different public health polices introduced in response to COVID-19 and societies' compliance to the imposed pandemic restrictions in selected countries.

I group: Sweden, Belgium, Spain – epidemiological strategies and seroprevalence of SARS-CoV-2 in HCWs

Since the pandemic's beginning, Sweden has adopted different than other European countries' policy against SARS-CoV-2: based on mutual trust and close partnership between authorities and the society. Its strategy aimed to stop the spread of infection and protect the elderly and vulnerable from the infection, but – contrary to other nations – while building a herd-immunity to COVID-19 and achieving quickly high seroprevalence in the general population.

The Swedish government has not implemented a full national lockdown: instead, it set basic recommendations (i.a., on hand washing, social distancing, isolation only for suspected/infected individuals) and focused on sustaining a viable healthcare system and stable economic [5,17].

Swedish strategy of keeping the society open has been both criticized and praised by the experts and public opinion. Although the mortality due to COVID-19 was higher than expected, especially among the elderly, this model seemed to be more effective than others during the first wave. Moreover, unlike in other countries, Swedish healthcare system had not become overwhelmed, and intensive care units' capacity – exhausted [17] Therefore, patients had not faced the consequences of healthcare disruption. However, wide spread of COVID-19, also within medical facilities, and among HCWs, has been observed.

Rudberg et al.'s study, conducted on 2 149 participants in Stockholm, demonstrated that the level of SARS-CoV-2 antibodies among HCWs was 19.10%. In the seropositive group, 5.9% experienced none and 78% mild symptoms, easily mistaken for other infections [5]. This shows the existing risk of difficulty in monitoring silent transmission in this community.

In study by Lidström et al. conducted in Uppsala during the first wave, out of 8 679 tested HCWs and support staff, 6.60% were seropositive [18]. Interestingly, individuals working in inpatient care units were at greater risk of SARS-CoV-2 infection than in COVID-19 specific units. Rashid-Abdi et al. assessed seroprevalence among 131 participants; 18 (15.00%) of them were seropositive for IgG antibodies [19]. Unfortunately, more complex restrictions had not been introduced despite those observations and the severe threat of silent, uncontrolled spread of infection.

During the first wave of the pandemic, Belgium was among the European countries with the greatest number of new daily confirmed infections; it also had the highest COVID-19 death rate per million inhabitants in the world. This data resulted from a delayed reaction to the epidemic threat at the beginning of the COVID-19: not isolating first symptomatic subjects and replenishing hospital supplies too late, which led to their shortages soon after the epidemic broke out [20]. On March 27, 2020 the Belgian government introduced legal provision to prevent the spread of SARS-CoV-2 [21]. In addition, a full, national lockdown was implemented (closure of schools, restaurants, shops, etc.; introduction of mobility restrictions, recommendations to work remotely); those restrictions, however, were not as strict as in other European countries [20,22]. This response was also delayed; approx. on March 31, 2020, Belgium reached the first-wave epidemiological peak. Due to dynamically increasing hospitalization and mortality rate (highest on April 15th), the containment epidemic measures were extended until May 3, 2020. As a downward trend was observed in the following days, on May 4, 2020, the Belgian government had gradually relaxed the restrictions while maintaining the sanitary regime [20]. This strategy has turned out to be effective; both gradual introduction of restrictions, as their lifting, have been considered as recommended actions in epidemic management, most importantly, avoiding a healthcare breakdown. Analysis of HCWs situation in Belgium during the first wave reflects the consequences of delayed public health interventions and COVID-19 threat ignorance.

A study by Martin et. al on the carriage and seroprevalence of SARS-CoV-2 among HCWs and hospital staff, performed in Brussels during the first wave, revealed 41 cases of SARS-CoV-2 (12.60% of study population). In this group, 75.60% were asymptomatic at the time of sampling. Infections were confirmed by RT-PCR and/or serology, although, during two sample collections, RT-PCR results were positive only in 3.00% and 2.40% cases, respectively [23]. Results of this study confirm the importance of routine screening of HCWs, regardless of symptoms present, and value of both RT-PCR and IgG evaluation – in this case 62.50% of SARS-CoV-2 infections would have been missed if RT-PCR alone had been performed [23].

In Spain, a sharp increase in COVID-19 spread was observed in early March 2020. At that time, football matches and nationwide feminist demonstrations were held that gathered thousands of spectators. The dramatic course of the pandemic was favored by country demographic structure - population 60+ years (high-risk group) constitutes 25.00% of Spanish population. After exceeding 1 000 new cases daily, the regional lockdown was introduced, i.a., in Madrid, Catalonia, and La Rioja. On March 13, 2020, Spanish authorities declared a state of emergency – a condition that grants the government the right to intervene in the distribution and rationing of goods (including food), temporal confiscation, and occupying factories and premises. This decision affected, among others, the mobility rights and healthcare management [24].

Between March 28 and April 9, 2020, during the peak of the first wave, Garcia-Basteiro et al. assessed the seroprevalence of SARS-CoV-2 antibodies (IgA, IgM and IgG) among HCWs in a large Catalonian referral hospital. Among 578 individuals, 54 (9.30%) were seropositive for IgA and/or IgM and/or IgG against SARS-CoV-2. COVID-19 infection (i.e., presence of antibodies or past/present positive RT-qPCR result) was confirmed in 11.20% subjects. The rate of IgG antibodies was 7.60%. When it comes to 3.63%, they were seropositive without any evidence of previous infection. While 40.00% of the HCWs with evidence of current/past infection had not been previously diagnosed with coronavirus infection; 23.10% of cases were asymptomatic [7].

A cross-sectional study by Gras-Valenti et al., conducted in tertiary hospital and 12 primary care centers in Alicante, revealed that among 4 179 HCWs, the overall prevalence of SARS-CoV-2 IgG antibodies was 6.60% (8.70% in physicians, 3.20% among staff members not associated with healthcare). The occupation was the only factor significantly associated with the presence of SARS-CoV-2 antibodies [25]. In a study by Moncunill et al. on seroprevalence and antibody kinetics, conducted in Barcelona during the COVID-19 spring 2020 pandemic peak, the prevalence of SARS-CoV-2 among 578 HCWs was 11.20%. A follow-up survey performed 1 month later in this community, including 565 subjects, indicated that prevalence of infection measured by RT-qPCR was 14.90%, and the seroprevalence – 14.50%. Finally, 5.00% of the new infections in 501 participants with no prior evidence of infection were found during the study. Moreover, IgM, IgG, and IgA levels in this group decreased within 3 months (antibody decay rates 0.15, 0.66 and 0.12, respectively). When it comes to 68.33% HCWs, they had seroreverted for IgM, 3.08% for IgG and 24.29% for IgA [26].

Low seroprevalence rate in Spain in the early months of the pandemic could result from too short time for IgG response to COVID-19, rapid decay of IgG antibody, or effectiveness of undertaken prevention and infection control measures.

II group: The United Kingdom, Italy, Switzerland – epidemiological strategies and seroprevalence of SARS-CoV-2 in HCWs

The United Kingdom, from the very beginning, pursued a strategy similar to Sweden. To avoid blockages and reduce peak health care needs, UK government allowed a relatively large number of infections to achieve the undefined goal of herd immunity. However, contrary to Sweden, severe restrictions were put in place when the number of infections had spectacularly increased. On March 23, 2020 a national lockdown and "stay-at-home" order were announced. The police were authorized to enforce the law, including imposing financial penalties [27].

Implementation of the Swedish model during the first months of the pandemic resulted in an expected increase in the antibodies rate in UK population, but at the same time – a high number of new daily confirmed cases, also within a medical environment.

Shields et al. in their study, conducted on 516 HCWs, revealed that the overall incidence of SARS-CoV-2 antibodies in this group at that time was 24.40%, while the daily incidence of new cases in UK – 80 per 1 million inhabitants (Table 1) [28]. In other study by Shields et al. on 956 HCWs who had self-isolated due to COVID-19, IgG antibodies were found in 347 (36.30%) individuals, which constitutes the highest percentage among all cited studies [29]. With the introduction of hard lockdown and the departure from the Swedish model, a marked decline in new infections was observed in the following weeks. On the other hand, when comparing the May-June studies on large research groups, it is visible that the average IgG antibody ratio was lower, it was 12.00% (range: 6.05-36.30%). In the study by Razvi et al., the mean IgG level in group of 2 521 HCWs was 19.40% [30] In the study by Martin et al. on 10662 HCWs, the seroprevalence was 10.80% [31]. In the research by Bampoe et al. on the presence of IgG antibodies, among 200 HCWs 14.50% were seropositive [32]. Another study, conducted by Poulikakos et al. on 281 HCWs, demonstrated that 6.00% of subjects were seropositive for IgG antibodies [33].

The COVID-19 epidemic in Italy started in February, 2020, right after the outbreak in China. When comparing the mortality rate during the first wave of the pandemic between those two countries, in Italy it was 9.00%, the highest in Lombardy (>10.00%), whereas in Wuhan – 5.80% and remained <1.00% in the rest of the People's Republic of China. The high incidence rate in Lombardy could be associated with the touristic and business nature of this region and many people working in hospitals – hence many highly exposed to novel pathogen subjects, and many sources of pathogen transmission [34]. Indeed, data could be biased by the number of tests performed at that time in those countries, more significant in Italy, and the fact that they were mainly performed on symptomatic individuals.

Epidemic data from Italy and China had often been compared, especially during the first wave of COVID-19. The unexpected surplus of lethality, especially in northern Italy, could be explained by various factors. First of all, the higher mortality in Italy could be associated with a population older than in China and with a greater number of co-morbidities, therefore at a greater risk of disease-related complications and fatal outcome. Second, differences in death classification between these two countries could also contribute to under/overestimated mortality rate due to COVID-19.

However, these phenomena cannot explain differences in the distribution of cases and deaths in Italy, compared to other European countries [35]. Another hypothesis states that China and northern Italy were the first and hit the hardest by the pandemic due to severe atmospheric pollution. The conditions in the Wuhan area and Hubei province (climatic zone, industrialization level, air pollution) are similar to those in the northern part of Italy. Numerous studies confirmed that living in areas with high levels of pollution may lead to a greater susceptibility of the population to the development of chronic respiratory diseases, and thus to any infectious agents [36,37].

Nevertheless, Italy was the first European country to face the COVID-19 pandemic; Italian authorities had no experience and were not prepared to deal with the rapidly spreading disease. According to many critics, they reacted too late to the new epidemic threat. However, it is worth noting that Italy was the first European country that introduced restrictive anti-coronavirus measures, the first that imposed the lockdown on the most affected region of Lombardy, and when the number of new confirmed infections had risen to 12 000 – on the entire country, which undermines the popular opinion that the government was playing down the problem in the first period of the pandemic [27].

Lahner et al. assessed the seroprevalence in a large group of 1 084 HCWs in hospitals in Italy between March and April, 2020. The overall seroprevalence for IgG was 0.70%, while the mean of daily new cases per 1 million inhabitants in Italy was 69 during the study period (Table 1) [38]. No difference in seroprevalence concerning profession or sex was observed. Another large study conducted by Plebani et al. on a cohort composed of 7 999 HCWs of Veneto Region in Italy between February-May, 2020, revealed that 1.70% individuals were positive for IgG antibodies [39]. Finally, Calcagno et al., in their research on 5 444 HCWs, held between April and May, 2020, confirmed that the overall seroprevalence in this group was 6.90%, while in Italy, the mean of daily new cases per 1 million inhabitants was 30 during the study period (Table 1) [40].

Switzerland had been hit relatively hard by the first wave of the pandemic, but had dealt with it quickly. Inland's geographic location, complex topography, climate, and being home to many international companies, with high turnover of business travelers, made this country vulnerable to the virus spread [41]. First COVID-19 cases appeared here at the turn of February and March 2020. Soon after, a rapid increase in the number of new cases was observed; by the end of March, there was over a thousand infections per day – a very high number, considering the country's area.

On March 16, 2020, Swiss authorities declared a state of emergency. A three-phase strategy, based on the gradually introduced restrictions, was adopted. The public compliance to the safety procedures and infection control was very good; as soon as the first COVID peak was reached, a quick drop in new daily cases was observed. As a result, on April 27, 2020, restrictions were slowly lifted [42]. In early May, the first wave of infections was over.

In large prospective cohort study conducted in two tertiary-care hospitals, Kohler et al. examined the prevalence of SARS-CoV-2 among Swiss HCWs, using 3 different tests: LFIA, CMIA and ECLIA. Overall seropositivity was 1.00%. At the baseline, 58 of 1 012 participants gave a total 5.70% of positive signals in at least 1 test. While 20.00% of positive subjects were asymptomatic [43]. The low rate of seroconversion resulting in this study confirms the effectiveness of applying of safety protocols and hygiene measures among HCWs in highly affected pandemic region. On the other hand, high percentage of positive asymptomatic individuals shows the scale of silent infection; and highlights the importance of routine SARS-CoV-2 testing in HCWs.

III group: France, Germany, Austria, Norway, Poland, Greece - epidemiological strategies and seroprevalence of SARS-CoV-2 in HCWs

France was one of European countries most affected in terms of COVID-19 mortality during the first wave. The highest seroprevalence rate and daily number of new confirmed cases (31 per million) were reported between March and April 2020 (Table 1). It must be stressed, however, that France acted decisively from the start of the pandemic, introducing the first restrictions on March 17, 2020. A stringent national quarantine was implemented; each home departure had to be confirmed with a handwritten statement. The pandemic had very soon and severely affected national economy and industrial policy: it resulted, i.a., in the closure of 15 factories in the country by one of the leading automotive giants - Peugeot Group. The government's imposition of blockades had also impacted the domestic pharmaceutical industry, 60.00% of which is based on a Chinese supply chain from other countries, resulting in high unemployment and increased public discontent despite the government's countermeasures in the form of crisis packages [44,45].

Still, regardless of the lockdown and undertaken public health measures, hospitals in large French cities had become overwhelmed shortly after the outbreak of COVID-19 in this country. Moreover, SARS-CoV-2 testing was not widely conducted: due to laboratory limitations, resulting from budget cuts, much fewer tests were performed in France than, e.g., in Germany [44,45].

Delmas et al., who conducted a screening for IgG SARS-CoV-2 antibodies among 4 607 HCWs in a university hospital in Paris, revealed that seroprevalence in this group during the first months of epidemic was similar to that among German HCWs (11.50% vs.15.10%), as assessed by Finkenzeller et al. (Table 1) [46,47]. Both studies were conducted in areas heavily affected by COVID-19, with the highest infection rate at that time.

These results confirm other studies conducted at this time. Pere et al. who examined the seroprevalence among 3 569 HCWs in Paris hospital between May and June, 2020, indicated that 423 subjects were seropositive (11.90%) [48]. In other study by Mesnil et al., conducted in Paris during the first months of COVID-19, 52 out of 462 HCWs (11.00%) were positive for IgG antibodies, while the daily number of confirmed cases during this month in France was 5 per million population (Table 1) [49]. Interestingly, in this study there was no significant difference in the seroconversion between HCWs and non-HCWs, and between HCWs working in COVID-19 and non-COVID-19 units, which again, highlights the role of proper epidemic management and the compliance to the safety protocols in medical settings.

The beginnings of COVID-19 epidemic in Germany were comparable to that in other European countries. First national recommendations were limited to informative campaigns and isolation of the infected. The situation changed dramatically in late February 2020, when the number of confirmed cases had increased (Figure 3). Even then, German government only recommended necessary blocking measures, such as school closure or the cancellation of mass events of over 1 000 participants. The number of confirmed infections increased sharply in two weeks, from less than 100 to 4 000 in mid-March. As a result, the borders were closed on March 17 and a general blockade was carried out on March 18, 2020 [50]. The peak of the first wave was reached in early April 2020 (Table 1). Despite having a highly efficient healthcare system, Germany reacted too late compared to some other countries [50].

In a study by Korth et al. on the seroprevalence among HCW, 316 individuals were divided into three groups, depending on their exposure to COVID-19 patients. SARS-CoV-2-IgG antibodies were detected in five subjects (1.60%). While 80.00% of them reported COVID-19-compatibile symptoms in the last 3 months. When it comes to 80.00% of respondents, they were tested negative via PCR. The seroprevalence was higher in intermediate-risk-group (daily contact with known/suspected positive patients at admission) than in high-risk-group (daily contact with know/suspected positive patients): 5.40% vs. 1.20%, respectively [51]. Schmidt et al. in his study conducted in April 2020 in a large neurological center in northern Germany, detected IgG antibodies against SARS-CoV-2 in 2.70% of HCWs. Most of the participants were asymptomatic; only 36.40% of the seropositive subjects had flu-like symptoms [52]. The incidence of IgG antibodies was significantly higher in the following weeks; the daily number of confirmed cases on average of study period time was 5 per million of the population (Table 1). Finkenzeller et al. examined seroprevalence of SARS-CoV-2 IgM/IgG antibodies among 2 824 individuals working in a hospital in the most affected region in Germany: 1 838 HCWs and 986 non-medical workers – 11.10% of were seropositive. Seroprevalence of SARS-CoV-2 among medical workers was significantly higher than among non-medical (15.10% vs. 3.70%) [47].

The SARS-CoV-2 epidemic reached Austria very quickly due to its inland location and winter tourism. The Austrian government reacted almost immediately: on March 16, 2020, it declared a state of emergency, introducing restrictions that were in force almost throughout the European Union, but not limiting the economic activity so restrictively [53-55]. Shopping centers, restaurants, hotels, schools, and universities were closed, but factories, construction sites, grocery stores and pharmacies could operate under epidemic conditions. Additionally, several aid programs were introduced to protect entrepreneurs and employees. As the national quarantine had resulted effective, after April 15, 2020, Austrian government decided to unfreeze conditionally some businesses and open schools at two-week intervals. Due to the advanced healthcare system, a modern epidemiological surveillance program, based on digital contact tracing, and a robust testing strategy (also for asymptomatic people), Austria was one of the European countries that dealt with the first wave of the COVID-19 epidemic reasonably quickly – the first wave in Austria lasted until April 30, 2020 [55,56].

In the study on seroprevalence among HCWs, conducted by Orth-Höller et al. in Tyrol, a region highly affected by the COVID-19, among 377 individuals with unknown SARS-CoV-2 status, only 1 was tested positive for SARS-CoV-2-specific IgG antibodies in two subsequent serum samples with high antibody levels (ratios >5). The study showed surprisingly low seroprevalence in study group (0.30%), while the mean of daily new cases in Austria during study period was 76 per 1 million inhabitants (Table 1) [57]. In another study by Hackner et al., conducted in April 2020 among 130 HCWs, the seroprevalence of IgG SARS-CoV-2 antibodies was 0.80%, while the daily number of confirmed cases during this month was 19 per million population (Table 1). The low seroprevalence could result from adherence to strict restrictions by the society and effectiveness of security measures used in hospitals [58].

Norway adopted an opposite pandemic management strategy compared to other European countries, considered one of the most effective during the first wave of COVID-19. It quickly introduced a strict lockdown, including closure of businesses and schools, travel and mobility ban; however, a formal blockade was avoided, which led to greater society's acceptance of the situation and compliance to imposed restrictions, thus contributed to fewer deaths [16,59]. In the study by Trieu et al., among 607 HCWs the seroprevalence of IgG was 5.30%. Most of the individuals had symptoms, and only 36.40% of cases were asymptomatic [60]. In the other study by Basso et al., 57 quarantined HCWs were tested for COVID-19 – all of them tested negative for SARS-CoV-2 RNA and IgG antibodies. Again, those results confirm the role of hand hygiene and prevention and infection control procedures in limiting the spread of the virus in high-risk settings [61].The first confirmed case in Poland took place on March 4, 2020. Within next 24 days, the total number of confirmed cases increased to 1389, and the incidence rate was 3.01 per 100 000 inhabitants62 . The most significant number of recorded cases was confirmed in the largest Polish cities, especially those with international airports, which could contribute to the dynamic spread of the COVID-19 pandemic in the country due to the winter break in Poland at that time and a large percentage of tourists returning from the popular ski resorts in northern Italy [62]. The state of epidemic threat was introduced on March 14, and the epidemic state – on March 20, 2020. On April 16, 2020, the order to cover the mouth and nose in public places was introduced. On March 25, 2020, strict mobility restrictions were introduced. From April 1, shopping centers, restaurants, entertainment establishments (cinemas, theaters, museums), beauty and hair salons, etc., were closed; even entrance to forests and parks was temporarily banned [63]. Although in the initial stage of the outbreak of the first wave, a systematic increase in new infections per day was observed within 30 days, in the following months, the trend decreased, stabilizing at the level of about 300-400 cases per day (Figure 3) [62]. Therefore, the first stage of easing the restrictions began on April 20, 20, 2020 [63]. Poland was one of the countries least affected by the COVID-19 epidemic during the first wave. This could be due to quickly introduced epidemic restrictions. On the other hand, the reported low incidence rate was due to the low number of tests performed in the first weeks of the epidemic.

Bułdak et al., in the first study on seroprevalence among Polish HCWs, examined 199 subjects working in two large hospitals in different regions of Poland. The seroprevalence rate of IgG antibodies was 1.20% among HCWs from the University Hospital in Opole, and 10.00% – among HCWs from the regional specialist hospital in Bytom in Upper Silesia – the region hit hardest by the first wave of the pandemic [12]. It is also worth noting that results of this research work, unlike many others, did not confirm the activity of IgA and IgM antibodies in subjects with active viremia confirmed by RT-qPCR. This observation excludes the diagnostic validity of these two classes of antibodies which were considered during the first wave of the pandemic. Also, contrary to other works, this study included at least one collection window, which increases the diagnostic significance of the obtained serological results [12].

The first cases of the coronavirus in Greece were registered on February 26, 2020, and involved people returning from Italy. A day later, the government canceled all carnival events; on the following days, schools, restaurants, museums, shopping centers, sports facilities, etc., were closed. As the number of infected rose, on March 22, 2020, mobility restrictions were introduced. Undertaken actions had led to effective inhibition of the pandemic spread; therefore, since May 4, the government started to reduce the restrictions gradually.

Despite the long-term economic crisis, the lack of adequate healthcare resources and the refugee crisis, according to the public opinion, Greek government reacted early, and managed effectively the epidemic situation [64,65]. In the study by Vlachoyiannopoulos et al., the seroprevalence rate among 321 HCWs was 2.18%. None of 7 positive subjects was PCR-positive. The study took place between April-May, 2020, at 2 per million of daily numbers of confirmed cases in Greece (Table 1) [66]. During next few weeks a decrease in seropositivity was observed (Table 1). In a national cross-selectional study by Galanis et al., conducted from June to July, 2020, out of 57 418 HCWs, 379 (0.66%) were tested positively for IgG antibodies. The overall adjusted seroprevalence was 0.43%, at the same daily number of confirmed cases as in the previous months (Table 1), which is consistent with the low incidence of SARS-CoV-2 in Greece during the first months of pandemic [67,68]. According to the national polls, 87.00% of Greeks positively assessed public health measures undertaken by the government during the pandemic's beginning [64].

CONCLUSIONS

The importance of serological testing in epidemic management

This paper aimed to summarize and critically analyze the existing evidence related to SARS-CoV-2 prevalence among HCWs and investigate the eventual association between seropositivity and occupational risk in this group and different epidemic strategies applied during the beginning of the pandemic in selected European countries.

Serological tests of high specificity and sensitivity confirm previous symptomatic infection with SARS-CoV-2. However, data to what extent asymptomatic and paucisymptomatic infections are captured with SARS-CoV-2 serology and the antibody response duration are still scarce [19].

The low rate of seroconversion among HCWs during the first wave of COVID-19 pandemic, observed in European hospitals, regardless of their profile, suggests that it is possible to prevent, or at least limit SARS-CoV-2 transmission, even at high infection rate in high-risk departments, and regions hit hardest by the epidemic.

Results of this work highlight the importance of systematic testing, optimally using combined molecular and serological surveys, PPE, and infection prevention and control measures. Seroprevalence routine screening in HCWs seems critical

TABLE 1. Seroprevalence of anti-SARS-CoV-2 IgG antibodies among HCWs during the first months of COVID-19 outbreak in selected European countries according to literature review.

Country	Authors	Data collection/ study period (2020)	Sample size (n)	Antibodies detected	Laboratory technique‡	PCR before serology (+/-)	Daily new cases per 1M individuals (average of study period time)	Findings
Sweden	Rudberg A.S. et al.[5]	April 14 – May 8	2 149	IgG	xMAP assays	-	54	IgG:19.10%
	Lidström A.K. et al.[18]	May 27 – June 25	8 679	IgG	CMIA	-	87	IgG:6.60%
	Rashid-Abdi M. et al.[19]	May 4 – August 19	131	IgG	CMIA	+	54	IgG:15.00%
Belgium	Martin C. et al.[23]	April 15 – May 18	326	IgG	ELISA	+	56	IgG:11.00% and 12.00%
Spain	Garcia-Basteiro A.L. et al.[7]	March 28 – April 9	578	IgG/IgM/IgA	ELISA	+	154	IgG:7.60%
	Moncunill G. et al.[26]	April 27 – May 6	565	IgG/IgM/IgA	ELISA	+	24	IgG:11.30%
	Gras-Valenti P. et al.[25]	April 24 – May 8	4 179	IgG	ELISA	-	29	IgG:6.60%
United Kingdom	Shields A. et al.[28]	April 24 – 25	516	IgG/IgM/IgA	ELISA	+	80	IgG:24.40%
	Shields A.M. et al.[29]	April 27 – June 8	956	IgG/IgM/IgA	ELISA	+	39	IgG:36.30%
	Poulikakos D. et al.[33]	May 4 – May 6	281	IgG	CLIA	+	48	IgG: 6.00%
	Bampoe S. et al.[32]	May 11 – June 5	200	IgG	CMIA	-	31	IgG:14.50%
	Razvi S. et al.[30]	May 28 – June 8	2 521	IgG/IgM	ECLIA	-	21	IgG:19.40%
	Martin CA. et al.[31]	May 29 – July 13	10 662	IgG	CMIA	+	87	IgG:10.80%
Italy	Plebani M. et al.[39]	February 22 – May 29	7 999	IgG/IgM	CLIA	+	39	IgG:1.70%
	Lahner E. et al.[38]	March 18 – April 27	1 084	IgG/IgM	CLIA	+	69	IgG:0.70%
	Calcagno A. et al.[40]	April 17 – May 20	5 444	IgG	CLIA	+	30	IgG:6.90%
Switzerland	Kohler P.P. et al.[43]	March 19 – April 3	1012	IgG/IgM	CMIA ECLIA LFIA	-	120	IgG:1.00%
France	Pere H. et al.[48]	May 2 – June 26	3 569	IgG	CMIA	-	6	IgG:11.90%
	Delmas C. et al.[46]	May 14 – June 17	4 607	IgG	CMIA	+	6	IgG:11.50%
	Mesnil M. et al.[49]	June 8 – June 22	462	IgG	ECLIA	+	5	IgG:11.00%
Germany	Korth J. et al.[51]	March 25 – April 21	316	IgG	ELISA	-	49	IgG:1.60%
	Schmidt S.B. et al.[52]	April 20 – 30	385	IgG	ELISA	+	21	IgG:2.70%
	Finkenzeller T. et al.[47]	June 29 – July 26	1 838	IgG/IgM	ECLIA	+	5	IgG:15.10%
Austria	Orth-Höller D. et al.[57]	March 20 – 27	377	IgG/IgA	ELISA	+	76	IgG:0.30%
	Hackner K. et al.[58]	April	130	IgG/IgM	ELISA LFIA	+	19	IgG:2.30%
Norway	Trieu MC. et al.[60]	March 6 – May 15	607	IgG/IgM/IgA	ELISA	+	30	IgG:5.30%
	Basso T. et al.[61]	n/a (spring until June)	57	IgG/IgM	ELISA ECLIA CLIA	+	23	IgG:0.00%
Poland	Bułdak RJ et al.[12]	July 6 – August 14	199	IgG/IgM/IgA	ELISA	-	~ 19.5 (Opole voiv. – 13; Upper Silesia – 26)	IgG:1.20% and 10.0%
Greece	Vlachoyiannopoulos P. et al.[66]	April 24 – May 5	321	IgG	ELISA	+	2	IgG:2.18%
	Galanis P. et al.[67]	June 1 – July 9	57 418	IgG	CLIA	-	2	IgG:0.43%

‡ Abbreviations: CMIA – chemiluminescent microparticle immunoassay; CLIA – chemiluminescent immunoassay; ECLIA – electrochemiluminescence; ELISA – enzyme-linked immunosorbent assay; xMAP assays – multiplexing method; LFIA – lateral flow immunoassay.

§ Volunteers with a positive SARS-CoV-2 test in qRT-PCR, with active form of respiratory tract infection and general poor health were excluded from the study.

to monitor occupational risk in this group and prevent the spread of the virus in medical settings. Observations made within this review may constitute a base for developing good practices in epidemic management in healthcare facilities and protecting HCWs and the patients.

Lessons learned from those first months of the pandemic could become helpful during the successive SARS-CoV-2 waves and next potential outbreaks. Moreover, they take on a greater significance in the light of recent data and the fact that even individuals vaccinated against COVID-19 can contract and transmit the virus.

Study limitations:

Comparison of serological test results obtained during the pandemic's beginning among selected European countries has been challenging due to the different number of tests performed per capita, different public health measures applied, and many variables which could affect the dynamics of infection development in a given population. Furthermore, an inadequate number of tests resulting in a high percentage of positive tests could disturb the correct estimation of the pandemic course, limiting the credibility of the data.

Conflict of Interest:

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Abbreviations:

CLIA	chemiluminescence immunoassay;
CMIA	chemiluminescent microparticle immuno assay;
COVID-19	coronavirus disease 2019;
ECLIA	electrochemiluminescent immunoassay;
ELISA	enzyme-linked immunosorbent assay;
HCWs	healthcare workers;
IgA	immunoglobulin A;
IgG	immunoglobulin G;
IgM	immunoglobulin M;
LFIA	lateral flow immunoassay;
RT-qPCR	real-time quantitative reverse transcription polymerase chain reaction;
RNA	ribonucleic acid;
S protein	spike protein;
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2.

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Corresponding author
dr hab. Rafał Bułdak, prof UO
Department of Clinical Biochemistry and Laboratory Diagnostics,
Institute of Medical Sciences, University of Opole, Poland
E-mail: rafal.buldak@uni.opole.pl