VACINAS COVID-19 E AVALIAÇÃO PILOTO DA REAÇÃO IMUNOLÓGICA NUMA POPULAÇÃO DE DOCENTES/MÉDICOS DENTISTAS

Covid-19 Vaccines And Pilot Evaluation Of The Immunological Reaction In A Teaching/Dental Professionals Population

Dissertação de Mestrado

Mestrado Integrado em Medicina Dentária

Gabriëlla Anaïs Da Costa Marques

Orientador:

Prof. Doutora Patricia Manarte Monteiro

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My parents, my family, whom I thank for giving me this opportunity and their support to finish this adventure.

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RESUMO

Objetivo: Avaliar os anticorpos anti-SARS-CoV-2 plasmáticos, as imunoglobulinas G (IgG) e IgM, anti-subunidade S1 da proteína espícula, domínio de ligação ao recetor (RBD), um mês após a administração da primeira dose das vacinas contra a COVID-19, numa população com dupla profissão, professores universitários e médicos dentistas, em ambiente académico. Adicionalmente, realizar uma revisão sistemática das principais vacinas contra COVID-19 e indicadores serológicos utilizados para a avaliação das respostas imunitárias, com enfoque específico na imunoglobulina G (IgG).

Metodologia: Estudo piloto transversal, observacional, analítico, aprovado pela Comissão de Ética da UFP (FCS/PI-172/21, 9 de junho de 2021). Quarenta e sete dos 62 professores universitários/dentistas concordaram em participar voluntariamente, após terem sido ou não administrados com vacinas COVID-19. Os níveis de anticorpos IgM e IgG anti-S1-RBD do SARS-CoV-2 foram verificados um mês após a administração da primeira ou da segunda dose de vacinas, utilizando a técnica de ensaio imunoenzimático (ELISA) por amostra de sangue (plasma). Foi realizada uma análise sistemática nas bases de dados B-On e PubMed de estudos observacionais transversais realizados entre 2019-2024 sobre vacinas contra a COVID-19 e que incluíram resultados serológicos com anticorpos IgG profissionais dentistas/profissionais de saúde de medicina dentária, conforme análise pelo STROBE (*Strengthening the Reporting of Observational Studies in Epidemiology*).

Resultados: A positividade para IgG foi detetada em 91,5% (n=43) da amostra, com apenas 4 indivíduos com níveis de anticorpos abaixo do limite mínimo de referência (valores séricos <1,00 AU/mL). Entre os vacinados (91,5%, n=43), todos os participantes apresentaram resultados medianos e positividade/reatividade categórica aos anticorpos IgG SARS-Cov-2 contra a subunidade S1 da proteína spike. Os valores medianos de IgG tendem a ser mais elevados em indivíduos vacinados com um historial de infeção por SARS-CoV-2. A maioria dos indivíduos recebeu a vacina da AstraZeneca®, tanto na primeira como na segunda dose. A análise sistemática resultou em 11 estudos, com seropositividade que variou significativamente de 0,43% a 96,99%.

Conclusão: A sero-prevalência para a IgG foi muito elevada, tal como a taxa de vacinação na população estudada. A sero-prevalência de IgM foi muito baixa. Não foi encontrada associação significativa entre a idade, o sexo, a existência de patologias crónicas ou a atividade clínica/ensino clínico e o número de doses de vacina ou a ausência de vacinação. A análise da evidência transversal revelou uma grande variabilidade nas taxas de sero-prevalência relacionadas com uma vasta gama de fatores de influência.

Palavras chave: Infeção SARS-CoV-2, vacinas SARS-CoV-2, COVID-19 vacinas, Médicos Dentistas, Professores de Medicina Dentária, trabalhadores da área da saúde, imunoglobulina G, anticorpo IgG.

ABSTRACT

Aims: To assess the plasma immunoglobulin G (IgG) and IgM antibodies to the SARS-CoV-2 spike 1 (S1) subunit protein, receptor-binding domain (RBD), one month after the first doses of COVID-19 vaccines, among a population of both professions, university professors and dentists, in a dental academic environment. Furthermore, to perform a systematic review of the main COVID-19 vaccines and the key serological indicators used for evaluation of immune responses, with a specific focus on immunoglobulin G (IgG).

Methodology: Cross-sectional, analytical observational, pilot study approved by the Ethic committee of UFP (FCS/PI-172/21, June 9, 2021). Forty seven of 62 university professors/dentist, agree to participate, after been or not been administrated with COVID-19 vaccines. SARS-CoV-2 IgM antibody and IgG anti-S1-RBD levels were checked one month after the first (or second) dose of vaccines, using the enzyme-linked immunosorbent assay (ELISA) technique by blood (plasma) sample. A systematic analysis of COVID-19 vaccines was conducted on the *B-On* and *PubMed* of cross-sectional studies performed between 2019-2024 that included serological outcomes with IgG antibody, among dentists/dental care professionals/healthcare professionals. The *Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement was applied.*

Results: Positivity for IgG was detected in 91.5% (n=43) of the sample, with only 4 individuals having antibody levels below the minimum reference limit (serum values <1.00 AU/mL). Among the vaccinated(91.5%, n=43)all participants showed median results and categorical positivity/reactivity to SARS-Cov-2 IgG antibodies against the S1 subunit of the spike protein. The median IgG values tend to be higher in vaccinated individuals with a history of SARS-CoV-2 infection. Most subjects received the vaccine from AstraZeneca®, both in the first and second doses. The systematic analysis resulted in 11 studies, with seropositivity that varied significantly, ranging from 0.43% to 96.99%.

Conclusion: Seroprevalence for IgG was very high, as the vaccination rate among the studied population. Seroprevalence for IgM was very low. No significant association was found for age, gender, the existence of chronic pathologies, or clinical activity/clinical teaching and the number of vaccine doses or lack of vaccination. The analysis of cross-sectional evidence revealed wide variability of seroprevalence related to wide range of influencing factors.

Keywords: SARS-CoV-2 infection, SARS-CoV-2 Vaccine, COVID-19 vaccine, Dental Care professionals, Dental Academics professors, Healthcare workers, Immunoglobulin G, IgG antibody.

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ABBREVIATIONS

ACE2	Angiotensin Converting Enzyme 2
AGPs	Aerosol Generating Procedures
AU/ml	Arbitrary Units per Milliliter
BAU/mL	Binding Antibody Units per mL
COVID-19	Coronavirus Disease 2019
DNA	Deoxyribonucleic Acid
ELISA	Enzyme-Linked Immunosorbent Assay
EMA	European Medicines Agency
FDA	Food and Drug Administration
FHS-UFP	Faculty of Health Sciences of University Fernando Pessoa
HE-UFP	School Hospital of University Fernando Pessoa
IBM	International Business Machines Corporation
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IU/ml	International Units Per Milliliter
MERS-CoV	Middle East Respiratory Syndrome-Related Coronavirus
mRNA	Messenger Ribonucleic acid
PCR	Polymerase Chain Reaction
PICO	Patient/Population, Intervention, Comparison and Outcomes
POS	Post-onset of symptoms
RB	Receptor-Binding
RBD	Receptor-Binding Domain
RNA	Ribonucleic Acid
RT-PCR	Reverse Transcription Polymerase Chain Reaction

RT-qPCR Reverse Transcription Quantitative Polymerase Chain Reaction

S1 Spike-protein 1

SARS-CoV-2 Severe Acute Respiratory Syndrome Coronavirus 2

sCOVG Atellica® IM SARS-CoV-2 IgG

SD Standard Deviations

SPSS Statistical Package for the Social Sciences

STROBE Strengthening the Reporting of Observational Studies in Epidemiology

U.S. United States

UFP University Fernando Pessoa

VE Vaccine Efficacy

1. INTRODUCTION

The SARS-2 coronavirus is responsible for the COVID-19 pandemic, which has affected the public health and the society globally from December 2019. It was reported that in Wuhan, China, appeared the first cases of this infectious respiratory disease. Since then, it has been quickly spreading, leading to widespread illnesses and the pandemic set (Guan et al., 2020). The SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus 2) belong to the genus Coronavirus, the family Coronaviridae, and the order Nidovirales an extensive and varied group of enveloped with a unique strain of RNA (ribonucleic acid) viruses that are mostly spread by respiratory droplets and aerosols. These viruses are known as coronaviruses because, when seen under an electron microscope, their viral envelopes resemble crowns (Pal et al., 2020). Coronaviruses come in several forms. SARS-CoV-2, which produced the SARS pandemic in 2002–2003, and MERS-CoV, which caused the Middle East Respiratory Syndrome (MERS) in 2012, are two examples (Pollard et al., 2020).

Airborne transmission is defined as the spread of an infectious agent caused by the dissemination of droplet nuclei (aerosols) that remain infectious when suspended in air over long distances and time (WHO, 2014). Such transmission is distinct from droplet as it is based on a smaller particle size, enabling a greater travel distance and the potential to remain suspended in air for prolonged periods. Aerosols are emitted to varying degrees and sizes depending on the activity in question such as breathing, talking, singing and residually following coughing or sneezing. Main differentiation of airborne from droplet transmission is the infection risk of aerosols through airborne contamination, and the virulence of the respective pathogen (Comber et al., 2021).

Airborne transmission of SARS-CoV-2 can occur during dentistry and medical procedures that generate aerosols, the so called aerosol generating procedures (AGPs). The ability of the virus to survive outside living organisms, in aerosol or on fomites has also been recognized (Amato et al., 2020).

Among medical practitioners, dentists and dental staff may have an increased risk of being infected with airborne pathogens such as SARS-CoV-2 because they are always exposed to droplets and aerosols produced during specific treatment procedures. However a COVID-19 low infection rate of dentists was reported, and that may be due to the rigorous safety protocols implemented (Goriuc et al., 2022).

In both dental care and dental academic environments direct contact of dentists that are also academic teachers, can occur on behalf of the aerosol-generating procedures (AGPs) but also the salivary droplets, by contact with dental care an academic settings, with dental staff, academic personnel and dental students.

SARS-CoV-2 appears to mainly be spread via droplets and close contact with infected symptomatic or asymptomatic cases (Wang et al., 2022). COVID-19 symptoms include fever, a persistent cough, breathing difficulties, a sore throat, sleepiness, and loss of taste or smell. Some persons may be asymptomatic yet can transmit the infection (Canedo-Marroquín et al., 2020).

Academics working in the field of dentistry have been subjected to a high level of stress during the COVID-19 pandemic, not only related to teaching and research activities but also to concerns related to the possibility of contaminating their family members (Goriuc et al., 2022).

Individuals can help reduce the spread of the virus and protect public health by adhering to preventive measures such as frequent handwashing, wearing masks, and practicing physical distancing, as well as sharpened infectious disease guidance and appropriate protection equipment. It has been suggested that healthcare workers, such as dental professionals, give antimicrobial mouthwashes to patients prior to procedures, as well as use ocular protection and full body disposable gowns in addition to the usual protection equipment (Ting et al., 2023).

It is important to note that SARS-CoV-2 has undergone mutations since its initial emergence, resulting in many variations or lineages. The Alpha, Beta, Gamma, and Delta variants were notable examples. These variants can differ in terms of transmissibility, illness severity, and ability to elude the immune response partially (Papanikolaou et al., 2022).

COVID-19 vaccines have been developed and validated by the FDA (Food and Drug Administration, U.S) and the EMA (European Medicines Agency) since 2020 year to prevent SARS-CoV-2 infection elicit an immune neutralizing response (Angeli et al., 2021). The administration of the first vaccines, as well as the continuing of the vaccination programs in several countries, has resulted in a temporary stabilization and reduction of the number of COVID-19 cases morbidity and deaths.

Vaccines against COVID-19 which include, live attenuated vaccines, inactivated vaccines, recombinant protein vaccines, vector vaccines, DNA vaccines and RNA vaccines have played an important role in combating the pandemic and protecting public health, with each type employing remarkable scientific approaches to stimulate immunity against the SARS-CoV-2 virus. However, vaccine efficacy (VE) can be jeopardised by the rapid emergence and spread of SARS-CoV-2 variants of concern that could escape from neutralising antibodies and/or cell-mediated immunity (Hadj Hassine, 2022).

Vaccines increase the endogenous synthesis of SARS-CoV-2 Spike proteins from a variety of cells. Those Spike (S) proteins assembled in the cytoplasm migrate to the cell surface and protrude with a native-like conformation. Those proteins are recognized by the immune system, which rapidly develops an immune response, that appears to be quite vigorous in the presence of DNA vaccines (encode viral vectors), as well as in subjects who are immunized by previous exposure to SARS-CoV-2. The resulting pathological features may resemble those of active coronavirus disease (Angeli et al., 2021).

The receptor-binding domain (RBD) of S proteins synthetized by cells, targeted by vaccine and destroyed by the immune response, circulate in the blood and systematically engage with angiotensin converting enzyme 2 (ACE2) receptors (expressed by a variety of cells including platelets) and promote, ACE2 internalization (proteolytic activation of the S protein, endocytosis and membrane fusion) and degradation (Jackson et al., 2022).

With the introduction of multiple vaccines and several ongoing vaccine trials, identifying prior exposure or immunogenicity of the vaccine in individuals, becomes critical.

Serological assays as immunological tests, played a crucial role in the proactive management of symptomatic and a large fraction of asymptomatic human SARS-CoV-2 infections, facilitating the assessment of coronavirus exposure prevalence and the detection and monitoring of antibody levels, the seroconversion (Long et al., 2020). In the context of post-vaccination against COVID-19, immune-assays can also be employed to detect antibodies. These evaluations involve the quantification of specific components, namely immunoglobulins IgG and IgM, which serve as conventional serological markers for assessing the immunological response to COVID-19 vaccines. Immunoglobulin G (IgG) is an antibody type produced by the immune system to combat infections and foreign agents within the body. In the case of COVID-19, IgG antibodies are generated by the immune system in response to SARS-CoV-2 infection. Detecting IgG antibodies against COVID-19 can provide insight into an individual's prior exposure to the virus.

The IgM antibody is a significant aspect of an ongoing or current infection, as it is the first to develop after exposure to the pathogen. The IgG antibody is a protective antibody that indicates recovery from disease or infection. It is the most abundant antibody in the immune system and can protect against infection by preventing viral entry into host cells (Luo et al., 2021). The stage of infection can be determined based on IgM and IgG levels (Hou et al., 2020). Viral antigen-specific antibodies can be detected in SARS-CoV-2 exposed individuals within 5–12 days post-onset of symptoms (POS) for IgM immunoglobulin and IgA antibodies and 14 days for IgG antibodies. IgG antibodies are long-lived, detectable for up to 12 months, making them recent and long-term markers of exposure to SARS-CoV-2 compared to short-lived IgA and IgM (Jagtap et al., 2021).

This work aimed to assess the plasma immunoglobulin G (IgG) and IgM antibodies to the SARS-CoV-2 spike 1 (S1) subunit protein, receptor-binding domain (RBD), one month after the first doses of COVID-19 vaccines administration, among a population of both professional, academic professors and dentists, in a dental academic environment, by a cross-sectional pilot study performed in the year 2021. Furthermore, had as purpose to perform a systematic review of the main COVID-19 vaccines and the key serological antibody markers, used for evaluation of immune responses, with a specific focus on immunoglobulin G (IgG) or IgG antibody, of dental care/dental educations, as dentists/dental care professionals/healthcare professionals.

2. MATERIAL AND METHODS

This work was divided into two main sections:

1. - A cross-sectional, analytical observational, pilot study of university professors/dentist, after been or not been administrated with COVID-19 vaccines. SARS-CoV-2 IgM antibody and IgG anti-S1-RBD levels were checked one month after passing the first doses (one or more) of vaccines, using the enzyme-linked immunosorbent assay (ELISA) technique by blood (plasma) sample.

And,

2. - A systematic review of observational, cross-sectional, longitudinal and retrospective studies performed between 2019-2024, about COVID-19 vaccines and serological outcomes of IgG immunoglobulin antibody, among the field of dental care/dental educations, as dentists/dental care professionals/healthcare professionals.

2.1. The cross-sectional pilot study

2.1.1. Type of study, ethics committee, location and methodology

All data of this observational cross-sectional pilot study were provided for the preparation of this Dentistry master work by the responsible researcher (P.M.M) based on the research project submitted and approved by the UFP Ethics Committee (FCS/PI-172/21; 9 June 2021). The study was carry out in the Faculty of health Sciences of University Fernando Pessoa (FHS-UFP).

In the first phase, a google form survey was carried out in June 2021, on demographic data, history of systemic pathologies, history of SARS CoV-2 infection and/or COVID-19, data of COVID-19 vaccine and, work contact (in hours) within the scope of dental education (clinical training in the dentistry master degree) and/or dental care professional activity, to the study population who freely, informedly and voluntarily agreed to participate.

Then, to analyse the potential contact and immunity by anti-S1-RBD SARS CoV-2 IgM antibody and IgG antibody levels, respectively, were checked one month after the time frame of the first or the second doses according to the administration of the respective COVID-19 vaccines. Only were included dental academic professors that were also dentists that worked at dental academic and dental care environments between September

2020 and July 2021. Biological samples were collected by a suitably qualified professional (clinical analysis technicians and HE-UFP nurses) at the FHS-UFP Pedagogical clinic. The samples were analysed by the HE-UFP Unilabs laboratory.

2.1.2. Population, Sample inclusion and exclusion criteria

The population (N=62) involved dental academic professor also dentists of the University Fernando Pessoa Integrated Dentistry Master's Degree. A convenience sample (n= 47) was constituted.

2.1.2.1. Inclusion Criteria

COVID-19 vaccinated or not vaccinated participants who freely consented to take part in the study, by answering the totally of the survey and then, that consent take part of the blood samples collection and antibodies analysis.

Only were included dental academic professors that were also dentists that worked at dental academic and/or dental care environments between September 2020 and July 2021.

2.1.2.2. Exclusion Criteria

Academic staff, dental students, and dental academic professors that were also dentists that do not fulfilled the google form survey totally and those who expressed, by the written consent, not to take part of the blood samples collection and antibodies analysis.

2.1.3. Biological Samples assay and analysis

The Atellica® IM SARS-CoV-2 IgG (sCOVG) test - Siemens Healthcare Diagnostics - was used for in vitro diagnosis and for the qualitative and quantitative detection of IgG antibodies levels, including neutralizing antibodies to SARS-CoV-2 in serum and plasma (lithium heparin) obtained by venipuncture or capillary puncture using the Atellica® IM Analyzer (Siemens Healthineers 2023).

The results of the Atellica® IM sCOVG assay used in this study to quantify IgG and IgM antibodies levels were categorized as: serum values <1.00 UA/mL considered non-reactive, i.e. negative for SARS-CoV-2 IgG/IgM antibodies and, serum values ≥1.00

UA/mL considered reactive, i.e. positive for SARS-CoV-2 IgG/IgM antibodies (Siemens Healthineers 2023).

2.1.4. Complications and risks

The application of the survey involved no risks for the participants. An informative email was sent to all dental professors/ dentists containing all the information about the survey on how to access to it, and whether or not they agreed to take part. With regard to the blood collection procedure, the participants were previously informed that the main complications would be those inherent to the usual practice of venipuncture. The blood samples were taken by a duly qualified professional who was authorised to carry out the collection and to monitor the preservation and packaging of the samples (according to Annex III of Guideline 015/2020, DGS, 23/3/2020) (DGS, 2020).

2.1.5. Data and research confidentiality

All data were confidential since all serologic test were prescribed by the Occupational Health Medicine professional of UFP. All analytic data were directly send by that medicine professional to each participant of the study, after IgG and IgM antibodies quantification. The biological samples were stored by Unilabs- HE-UFP and managed in terms of prescription, analytical results and their destruction at the end of the study, by one member of the research team (Occupational Health doctor, professional of UFP).

2.1.6. Data statistical analysis

Data from the epidemiological research study (survey and serologic assay) were transferred to a spreadsheet of Microsoft Office Excel® software and, statistical analysis was carried out using IBM® SPSS® Statistics vs. 28.0, considering a significance level of 0.05 in all statistical inference situations.

A descriptive and inferential analysis of the effect of the survey variables collected and of the blood samples taken from each participant was performed. Quantitative and qualitative variables were described using the mean (and standard deviation), median (quartiles), as well as the minimum and maximum values. Inference was carried out using appropriate techniques, chosen after checking the assumptions of parametric techniques.

If the parametric technique could not be used, then a non-parametric test was carried out to determine differences between study groups, meaning the population median. The statistical tests carried out used a significance level of 0.05 (α=0.05).

Nominal categorical variables were described using counts and percentages and ordinal variables using the median of observations when appropriate. Prevalence measures were presented as percentage and with the respective 95% confidence interval, calculated using the Wald method or the exact method, depending on the applicability of the expressions to each situation. The bivariate description of qualitative variables was carried out using contingency tables, with counts and percentages.

In most situations, the distribution of the quantitative variable was not normal and given the high level of asymmetry in the observed distributions, the comparison of measures of central tendency was carried out using non-parametric tests, the median of the observations (Kruskal-Wallis test for more than 2 groups, and/or Mann-Whitney U test for 2 independent groups).

2.2. The Systematic analysis of cross-sectional studies on COVID-19 Vaccines and IgG antibody serological markers

A systematic review of observational, cross-sectional, longitudinal and retrospective studies performed between 2019-2024 of COVID-19 vaccines and serological outcomes of IgG immunoglobulin antibody, among the field of dental care/dental educations, as dentists/dental care professionals/healthcare workers was performed, following the STROBE Strengthening the reporting of observational studies in epidemiology (STROBE) guidelines (STROBE, 2024).

The research question, based on the PICO model, was as follows: does IgG levels from blood samples of dentists/dental care professionals/dental academic professors shows reactivity (higher level values than the respective assay reference values) after administration of COVID-19 vaccines?

2.2.1. Search Strategy and Data Collection Process

A comprehensive search was performed by two team members (G.M. and L.T.) of electronic database PubMed and B-on was conducted. The search strategy incorporated terms from Mesh (Medical Subject Headings), such as: “COVID-19”, “SARS-CoV-2”, “Healthcare workers”, “Immunoglobulin G”. Pertinent search terms as “vaccine”, “dentist”, “dental professionals”, “dental academics/education”, “IgG antibody” were joined by Boolean operators (“OR” and “AND”). The most recent search was conducted in January 2024. Search terms were included in the title and/or abstract and were suitably modified for each database. The search strategy is presented in **Table 1**.

Table 1. Search strategy used in the electronic database.

SEARCH FIELD	MESH TERMS OR KEYWORDS
Search field 1	“SARS-CoV-2 Vaccine” OR “COVID-19 vaccine” AND “Healthcare workers” AND “Immunoglobulin G” OR “IgG Antibody”
Search field 2	“SARS-CoV-2 Vaccine” OR “COVID-19 vaccine” AND “Healthcare workers” AND “Immunoglobulin G” OR “IgG Antibody” Filter from 2019-2024
Search field 3	“SARS-CoV-2 Vaccine” OR “COVID-19 vaccine” AND “Dental Professional” OR “Dental Academics” OR “Dental care” AND “Immunoglobulin G” OR “IgG Antibody”

2.2.2. Inclusion criteria, exclusion criteria and eligibility

Only original research articles that focus on observational, cross-sectional, longitudinal, and retrospective cohort studies on COVID -19 vaccines applied to healthcare workers with quantitative serological response of anti-spike IgG titter response after SARS-CoV-2 vaccines, and published in the last 6 years (2019 to 2024 years), in English language were included. The studies have been screened for their relevance, and those that met the inclusion criteria have been reviewed in detail namely: only Healthcare professionals/workers that included Doctors, Dentists, Nurses, staff.

To assess the IgG immunoglobulin or IgG antibody levels (measured in BAU/mL, IU/mL, or AU/mL) of the observational, prospective and retrospective studies outcomes, studies were collected and analysed according to the PICO strategy: *Population*: Dental care, dentists and dental education, dental academic professors; *Intervention: Positive* reactivity of IgG (levels higher than the respective assay reference value) from blood/plasma samples after COVID-19 vaccination; *Comparison: Non-positive reactivity (*lower level values than the respective assay reference value) of IgG; *Outcomes:* IgG antibody levels measured in BAU/mL, IU/mL, or AU/mL, according each assay performed.

Types of publications on COVID-19 vaccines other than those considered in the inclusion criteria such us, case control studies, and cohort applied exclusively to other professional cohorts, even those working in hospital or other health/education environments, but which were not directly involved in dental-healthcare, such as administrative staff. Also were excluded studies conducted on saliva, dry blood, other samples than blood/plasma, studies involving animals (like rats), studies focus on other virus than SARS-CoV-2 or not focused on anti-S1 or RBD subunit (as anti-S2 subunit).

2.2.3. Study Screening and Selection

Articles found through the applied search terms were exported to the Mendeley Desktop Reference Manager v2.103.1 software in order to identify and eliminate duplicates. A first screening of records titles and abstracts was carried out by two independent examiners (G.M. and P.M.M), according the inclusion and exclusion criteria, the main purpose of this review and the PICO approach. The remaining studies were assessed for eligibility, inclusion and exclusion criteria and qualitative synthesis by Full-text assessment and screening.

2.2.4. Study Data

Summaries of the best available evidence to address the specific research question by the comprehensively literature search, in-depth analysis and synthesis of results was done. Reference records, and authors and year of publication was done. The qualitative methodology of examination included the observational studies aims, materials and methods, the assays used, and their main results in terms of the independent variables, the IgG levels outcomes, according to the evaluation assay and respective of reference value.

2.2.5. Quality Assessment

The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement was assessed as quality tool for the selected studies. All questions were derived directly from the STROBE guideline (STROBE, 2024). The STROBE checklist comprised 22 items related to the title and abstract (item 1), introduction (items 2 and 3), methods (items 4–12), results (items 13–17), discussion (items 18–21) and information on funding (item 22)It was decided to have scores of 0: if the particular checklist item was not fulfilled, a score of 1: if the particular checklist item was fulfilled with the page number, and Score of "n.a": if particular checklist item was not applicable for the specific publication. Item scores for each study were summed to create a total quality score out of 22 and this was represented as a percentage of the total possible score. The researchers devised cut-off scores in order to allow ease of description of the quality of each of the studies. Studies that scored below 50% were considered to be of 'poor quality' and were excluded from the review. Studies scoring 50-74% were rated to be of moderate quality and studies scoring above 75% were graded as high quality. Both moderate and high-quality studies were included in this review (Vandenbroucke et al., 2007).

2.2.6. Data Synthesis

The serological samples were analysed for the variable of IgG levels and the resulting values, measured in BAU/mL, IU/mL, or AU/mL, were recorded along with their corresponding Standard Deviations (SD). To synthesise the outcomes, the studies were classified based on the noteworthy findings regarding IgG levels observed in relation to the administered vaccine, as well as the population under investigation.

3. RESULTS

3.1. Observational, Cross-Sectional, Pilot Study Result

The vaccination rate in the sample of this study was of 91.5% (n=43) until July 2021 (**Table 2**) and 93.6% (n=44) until June 2022 (**Table 3**).

Table 2. Inferential Analysis Between Demographic Factors, Health Status, Professional Activity of Respondents, and Number of SARS-CoV-2 Vaccine doses (Until July 2021)

Demographic Variables, General Health, and Professional Activity		Number of vaccine doses administered (as of July 2021)			P value
		0	1*	2	
		n=4	n=7	n=36	
Gender	Female	4 (100%)	3 (42.9%)	25 (69.4%)	0.138[1]
	Male	0 (0%)	4 (57.1%)	11 (30.6%)	
Age (years)	Average(DP)	45.8 (13.7)	39 (9.4)	42.7 (8)	0.705[2]
	Median (IQR)	46.5 (33-57.8)	42 (31-47)	42 (39.3-46)	
	Min-Max	32-58	27-52	26-65	
Diabetes	Yes	0 (0%)	0 (0%)	1 (2.8%)	0.855[1]
	No	4 (100%)	7 (100%)	35 (97.2%)	
Cardiovascular Disease (excluding Hypertension)	Yes	0 (0%)	1 (14.3%)	0 (0%)	0.054[1]
	No	4 (100%)	6 (85.7%)	36 (100%)	
Chronic Lung Disease (excluding Asthma)	Yes	0 (0%)	0 (0%)	0 (0%)	n.a.
	No	4 (100%)	7 (100%)	36 (100%)	
Asthma	Yes	0 (0%)	1 (14.3%)	1 (2.8%)	0.350[1]
	No	4 (100%)	6 (85.7%)	35 (97.2%)	
Obesity (BMI≥30 kg/m2)	Yes	0 (0%)	0 (0%)	3 (8.3%)	0.613[1]
	No	4 (100%)	7 (100%)	33 (91.7%)	
Autoimmune Disease (ex. Rheumatoid Arthritis, Lupus)	Yes	0 (0%)	1 (14.3%)	0 (0%)	0.054[1]
	No	4 (100%)	6 (85.7%)	36 (100%)	
Inflammatory Disease	Yes	0 (0%)	0 (0%)	1 (2.8%)	0.855[1]
	No	4 (100%)	7 (100%)	35 (97.2%)	
Chronic Liver Disease	Yes	0 (0%)	0 (0%)	0 (0%)	n.a.
	No	4 (100%)	7 (100%)	36 (100%)	
Cancer (in the last 5 years)	Yes	0 (0%)	0 (0%)	1 (2.8%)	0.855[1]
	No	4 (100%)	7 (100%)	35 (97.2%)	
Immunodeficiency (Primary or Acquired)	Yes	0 (0%)	0 (0%)	0 (0%)	n.a.
	No	4 (100%)	7 (100%)	36 (100%)	
Hematologic or Coagulation Disorder	Yes	0 (0%)	0 (0%)	2 (5.6%)	0.727[1]
	No	4 (100%)	7 (100%)	34 (94.4%)	
Other Chronic Condition (CC)	Yes	0 (0%)	0 (0%)	2 (5.6%)	0.727[1]
	No	4 (100%)	7 (100%)	34 (94.4%)	
March/2020-May/2020 engaged in clinical Activity MD	Yes	3 (75%)	5 (71.4%)	22 (61.1%)	0.776[1]
	No	1 (25%)	2 (28.6%)	14 (38.9%)	
June/2020-June/2021 engaged in clinical teaching activities in MIMD and MD activities	Yes	4 (100%)	6 (85.7%)	34 (94.4%)	0.593[1]
	No	0 (0%)	1 (14.3%)	2 (5.6%)	

Statistical Test applied: 1 – T. Qui2 ; 2–T. Kruskal- Wallis; * Includes individuals with a previous diagnosis of SARS-CoV-2/COVID-19 infection and with na indication for the administration of only one dose of the vaccine until July 2021; n.a – not applicable

No significant association was observed (**Tables 2 and 3**) between age, gender, presence of chronic pathologies, or clinical activity/clinical teaching regarding the number of vaccine doses or absence of vaccination.

Table 3. Comparative Analysis of Demographic Variables, General Health, with the Total Number of Doses of SARS-CoV-2 Vaccine (3rd Collection – Until June 2022)

Demographic Variables, General Health, and Professional Activity		**Number of vaccine doses administered (as of June 2022)**		**P value**
		0	**2 to 3**	
		n=3	**n=44**	
Gender	Female	3 (100%)	29 (65.9%)	0.220[3]
	Male	0 (0%)	15 (34.1%)	
Age (years)	Average (DP)	50.3 (12.4)	41.8 (8.3)	0.102[2]
	Median (IQR)	57 (36-57)	42 (38.3-46)	
	Min-Max	36-58	26-65	
Diabetes	Yes	0 (0%)	1 (2.3%)	1.000[1]
	No	3 (100%)	43 (97.7%)	
Cardiovascular Disease (excluding Hypertension)	Yes	0 (0%)	1 (2.3%)	1.000[1]
	No	3 (100%)	43 (97.7%)	
Chronic Lung Disease (excluding Asthma)	Yes			n.a.
	No	3 (100%)	44 (100%)	
Asthma	Yes	0 (0%)	2 (4.5%)	1.000[1]
	No	3 (100%)	42 (95.5%)	
Obesity (BMI≥30 kg/m2)	Yes	0 (0%)	3 (6.8%)	1.000[1]
	No	3 (100%)	41 (93.2%)	
Autoimmune Disease (ex. Rheumatoid Arthritis, Lupus)	Yes	0 (0%)	1 (2.3%)	1.000[1]
	No	3 (100%)	43 (97.7%)	
Inflammatory Disease	Yes	0 (0%)	1 (2.3%)	1.000[1]
	No	3 (100%)	43 (97.7%)	
Chronic Liver Disease	Yes	0 (0%)	0 (0%)	n.a.
	No	3 (100%)	44 (100%)	
Cancer (in the last 5 years)	Yes	0 (0%)	1 (2.3%)	1.000[1]
	No	3 (100%)	43 (97.7%)	
Immunodeficiency (Primary or Acquired)	Yes			n.a.
	No	3 (100%)	44 (100%)	
Hematologic or Coagulation Disorder	Yes	0 (0%)	2 (4.5%)	1.000[1]
	No	3 (100%)	42 (95.5%)	
Other Chronic Condition (CC)	Yes	0 (0%)	2 (4.5%)	1.000[1]
	No	3 (100%)	42 (95.5%)	

Statistical test applied: 1 – T. Fisher; 2–T. t-student; 3 – T. Qui2; n.a – not applicable

For the purpose of monitoring vaccination history and doses of SARS-CoV-2 vaccine throughout the period of this research, each participant (n=47) filled in a data update form provided at the time of each blood collection (July 2021and June 2022- Results of IgG not part of this study).

In the first collection, conducted in July 2021, positivity for IgG was detected in 91.5% (n=43) of the sample, with only 4 individuals having antibody levels below the minimum reference limit (serum values <1.00 AU/mL) of the assay (**Table 4**). When analysing positivity for IgM, 10.6% (n=5) had values exceeding the minimum reference limit (**Table 4**).

Table 4. Inferential analysis of age, gender, history of SARS-CoV-2iInfection, vaccination Status, Positivity/Reactivity, and IgG and IgM Titration Values - 1st Analysis, July 2021

Age	Gender	Previous SARS-CoV-2 Infection	Vaccinated	IgG Pos/Neg*	N	IgG median value (AU/mL)	IgG level or min-max (AU/mL)	IgM median value (AU/mL)	IgM level or min-max (AU/mL)
<30 years	F	No	Yes	Pos	1	-	29.900	-	0.300
	M	Yes	Yes	Pos	1	-	105.500	-	0.400
		No	Yes	Pos	1	-	84.100	-	0.100
30-39 years	F	No	Yes	Pos	5	8.100	1.4-73.0	0.200	0.100-0.400
			No	**Neg**	**2**	**0.500**	0.500	0.300	0.300
	M	No	Yes	Pos	4	29.500	2.2-142.4	0.250	0.200-0.400
40-49 years	F	Yes	Yes	Pos	1	-	84.100	-	0.100
		No	Yes	Pos	18	18.100	1.1-308.9	0.400 [a]	<0.10-1.20 [a]
	M	Yes	Yes	Pos	1	-	10.300	-	0.900
		No	Yes	Pos	6	32.050	6.2-65.6	0.200 [b]	<0.10-1.30 [b]
≥50 years	F	Yes	Yes	Pos	1	-	288.100	-	0.400
		No	Yes	Pos	2	5.950	4.5-7.4	0.850 [c]	0.30-1.40 [c]
			No	**Neg**	**2**	**0.500**	0.500	0.250	0.100-0.400
	M	No	Yes	Pos	2	8.350	6.8-9.9	0.149	<0.10-0.200

*IgG Pos/neg – Categorization of Positive/Reactive IgG Antibody for values ≥ 1 UA/mL; Categorization of Negative/Non-reactive IgG Antibody for values <1 AU/mL. n.a – Not Applicable a – Positive IgM value in 3 individuals (IgM=1.1; 2; 1.2 AU/mL) ; F= Female; M= Male; N= Number of subjects;
b – Positive IgM value in 1 individual (IgM=1.3 AU/mL)
c – Positive IgM value in 1 individual (IgM=1.4 AU/mL)

In July 2021, the first blood analysis **(Table 4)** it was observed that only 4 individuals in the sample had not received any dose of the vaccine against the virus, all of them being female subjects. Two were between the ages of 30 and 39, and the other two were over 50. None of these 4 women had a previous history of SARS-CoV-2 infection, and the serum results showed negativity/non-reactivity to SARS-CoV-2 IgG antibodies against the S1 subunit of the spike protein, with IgG values less than or equal to 0.5 AU/mL. Among the vaccinated individuals (n=43), all showed median results and categorical positivity/reactivity to SARS-CoV-2 IgG antibodies against the S1 subunit of the spike protein.

Out of the total sample (n=47), in July 2021, only 4 individuals reported having a previous diagnosis of COVID-19. Two were male (one under 30 and the other between 40 and 49 years old), and two were female (one between 40 and 49 years old and the other over 50). This group of 4 individuals predominantly had higher median IgG values compared to those who did not have a history of disease or prior infection with SARS-CoV-2 at that time. It is also observed that, predominantly, the median IgG values tend to be higher in vaccinated individuals with a history of SARS-CoV-2 infection. When analysing the IgM values of these 4 individuals, it was found that in the individual with the most recent infection history (May 2021), the IgM values are close to the minimum limit of positivity for IgM (**Table 4**).

Table 5 shows the absolute and relative frequency of individuals and their SARS-CoV-2 vaccines doses received at the time of the first blood collection (July 2021) and until the last blood collection (June 2022).

Table 5. Absolute and Relative Frequency (n and %) of Unvaccinated Individuals and Individuals Vaccinated with One, Two, and Three Doses of SARS-CoV-2 Vaccine, from the 1st Collection in July 2021 to the Last Collection in June 2022

Vaccination Status (number of doses)	Start of Study	End of Study
0	**4 (8.5%)**	**3 (6.4%)**
1	7 (14.9%)	0
2	36 (76.6%)	9 (19.1%)
3	n.a	35 (74.5%)

n.a - Not Applicable

At the 1st blood collection, i.e. until July 2021, 8.5% (n=4) of the individuals were unvaccinated, 14.9% (n=7) had one dose of vaccine and 76.6% (n=36) had already had 2 doses of the SARS-CoV-2 vaccine (**Table 5**). All of the unvaccinated (n=4) were female, with an average age of 45.8±13.7 years. In June 2022 (end of the study) only 6.4% (n=3) of the individuals were unvaccinated, 19.1% (n=9) had received 2 doses of vaccines and 74.5% (n=35) had received 3 doses of the SARS-CoV-2 vaccine.

Table 6 shows the frequency of vaccine doses (by manufacturer) administered from before the 1st blood test (July 2021) until the end of the study (June 2022). At the 1st dose, 68.2% (n=30) of the subjects received the vaccine from AstraZeneca©, 22.7% (n=10) received the vaccine from Pfizer- BioNTech© and 9.1% (n=4) were given the vaccine from the manufacturer Moderna©. Around 45.5% (n=20) of the individuals received the second dose of the vaccine from AstraZeneca© (n=20), 45.5% from Pfizer - BioNTech© (n=20) and 9% (n=4) received the second dose from Moderna©. No individual was given the Janssen-Johnson vaccine&Jonhson©. Around 88.6% (n=31) were given the Pfizer-BioNTech© vaccine as their third dose of vaccination and 11.7% (n=4) were given the Moderna© vaccine.

Table 6. Absolute and Relative Frequency (n, %) of COVID-19 Vaccine Types (Manufacturer Designation) in Vaccinated Individuals (n=44) and number of administered doses in June 2022

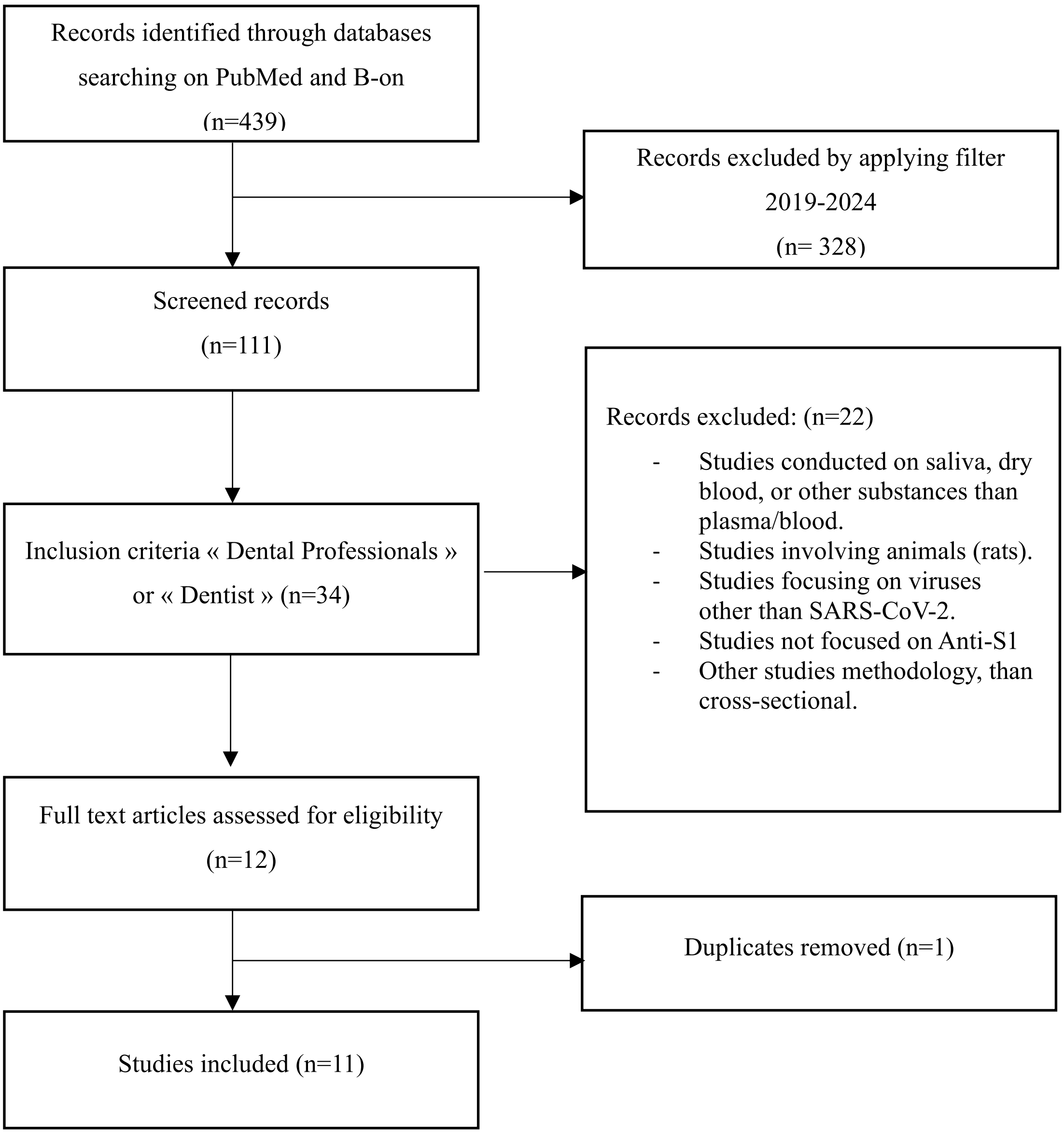
COVID-19 Vaccine Manufacture	1st Dose	2nd Dose	3rd Dose
AstraZeneca ©	30 (68.2%)	20 (45.5%)	0
Pfizer-BioNTech ©	10 (22.7%)	20 (45.5%)	31 (88.6%)
Moderna ©	4 (9%)	4 (9%)	4 (11.7%)
Janssen ©	0	**0**	0

3.2. Systematic Review Results

3.2.1. Studies selection and flow diagram of cross-sectional, observational studies

A total of 439 preliminary references were identified by searching the electronic database (**Figure 1**). After applying the filter of publication between 2019 and 2024, 111 articles were selected for screening. After screening, 34 articles were examined at full-text level. Twenty-two articles were excluded for not meeting the inclusion criteria and due to their serological sampling strategy, focus on animals, examination of viruses other than SARS-CoV, lack of emphasis on the Anti-S1 or RBD Subunit, and not being cross-sectional studies. Twelve studies met the eligibility criteria, with 1 being excluded for being a duplicate. Hence, 11 articles were included in this review for the collection of qualitative data. The selected studies and their main characteristics are described in **Table 7** (and in **Table 9** in the Annex 1).

Figure 1. STROBE flow chart diagram



Of the 11 included studies (**Table 7**), 7 were cross-sectional studies (Beltrán et al., 2023; Cintora et al., 2022; Duś-Ilnicka et al., 2022; Gallus et al., 2021; Mksoud et al., 2022; Nishida et al., 2021; Ribeiro et al., 2022), one was a prospective cross-sectional study (Souan et al., 2022), one was an observational cohort study (longitudinal) (Shields et al., 2021), one was an observational study (prospective) (Inchingolo et al., 2022), and one a prospective clinical cohort study (Duś-Ilnicka et al., 2023).

3.2.2. Quality assessment of selected studies

The detailed quality assessment of the selected studies is shown **in Table 8**, being based on the use of the STROBE Checklist for cross-sectional, observational, and cohort studies. Both moderate and high-quality studies were included in this review, as these were considered sufficiently robust for the synthesis. In total, 9 studies scored above 75%, thus being considered as high-quality studies (Beltrán et al., 2023; Duś-Ilnicka et al., 2022; Gallus et al., 2021; Inchingolo et al., 2022; Mksoud et al., 2022; Nishida et al., 2021; Ribeiro et al., 2022; Shields et al., 2021; Souan et al., 2022), while 2 studies scored between 50-74%, consisting in moderate quality studies (Cintora et al., 2022; Duś-Ilnicka et al., 2023).

Table 7. Main topics (Participants, age, gender, profession, COVID-19 vaccine, sample, serologic Units, IgG level, Seroprevalence) reported in the 11 reviewed cross-sectional studies

Author, Year	Participants (n)	Participant's Age (Mean value)	Gender n (%) Women	Gender n (%) Men	Participant's professions n (%)	"COVID-19 Vaccine	Sample Collection	Serologic Test Applied	Serologic Units	IgG Positivity Reference Value (Min/ Mean Value)	Seropositivity Prevalence n (%)
(Beltrán et al., 2023)	307	36 years (range 29-47)	243 (79.2	64 (20.8)	Dental practicioners : 86 (28) Nursing assistants : 78 (25,4) Physicians : 76 (24,7) Respiratory therapists : 67 (21,8)	BNT162b2 mRNA (Pfizer-BioNTech) Sinovac COVID-19 (CoronaVac) mRNA-1273 (Moderna) AstraZeneca (Vaxzevria	Blood	VIDAS® SARS-CoV-2 IgM/IgG kit	Relative Fluorescence value (RFV)	BL: 360.5±299.6; Follow-up2: 323.7 ± 228.6	Baseline : 249 (81.2) Follow up 1: 298 (97) Follow up 2 : 300 (97.7)
(Duś-Ilnicka et al., 2023)	42	Range 25-50 years	34 (81	8 (19)	Dentist : 25 (59.5) Chairside assistants : 17 (40.5)	BNT162b2 mRNA Vaccine (Pfizer/BioNTech) AstraZeneca COVID-19 Vaccine	Blood	Qualitative, Semi-quantitative, Quantitative IgG count for SARS-CoV-2/neutralizing antibodies.	AU/mL	Positivity 48–126,73 AU/ml Negativity 0–10 AU/ml.	N.A
(Cintora et al., 2022)	195	32.15 years (range 23.51-70.25)	120 (61.5	75 (38.5)	Endodontist : 11 (5.6) Orthodontist : 69 (35.4) Paediatric dentists : 7 (3.6) Students / professors: 68(34.9) Administrative: 40 (20.5)	N.A	Blood	2019-nCoV IgG/IgM Rapid Test Cassette (Sienna, T and D Diag, Canada	N.A	N.A	39 (20)
(Duś-Ilnicka et al., 2022)	127	Dentists: 33 years (SD 11.5) Chairside assistants: 48.5 (SD 11.7) Administrative workers: 44.5 (SD 15.1)	24 (18.9)	103 (81.1)	Dentists : 67 (52.8) Chairside assistants : 40 (31.5) Administrative workers : 20 (15,7)	N.A	Blood	COVID-19 [SARS-CoV-2] IgG ELISA, Demeditec Diagnostics GmbH, Lot. COVG-009	U/mL		7 (6.2)

Table 7. Continues

Author, Year	**Participants (n)**	**Participant's Age (Mean value)**	**Gender n (%) Women**	**Gender n (%) Men**	**Participant's professions n (%)**	**"COVID-19 Vaccine**	**Sample Collection**	**Serologic Test Applied**	**Serologic Units**	**IgG Positivity Reference Value (Min/ Mean Value)**	**Seropositivity Prevalence n (%)**
(Inchingolo et al., 2022)	230	20-30 (19,57%, n=45) 30-40 (22,61%, n=52) 40-50 (14,78%, n=34) 50-60 (23,04%, n=53) 60-70(20%,n=46			Dental physicians, Chair assistants, Hygienists, and Nurses : 90 (39,13) Radiology physicians, Technicians, and Nurses : 72 (31,30) Internal medecine area : 34 (14,78) Forensic medicine area : 34 (14,78)	BNT162b2 mRNA Vaccine (Pfizer-BioNTech)	Blood	LIAISON® SARS-CoV-2 TrimericS IgG assay. (DiaSorin, Saluggia, Italy)	BAU/mL	Positive >500	230 (100)
(Mksoud et al., 2022)	2784	44.8 years (SD 12.5)	2339 (84)	445 (16)	Dentist : 972 (34.9) Dental nurse : 955 (34.3) Dental prophylaxis nurse : 857(30.8)	N.A	Dry Blood Capillary blood samples	Anti-SARS-CoV-2-ELISA; Euroimmun, Lübeck, Germany	N.A	N.A	146 (5.2)
(Ribeiro et al., 2022)	324	40.2 years (range 21-71)	217 (67)	107 (33)	Dentists	N.A		OnSite COVID-19 IgG/IgM Rapid Test® (CTK, Biotech Inc,	N.A	N.A	62 (19.1)
(Souan et al., 2022)	510	Vaccinated: 35 (20.3-70.4) Unvaccinated: 33.1 (24.9-61.4)	219 (46,2)	255 (53)	Laboratory (lab directors, supervisors, research assistants and medical technologists Nursing Medical staffs (physicians, dentists, medical students, clinical research coordinators, radiology and endoscopy technicians). Medical support staff (dentalSupport staffOthers (administration, finance..) technicians,Pharmacists radiology technologists)	BNT162b2 mRNA Vaccine (Pfizer/BioNTech) Sinopharm COVID-19 Vaccine AstraZeneca COVID-19 Vaccine	Blood (Serum sample)	SARS-CoV-2 IgG II Quant assay (Abbott Ar- chitect SARS-CoV-2 IgG with ARCHITECT i1000SR analyzer; Abbott Laboratories, Chicago, IL, USA)	AU/mL	Positive: ≥50 Men : mean titer level 6687.4 (11.4-40,000) Women: mean titer level 5827.2 (0.0-40,000)	Vaccinated: 452 (96.99) Unvaccinated: 13 (68.42)

Table 7. Continues

Author, Year	Participants (n)	Participant's Age (Mean value)	Gender n (%) Women	Gender n (%) Men	Participant's professions n (%)	"COVID-19 Vaccine	Sample Collection	Serologic Test Applied	Serologic Units	IgG Positivity Reference Value (Min/ Mean Value)	Seropositivity Prevalence n (%)
(Gallus et al., 2021)	499	43.9 ± 14.4 years	338 (67)	166 (33)	Dentists: 175 (35,1) Dental technicians: 77 (15,4) Dental hygienists: 151 (30,3) Resident dental doctors: 14 (2,8) Prosthodontic students: 4 (0,8) Dental hygiene students: 12 (2,4) Dental office assistants: 38 (7,6) Nurses: 6 (1,2) Laboratory technicians: 5 (1) Administrative secretaries: 14 (2,8) Managers: 3 (0,6)	N.A	Serum, Plasma, Whole Blood	KHB® Diagnostic Kit for SARS-CoV-2 IgM/IgG (ab-RDT-KHB) from KHB Shanghai, China	N.A	N.A	54 (10.8)
(Nishida et al., 2021)	925	40.0 ± 11.8 years	740(80)	185 (20)	Medical Doctors/Dentists: 149 (16) Nurses : 489 (52.9) Medical technologists : 140 (14.2) Healthcare providers : 49 (5.3) Administrative staff : 98 (10.5)	N.A	Blood	Abbott ARCHITECT SARS-CoV-2 IgG Assay	N.A	N.A	4 (0.43)
(Shields et al., 2021)	1,507	37 (29-47)	1136 (75,4)	371 (24,6)	Dentist : 687 (45,6) Dental nurse : 528 (35) Dental hygienist: 116 (7,7) Receptionist : 80 (5,3) Clinical dental technician : 2 (0,1) Practice manager : 51 (3,4) Other dental health care: 22 (1,5) Auxiliary staff in dental practice/ /clinic : 13 (0,9) Other : 8 (0,5)	BNT162b2 mRNA Vaccine (Pfizer/BioNTech) AstraZeneca COVID-19 Vaccine	Blood	CE-marked, IgGAM enzyme-linked immunosorbent assay (ELISA) measures total anitbody response against the spike glycoprotein (product: MK654; The Binding Site). Measures IgG, IgA and IgM directed against the spike glycoprotein.	IU/mL		N.A

Table 8. Results of the assessment of cross-sectional, observational, and cohort studies by the use of the STROBE Checklist

First Author, Year	1- Title and Abstract	2- Background/rationale	3- Objectives	4- Study Design	5- Setting	6- Participants	7- Variables	8- Data sources/measurement	9- Bias	10- Study size	11-Quantitative variables	12- Statistical methods	13- Participants	14-Descriptive data	15- Outcome data	16- Main Results	17- Other analyses	18- Key results	19- Limitations	20- Interpretation	21- Generalisability	22- Funding	STROBE Quality*
(Beltrán et al., 2023)	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	0	1	1	0	0	1	High Quality
(Duś-Ilnicka et al., 2023)	1	1	1	1	1	1	0	1	0	0	0	1	1	1	1	1	1	1	1	0	0	1	Moderate Quality
(Cintora et al., 2022)	1	1	1	1	1	0	1	1	0	0	0	1	1	1	1	1	1	1	0	0	0	0	Moderate Quality
(Duś-Ilnicka et al., 2022)	1	1	1	1	1	1	1	1	0	0	1	1	1	1	1	1	1	1	1	0	0	0	High Quality
(Inchingolo et al., 2022)	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	0	1	1	0	0	1	High Quality
(Mksoud et al., 2022)	1	1	1	1	1	1	0	1	0	1	1	1	1	1	1	1	1	1	1	0	0	1	High Quality
(Ribeiro et al., 2022)	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	0	0	0	High Quality
(Souan et al., 2022)	1	1	1	1	1	1	1	1	0	0	1	1	1	1	1	1	0	1	1	0	0	1	High Quality
(Gallus et al., 2021)	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	0	0	1	High Quality
(Nishida et al., 2021)	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	0	1	1	0	0	1	High Quality
(Shields et al., 2021)	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	0	0	0	1	High Quality

* Score: 0 = if the particular checklist item is not fulfilled; 1 = if the particular checklist item is fulfilled; n.a = if particular checklist item is not applicable. Final Score: total score x 100 / 22. <50% = Poor quality; 50-74%= Moderate quality; >75% High quality

4. DISCUSSION

This cross-sectional analysed the SARS-CoV-2 IgM antibody and IgG anti-S1-RBD levels one month (July 2021) after the first doses (one or more) of COVID-19 vaccines and, using the enzyme-linked immunosorbent assay (ELISA) technique by blood (plasma) sample, of both dental academic/dentist professionals, after been or not been administrated with COVID-19 vaccines (data survey collected in July 2021 and in June 2022). The analysis of sociodemographic data and overall health status, professional activity, and the number of doses of SARS-CoV-2 vaccine administered was performed.

The population consisted of a total of 62 dentists teaching at MIMD-UFP in the 2020-21 academic year. Nine dentists teaching at the MIMD did not respond to the survey and were excluded. Of the remaining 53 who responded to the survey, only 47 (75.8%) met the inclusion criteria, answering the entire survey and freely consenting to participate in the collection of biological samples. Thirty-two (68.1%) were female and 15 (31.9 %) male. The average age was 42.38 years, ranging from a minimum of 26 to a maximum of 65 years, and did not differ significantly by gender (Student's t-test, $p>0.05$).

In order to monitor the conditions of SARS-CoV-2 infection, COVID-19 vaccination and adverse effects following vaccination against SARS-CoV-2, throughout the period of this research each participant (n=47) filled an update-form provided at the time of each serological collection (1st-July 2021 and 2nd -June 2022).

No significant associations were found between demographic variables, namely gender, age, the existence of chronic pathologies and SARS-CoV-2 infection. Professional practice (Dentistry master teaching/ professional activity as a dentist) did not show a significant relationship with the diagnosis of SARS-CoV-2 infection, either in the period prior to vaccination (until July 2021) - Table 2, or after 1 year, in the final period of the study, in July 2022 - Table 3.

At the time of the first biological sample collection there was no internationally recognised reference method or reference material for standardisation. On the market there were automated tests available processed in laboratory analysis equipment (tests for detecting virus RNA components by molecular biology, RT-PCR and semi-quantitative tests for detecting antibodies, e.g. ELISA) and non-automated tests or rapid tests, devices for in vitro diagnosis: ELISA) and non-automated tests or fast tests, in vitro diagnostic devices for carrying out single tests or small series, with low technical complexity, and which allow results to be obtained in 10-30 minutes, by immunochromatography (for detecting protein components of the virus - antigen tests; for detecting IgA, IgM and IgG antibodies). Fast tests tend to be less sensitive than semi-quantitative antibody detection tests, carried out by serological collection and automated (ECDC, 2020). The lack of monitoring could lead to inappropriate expectations regarding the quantification of potential immunity to SARS-CoV-2 infection or COVID-19 disease.

In our study about 8.5% (n=4) of the individuals reported a history of diagnosis of SARS-CoV-2 infection or COVID-19 disease in the initial phase of the pandemic, namely from March 2020 to July 2021 (time frame before the 1st blood collection carried out). Around 2.1% (n=1) reported SARS-CoV-2 infection between July 2021 and December 2021. The majority of infections occurred between December 2021 and June 2022 with 40.4% (n= 19) of the total sample reporting having had a SARS-CoV-2 infection.

Some studies reported infection rates in dentists ranging from 1% to 15% (Campus et al., 2021; Estrich et al., 2020; Galicia et al., 2020). In most of the countries, the activity associated with healthcare was closed for short periods until the scientific community emerged preventive protocols for clinical practice (Melo, Barbosa, et al., 2021; Melo, Manarte-Monteiro, et al., 2021). During the first period of confinement, the Portuguese national authorities ordered the suspension of dental care practice, except for conditions that were proven to be urgent and unavoidable. In this study, when asked (n=47) about the clinical activity carried out during this period (March to May 2020), around 63.8% (n=30) reported having carried out professional activity as a dentist. From June 2020 to June 2021, 93.6% (n=44) of the respondents reported that carried out both professional activity, as a dentist and academic activity as clinical teachers in the Dentistry master degree-UFP. There was no significant relationship between professional and academic activity and the risk of SARS-CoV-2 infection, which may give us the perception that the infection control standards adopted in clinical and academic environments have been respected and appropriate to the inherent occupational risk.

Portugal achieved one of the highest COVID-19 vaccination rates in the world (DGS, 2022). Health professionals, including dentists, were prioritized for vaccination in March 2021. No data was found regarding the dentists vaccination rates in Portugal. This study aimed to analyze those information. In this study, 93.6% (n=44) of the individuals (n=47) were vaccinated primarily by May 2021. Around 68% were vaccinated with the first dose of the AstraZeneca vaccine, but 33.3% chose to change the second dose to the Pfizer vaccine (Table 5 and 6). The remaining participants followed the protocolized vaccination schedule, i.e. two doses of the respective brands. By June 2022, only 72.3% had a booster dose. There was no great difference in the data compared to the general population (for the 25-49 age group – 68%).

Some studies have reported vaccination rates among dentists of 86% in Lebanon (until February 2021; (Nasr et al., 2021), 79.6% in the Czech Republic (until Sept 2021;), 85% in Israel (until April 2020) (Zigron et al., 2021), 78.5% in Greece (until Dec 2020) (Papagiannis et al., 2021), 71.6% in several French-speaking countries (until Dec 2020) (Verger et al., 2021).

No studies were found indicating the global trend and current percentage of COVID-19 vaccinated dentists. According to the systematic review carried out by Chowdhury et al in 2022, the global rate of refusal of vaccination by dentists was 19% (12.8%-25.2% with 95% CI) (Chowdhury et al., 2022). The majority give as reasons concerns about safety, efficacy, adverse effects and the excessively rapid development of vaccines. These data coincide with those from the meta-analysis carried out by Lin GSS et al 2022, whose results indicated an acceptance rate of vaccination against SARS-Cov2 among dentists of 81.1% (Lin et al., 2022).

Each one of COVID-19 vaccine types aimed to achieve the same goal, to prime the immune system to recognise and neutralise the SARS-CoV-2 virus.

The **mRNA vaccines**, including those developed by Pfizer-BioNTech and Moderna, represent a scientific advance in vaccine development. They contain messenger RNA (mRNA) which is a small piece of the virus's genetic material (mRNA). The spike protein in SARS-CoV-2 (SARS-2-S) interacts with the human ACE2 receptor to gain entry into a cell to initiate infection. Both Pfizer/BioNTech's BNT162b2 and Moderna's mRNA-1273 vaccine candidates were based on stabilized mRNA encoding prefusion SARS-2-S that can be produced after the mRNA is delivered into the human cell and translated. SARS-2-S (Signal peptide) is cleaved into S1 and S2 subunits, with S1 serving the function of receptor-binding (RB domain; RBD) and S2 serving the function of membrane fusion. The cleavage of the S protein into S1 and S2 is an essential step in viral entry into a host cell, and needs to occur before viral fusion with the host cell membrane (Xia, 2021).

When injected into the body, the mRNA vaccines instructs cells to produce a harmless virus component known as the spike protein. This protein stimulates an immune response, instructing the immune system to recognize and attack the actual virus if it is encountered later (Zhang et al., 2023).

Furthermore, the **Viral vector vaccines**, such as those developed by Oxford-AstraZeneca and Johnson & Johnson, employs a harmless virus, typically an adenovirus as a delivery system or vector. The vector is modified to carry the genetic instructions to produce the spike protein of SARS-CoV-2. Once inside the body, the modified virus releases the instructions, leading to spike protein production and subsequent immune response.

Furthermore, the **protein subunit vaccines**, such as the Novavax vaccine, contain purified pieces of the virus, usually the spike protein or a fragment of it. These proteins are produced using recombinant DNA technology or by growing them in cells or organisms. When administered, the immune system recognizes the viral protein as foreign and mounts an immune response. At last, the Inactivated or Whole Virus vaccines, like some formulations of the Sinovac and Bharat Biotech vaccines, are made from either a weakened (attenuated) or inactivated form of the SARS-CoV-2 virus. These vaccines cannot cause the disease since the virus is no longer capable of replication. However, they still trigger an immune response, preparing the body to defend against future infection (Hosseini et al., 2021).

Part of this research aimed to analyze the state of potential contact of individuals (n=47) with the virus (anti-SARS CoV-2 IgM antibodies) and potential immunity (anti-SARS CoV-2 IgG antibodies to the S1 subunit of the spike protein). In the July 2021, IgG positivity was detected in 91.5% (n=43) of the sample, with only 4 individuals showing a quantity of antibodies below the minimum reference limit (serum values <1.00 UA/mL) of the test. When IgM positivity was analyzed, 10.6% (n=5) had values higher than the minimum reference limit (**Table 4**). IgM values above the reference limit were understood to indicate recent infection (maximum IgM peak occured on average 14 days after the onset of infection symptoms, and drops to zero around 35 days later) (Lu et al., 2020). Elevated serum IgG values can result from previous contact with SARS-CoV-2 and consequent infection, or from inoculation with the vaccine administered against the virus (Hosseini et al., 2021). It is therefore important to analyze and monitor data on each individual's history of illness and vaccine doses, and relate them to the potential humoral immune response of IgG antibodies. In July 2021 (**Table 4**) 4 women, two aged 30-39 and two over 50, had no dose of vaccine against the virus, no previous history of SARS-

CoV-2 infection and IgG values less than or equal to 0.5 UA/mL. Of the vaccinated individuals (n=43), all showed median and categorical results of SARS-CoV-2 IgG antibody positivity/reactivity against the target S1 subunit of the spike protein. Only 4 individuals reported having had a previous diagnosis of COVID-19, two of whom were male (one under 30 and the other aged between 40 and 49), and two female (one aged between 40 and 49 and the other over 50). The majority of this group of 4 individuals had the highest median IgG values, compared to those who had no history of previous illness or infection with SARS-CoV-2. It was also found that the median IgG values tended to be higher in vaccinated individuals with a history of SARS-CoV-2 infection.

The study conducted by Gallus et al. (2021) about 10% tested positive, aligning with Lombardy healthcare workers' rates. Notably, 20% were IgM positive and 96% IgG positive. Furthermore, the study showed that prevalence was higher in eastern and southern Lombardy, with males showing higher prevalence (14%) than females (9%). Over 20% of dental staff were smokers, yet no significant link with SARS-CoV-2 was found. Basically, Gallus et al. (2021) showed that dentists effectively protect themselves through PPE and sanitation measures. Still, administrative staff showed higher prevalence, thus suggesting the need for improved training and protective measures for these personnel (Gallus et al., 2021).

In a study conducted in Brazil, Ribeiro et al. (2022) found out that the seroprevalence of SARS-CoV-2 among dentists in the Federal District was about 19%, which is considerably higher than initially hypothesized by the authors. This rate was comparable to that observed in the general population of that same area. This research was relevant due to the scarcity of information about the prevalence of COVID-19 antibodies among dentists. Hence, it stands out as the first probabilistic sampling investigation conducted among Brazilian dentists. Some of the factors associated with seropositivity among this population included a previous diagnosis of COVID-19, loss of taste or smell, and confirmed diagnoses in household members. Interestingly, treating patients with ever was negatively associated with antibody presence, thus potentially indicating dentists' strict adherence to protective measures during patient care (Ribeiro et al., 2022).

In Japan, Nishida et al. (2021) study revealed that there was a low seroprevalence of SARS-CoV-2 IgG antibodies among hospital staff, with only 0.43% testing positive using a laboratory-based quantitative test (Abbott immunoassay). This prevalence was comparable to, or even lower, than that observed in the general population in Osaka during the same period. By comparing national and international data, the authors proved the effectiveness of infection control measures, considering that the prevalence in the hospital was significantly lower than the reported rates in China and comparable to rates in Japan's general population. Still, future longitudinal studies are recommended by Nishida et al. (2021), especially to assess the long-term effectiveness and monitor infection control measures over time (Nishida et al., 2021).

Consistent with other studies, Shields et al. (2021) found out that natural infection with SARS-CoV-2 often leads to robust and durable serological responses (Dan et al., 2021). Moreover, Shields et al. (2021) also showed that seropositivity resulting from natural infection confers longitudinal protection from reinfection, being similar to the results obtained by Lumley et al. (2021), and they identified antibody level of 147.6 IU/mL, associated with a minimum of 6 months of protection from reinfection, which only a small percentage of their cohort has exceeded, hence suggesting that natural infection alone may not generate sufficient herd immunity (Lumley et al., 2021). In terms of the serological testing, Shields et al. (2021) claim that while IgG responses remained stable over time, the investigation's findings suggest that some individuals may mount only transient serological responses not indicative of durable humoral immunity (Cook et al., 2021).

Duś-Ilnicka et al. (2022), on the other hand, included dentists from several specialties in their study (dental surgeons, periodontologists, orthodontist, conservative/restorative dentists, and prosthetic dental specialists). Nevertheless, they did not observe any variation in the results of SARS-CoV-2 among these professionals. Likewise, no significant differences were found among the investigated subgroups, which comprised dentists, dental assistants, laboratory workers, nurses, and administrative workers of the same workspace (Duś-Ilnicka et al., 2022). These findings were congruent with Sarapultseva et al. (2021), who also reported no differences in the presence of IgG antibodies among chairside assistants and dentists (Sarapultseva et al., 2021).

The study conducted by Mksoud et al. (2022) suggests that dentists and their teams may not be at a higher risk for patient-dentist transmission of SARS-CoV-2, with these findings being validated by the widespread adoption of FFP masks, ventilation measures, and the low virus load in the AGDP. The findings of this study, conducted in Germany, contrast with a UK study conducted amidst the peak of the first wave in May 2020, where dental team members faced higher infection rates due to insufficient PPE and knowledge on minimizing exposure. A similar trend of increased infection rates across different dental occupations was observed, albeit without statistical significance, suggesting a need for continued vigilance across all roles within the dental setting (Mksoud et al., 2022).

In their study, Cintora et al. (2022) found that the seroprevalence at the end of the de-escalation phase stood at 20% among all participants, with orthodontists exhibiting the highest prevalence at 34.8%. Most participants tested positive for IgG and negative for IgM, with IgG positivity at 79.5%. Overall, this investigation underscores the importance of ongoing vigilance and preventive measures within dental settings to mitigate the risk of COVID-19 transmission among dental professionals (Cintora et al., 2022).

In their study, Inchingolo et al. (2022) observed sustained antispike titers in most patients even after 270 days post-second dose, contrary to previous findings. Based on the authors, antispike titers >500 BAU/mL indicate prolonged protection, supported by the presence of SARS-CoV-2 memory CD8+ T cells, memory B cells, and memory CD4+ T cells in bone marrow. Moreover, antibody levels were not influenced by age and blood type, except for O negative blood groups, which exhibited more consistent antispike IgG levels. With regard to vaccine booster shots, the authors suggest their administration after 9 months, with prompt antispike titer detection to assess waning immunity (Inchingolo et al., 2022).

In turn, Souan et al. (2022) claim that healthcare workers reporting prior COVID-19 infections demonstrated significantly higher neutralizing IgG antibody titers post-vaccination across all vaccine types. More precisely, healthcare workers that received Pfizer and Sinopharm vaccines demonstrated higher titers if they were previously infected compared to those without prior infection. Still, and despite the overall effectiveness, 3% of vaccinated healthcare workers did not developing neutralizing IgG antibodies, especially among those without prior COVID-19 infections. Therefore, this study stresses the need for booster vaccination campaigns, especially for those who lack prior infection history, with the goal of enhancing their immunity against SARS-CoV-2 (Souan et al., 2022).

On the other hand, Beltrán et al. (2023) revealed that there was a low prevalence of active SARS-CoV-2 infection among healthcare workers, with dental practitioners showing the highest infection rates. Moreover, they demonstrate that interactions with patients and vaccination status influenced the infection susceptibility, with both nursing assistants and physicians having similar infection rates. Lastly, the authors found out that while a high percentage of healthcare workers tested positive for IgG antibodies, thus indicating a prior infection or vaccine response, IgG index values actually decreased over time (Beltrán et al., 2023).

Finally, Duś-Ilnicka et al. (2023) argue that the conducted quantitative diagnostic testing revealed that 9.52% of the dental workers tested positive for SARS-CoV-2 IgG antibodies before being vaccinated in April 2020. However, in qualitative testing only 1 out of 4 previously diagnosed volunteers tested positive, thus indicating potential issues with test specificity. Even though studies have explored the sensitivity and specificity of IgG tests, evidence is lacking for professionals working with oral bioaerosols. Hence, these authors suggest that future research must focus on validating diagnostic tests and assessing antibody dynamics over time to enhance the understanding of COVID-19 immunology in high-risk occupational settings (Duś-Ilnicka et al., 2023).

Outcomes of this epidemiological study should not be extrapolated to other populations, though the number of participants was representative (75.8%) of the population studied, both, dentistry academic teachers and dentist-professionals. However, the importance of applying and monitoring this action in professional populations in the fields of the environment, occupational health and education was discussed, since the safety of these professionals and their both professional skills were essential for the community response, and as teachers in the specific training of dentistry master degree, for safety education and health measures at learning field, as training the dentistry students, the future dentistry professionals.

Based on the systematic review performed five studies used specific **COVID-19 vaccines**, more precisely the following ones: 1) BNT162b2 mRNA Vaccine (Pfizer/BioNTech), Sinopharm COVID-19 Vaccine, and AstraZeneca COVID-19 Vaccine (Souan et al., 2022); 2) BNT162b2 mRNA Vaccine (Pfizer/BioNTech), and AstraZeneca COVID-19 Vaccine (Shields et al., 2021); 3) BNT162b2 mRNA Vaccine (Pfizer-BioNTech) (Inchingolo et al., 2022); 4) BNT162b2 mRNA Vaccine (Pfizer-BioNTech), Sinovac COVID-19 Vaccine (CoronaVac), mRNA-1273 Vaccine (Moderna), AstraZeneca Vaccine (Vaxzevria) (Beltrán et al., 2023); and 5) BNT162b2 mRNA Vaccine (Pfizer/BioNTech), and AstraZeneca COVID-19 Vaccine (Duś-Ilnicka et al., 2023). The remaining 6 studies not involved any type of COVID-19 vaccines.

Regarding the **sample collection** among the participants, most studies were based on blood samples (Beltrán et al., 2023; Cintora et al., 2022; Duś-Ilnicka et al., 2022, 2023; Inchingolo et al., 2022; Nishida et al., 2021; Shields et al., 2021), even though some of them were based on different types of samples, such as on blood serum samples (Souan et al., 2022), on both dry blood and capillary blood samples (Mksoud et al., 2022), and on a serum mixture, plasma and whole blood (Gallus et al., 2021).

Overall, the applied **serologic tests** in the selected studies were the following ones:

- *SARS-CoV-2 IgG II Quant assay* (Abbott Architect SARS-CoV-2 IgG with ARCHITECT i1000SR analyzer; Abbott Laboratories, Chicago, IL, USA) (Souan et al., 2022).
- *IgGAM enzyme-linked immunosorbent assay (ELISA*) measures total antibody response against the spike glycoprotein (product code: MK654; The Binding Site). Measures IgG, IgA and IgM directed against the spike glycoprotein (Shields et al., 2021).
- *LIAISON® SARS-CoV-2 TrimericS IgG assay* (DiaSorin, Saluggia, Italy) (Inchingolo et al., 2022).
- *VIDAS® SARS-CoV-2 IgM/IgG kit* (Beltrán et al., 2023).
- *2019-nCoV IgG/IgM Rapid Test Cassette* (Sienna, T and D Diagnostics Canada; Halifax, NS, Canada) (Cintora et al., 2022).
- *COVID-19 [SARS-CoV-2] IgG ELISA*, Demeditec Diagnostics GmbH, Lot. COVG-009 (Duś-Ilnicka et al., 2022).
- *Anti-SARS-CoV-2-ELISA*; Euroimmun, Lübeck, Germany (Mksoud et al., 2022).
- *Qualitative, semi-quantitative, quantitative IgG count for SARS-CoV-2 and SARS-CoV-2 neutralizing antibodies* (Duś-Ilnicka et al., 2023).
- *KHB® Diagnostic Kit for SARS-CoV-2 IgM/IgG* (ab-RDT-KHB) from KHB Shanghai, China (Gallus et al., 2021).
- *OnSite COVID-19 IgG/IgM Rapid Test*® (CTK, Biotech Inc., Poway, CA, USA) (Ribeiro et al., 2022).
- *Abbott ARCHITECT SARS-CoV-2 IgG Assay* (Nishida et al., 2021).

In turn, only 6 studies presented the specific **serologic units,** namely AU/mL (Duś-Ilnicka et al., 2022, 2023; Souan et al., 2022), IU/mL (Shields et al., 2021), BAU/mL (Inchingolo et al., 2022), and Relative Fluorescence Value (RFV) (Beltrán et al., 2023). Of those studies, five presented different IgG positivity reference values, demonstrating different circumstances. In the study conducted by Souan et al. (2022), the positive mean titer level for men was of 6687.4 (11.4 – 40,000) and for women was of 5827.2 (0.0 – 40,000). In the study conducted by Inchingolo et al. (2022), the positive value was above 500. At the baseline, Beltrán et al. (2023) recorded the positive value of 360.5±299.6, while in the second moment of the follow-up they recorded 323.7±228.6. On the other hand, in their study Duś-Ilnicka et al. (2022) recorded the following values: <9 U/mL – non-reactive; 9-11 U/mL – equivocal; and >11 U/mL – reactive. And Duś-Ilnicka et al. (2023) recorded the following values in their study: positivity – 48-126,73 AU/mL; negativity – 0-10 AU/mL.

The **seropositivity prevalence** varied across the studies. For instance, in the study developed by Souan et al. (2022), there were 452 (96.99%) vaccinated participants, while 13 (68.42%) were not vaccinated. In the study conducted by Inchingolo et al. (2022), the seropositivity prevalence was 230 (100%), comprising all participants. Beltrán et al. (2023) presented different levels of seropositivity prevalence, referring to different moments in their research: at baseline it was of 249 (81.2%), in the first follow-up it was of 298 (97%), and in the second follow-up it was of 300 (97.7%). In their study, Cintora et al. (2022) recorded a low seropositivity prevalence, more precisely of 39 participants (20%), and Ribeiro et al. (2022) recorded as prevalence 62 participants (19.1%). However, other authors recorded an even lower seropositivity prevalence, such as: Gallus et al. (2021) – 54 participants (10.8%); Duś-Ilnicka et al. (2022) - 7 participants (6.2%); Mksoud et al. (2022) – 146 participants (5.2%); and Nishida et al. (2021) – 4 participants (0.43%).

Lastly, the selected studies also investigated other variables, which might be correlated with the seropositivity prevalence, such as: history of COVID-19 (presence or absence) (Duś-Ilnicka et al., 2022; Souan et al., 2022), hemoglobin level (Souan et al., 2022), white blood cell level (Souan et al., 2022), lymphocytes, platelets, and neutrophils (Souan et al., 2022), ethnicity (Cintora et al., 2022; Shields et al., 2021), diabetes (Shields et al., 2021), smoking (Gallus et al., 2021; Shields et al., 2021), the influence of the blood type (Inchingolo et al., 2022), comorbidity (Beltrán et al., 2023; Ribeiro et al., 2022), working conditions (Beltrán et al., 2023; Duś-Ilnicka et al., 2022; Mksoud et al., 2022; Nishida et al., 2021), exposure outside work (Beltrán et al., 2023), use of protective equipment (Beltrán et al., 2023; Mksoud et al., 2022), symptoms associated with the infection (Cintora et al., 2022; Nishida et al., 2021), cohabiting members in the household (Duś-Ilnicka et al., 2022; Nishida et al., 2021; Ribeiro et al., 2022), Body Mass Index (Gallus et al., 2021), location (Gallus et al., 2021; Mksoud et al., 2022), and educational level (Ribeiro et al., 2022).

Based on all selected studies, our research on seroprevalence among dental professionals has provided valuable insights into the prevalence of SARS-CoV-2 antibodies, the effectiveness of protective measures, and the impact of vaccination and prior infection history.

Overall, the findings suggest that dental professionals effectively protected themselves through the use of PPE and sanitation practices. Nevertheless, administrative staff and dentistry students may require additional training and protective measures, as they often exhibited higher prevalence rates compared to clinical staff. The influence of vaccination and prior infection history on antibody levels among healthcare workers has also been highlighted. Vaccinated individuals, especially those with prior COVID-19 infections, demonstrated higher neutralizing antibody titers, underscoring the need for booster vaccination campaigns to enhance immunity against SARS-CoV-2.

Challenges such as test specificity issues in qualitative diagnostics and the need for validation of diagnostic tests in high-risk occupational settings have been identified. Future research should focus on longitudinal studies to assess the long-term effectiveness of infection control measures and monitor antibody dynamics over time. Additionally, efforts should be made to enhance understanding of COVID-19 immunology among dental professionals and improve diagnostic accuracy in seroprevalence studies.

In sum, the global findings after analyzing all articles underscore the importance of considering a broad range of variables when assessing immune responses to vaccination. Overall, the selected studies highlight the need for ongoing, nuanced investigations to better understand and optimize COVID-19 vaccine efficacy across different populations and contexts.

5. CONCLUSION

This cross-sectional pilot study was performed in July of the year 2021 among a population of both professional, dental academic professors and dentists, in a dental academic environment, and had as main goal to assess the plasma immunoglobulin G (IgG) and IgM antibodies to the SARS-CoV-2 spike 1 (S1) subunit protein, receptor-binding domain (RBD), one month after the first dose(s) of the COVID-19 vaccines administration to those professionals (vaccinated or not vaccinated). It made possible to draw the following conclusions:

- The sample consisted of 47 participants, 75.8 % of the total study population, 32 (68.1%) of whom were female and 15 (31.9 %) male with a mean age of 42.38 years (26 to 65 years); the range age did not differed by gender;

- 8.5% (n=4) diagnosed with SARS-CoV-2 infection until July of 2021 year;

- 8.5% (n=4) of the individuals had not been vaccinated against SARS-CoV-2 at the time of serological sampling, 14.9% (n=7) had one dose of vaccine and 76.6% (n=36) had two doses of the SARS-CoV-2 vaccine; All of the unvaccinated individuals (n=4) were women, with an average age of 45.8±13.7 years.

- As first dose 68.2% (n=30) of the individuals received the vaccine from AstraZeneca, 22.7% (n=10) received the vaccine from Pfizer- BioNTech and 9.1% (n=4) were given the vaccine from the manufacturer Moderna.

- No significant associations were found between demographic variables, namely gender, age and SARS-CoV-2 infection. The existence of chronic pathologies was also not found to be related to the previous diagnosis of COVID-19 disease. Professional activity, in terms of teaching/clinical teaching at the academic dentistry degree and/or professional activity as a dentist, was not significantly related to the diagnosis of SARS-CoV-2 infection in the period prior to vaccination.

- Vaccination rate was of 91.5% (n=43) until July 2021. No significant association was found for age, gender, the existence of chronic pathologies, or clinical activity/clinical teaching and the number of vaccine doses or lack of vaccination.

- From the quantitative analysis of SARS-CoV-2 positivity/reactivity for IgG and IgM antibodies (July 2021), the positivity rate for IgG and IgM was of 91.5% (n=43) and 10.6% (n=5), respectively.

- Two women aged 30-39 and two more over 50 years old, did not had any dose of vaccine against the virus, did not had previous history of SARS-CoV-2 infection and had IgG values equal or lower than 0.5 UA/mL. Of the vaccinated individuals (n=43), all showed median and categorical results of SARS-CoV-2 IgG antibody positivity/reactivity against the S1 subunit target of the spike protein.

Furthermore, this work performed a systematic review on behalf of the main COVID-19 vaccines and the key serological antibody markers, used for evaluation of immune responses, with a specific focus on immunoglobulin G (IgG), that allowed to enumerate the following conclusions:

- The studies investigated a variety of COVID-19 vaccines, with a notable emphasis on the BNT162b2 mRNA Vaccine (Pfizer/BioNTech). This suggests widespread use and interest in this particular vaccine across different research contexts.

- While most studies used blood samples to measure serologic responses, there were also studies utilizing serum, plasma, dry blood, and capillary blood. This highlights the flexibility and adaptability in methodologies for collecting and analyzing samples in vaccine research.

- A variety of serologic assays were used across the studies, indicating no single standardized test for measuring antibodies against SARS-CoV-2. This variety reflects the evolving landscape of serologic testing and the importance of cross-validation among different tests.

- Some studies presented different IgG positivity reference values, meaning that distinct circumstances were analyzed. Thus, IgG levels showed reactivity after the administration of COVID-19 vaccines in some investigations.

- The seropositivity prevalence among participants varied significantly, ranging from as low as 0.43% to as high as 100%. This wide range suggests differences in participant demographics, vaccination timing, and perhaps varying sensitivities and specificities of the serologic tests used.

- Several demographic, health-related, behavioral, and biological factors were examined for their potential correlation with seropositivity. These factors include history of COVID-19, ethnicity, comorbidities, lifestyle behaviors (e.g., smoking), and biological markers (e.g., blood type).

In sum, the selected studies collectively underscore the complexity and diversity in the immune response to COVID-19 vaccines. The variability in seropositivity rates and the wide range of influencing factors highlight the need for a nuanced understanding of vaccine efficacy across different populations and settings. The use of several serologic tests and sample collection methods further indicates an ongoing effort to refine and standardize measures of immune responses. The overall high quality of the studies included in the systematic analysis supports the credibility of these conclusions, as well as the importance of continued research to address the dynamic challenges posed by COVID-19 among the studied healthcare professionals.

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ANNEXES

Annex A.

Table 9. Descriptive Summary of the 11 reviewed cross-sectional studies

Author	Objective	Methods	Results	Conclusion
(Beltrán et al., 2023)	To describe SARS-CoV-2 seroprevalence, infections, and extent of PPE use during the COVID-19 pandemic among HCWs at three different times, including dental practitioners (DP), nursing assistants (NA), physicians (P), and respiratory therapists (RT), from Bogotá, Colombia.	After IRB approval, this cross-sectional study included 307 HCWs. Participants provided nasopharyngeal swabs and blood samples to detect viral RNA (RT-qPCR) and IgM/IgG anti-SARS-CoV-2 (ELFA-ELISA) at baseline (BL) and two follow-ups. Infection prevalence was defined as the number of positive-tested participants (RT-qPCR and/or IgM). Data on clinical status and biosafety habits were collected each time.	Differential infection prevalence was found among HCWs through the study timeline (BL: RT-qPCR = 2.6%, IgM = 1.6%; follow-up 1 (45 days after BL): RT- qPCR = 4.5%, IgM = 3.9%; follow-up 2 (60 days after BL): RT-qPCR = 3.58%, IgM = 1.3%. Dental practitioners showed a higher infection frequency in BL and follow- up 1. IgG-positive tested HCWs percentage progressively increased from BL to follow-ups among the whole sample while index values decreased. Limitations in N95 availability and a high perception of occupational risk were reported.	A low prevalence of active SARS-CoV-2 infections among HCWs groups was found. Over time, there was an increase in participants showing IgG antibodies, although the levels of these antibodies in the blood decreased. Additionally, HCWs reported limitations in the availability of PPE as well as a variation in their safety practices.
(Duś-Ilnicka et al., 2023)	The aim of our study was to monitor the immune response before and after the vaccine in a high-risk population, composed by dental professionals.	A clinical prospective study was carried out among dental professionals at the Academic Dental Polyclinic, Wroclaw Medical University (Wrocław, Lower Silesia region, Poland). Blood samples were collected at an interval of one year – March/April 2020, before the vaccination against COVID-19, and April 2021, after the vaccination. The analysis was performed on serum with four different methods: qualitative, semi-quantitative, and quantitative IgG count for SARS-CoV-2, and SARS-CoV-2 neutralizing antibodies.	A total of 42 healthy adult volunteers participated in the study. The results showed a statistically significant difference ($p < 0.05$) in antibody levels before and after vaccination (1st and 2nd measurement) for each test method. The tests that were used affected the results and the test that showed the strongest relationship with the result was the Qualitative test.	Dental professionals are the adult working population most at risk for COVID-19. Monitoring SARS-CoV- 2-status-related seropositivity can provide useful information occupational risk factors for dental professionals.

Table 9. Continues

Author	Objective	Methods	Results	Conclusion
(Cintora et al., 2022)	To determine the prevalence of COVID-19 infection among dental professionals at an Academic Center in Madrid (Spain) at the beginning of the pandemic's de-escalation phase.	A cross-sectional study was designed. COVID-19 infection was determined by membrane-based immunoassay qualitative detection of IgG and IgM antibodies in human whole blood. Age, sex, race and professional qualification recorded, as were symptoms compatible with COVID-19 infection whenever present. Data collected were analysed by means of descriptive and qualitative (X2) statistical analyses.	A total of 195 individuals were included (40 administrative professionals and 155 dentists). Seroprevalence at the end of the de-escalation phase was 20.0% among all the participants. The highest prevalence was found among orthodontists (34.8%) followed by the paediatric dentists (28.6%) and oral surgeons (14.7%) Most subjects were positive for IgG and negative for IgM (79.5%).	The seroprevalence of SARS-CoV among dental professionals at the end of the de-escalation phase after the first wave of the pandemic was almost double the seroprevalence of the general population. Orthodontists had the highest rates of SARS-CoV-2 infection.
(Duś-Ilnicka et al., 2022)	Since the SARS-CoV-2 outbreak in 2019, special safety protocols have been intro- duced in dentistry. Dental professionals were determined to be mostly at risk for contract- ing the virus due to aerosol-generating procedures used. This preliminary study starts the cycle of the laboratory protocols describing the quality and efficacy of laboratory tests in the SARS-CoV-2 immunoglobulin G (IgG) detection in the serum of asymptomatic dental personnel during the last quarter of 2020.	IgG levels were measured with the use of a semi-quantitative enzyme-linked immunosorbent assay (ELISA) in vitro diagnostic kit in the serum of a study group that con- sisted of 127 employees of the dental clinic divided into 3 subgroups: SUB1: dentists (n = 67); SUB2: dental assistants, dental hygienists, nurses, laboratory workers (n = 40); SUB3: administrative workers (n = 20). Pearson analysis of results from the questionnaires attached to the study protocol were provided to assure that the results compare to the par- ticipants' impressions about their general health.	Positive ELISA IgG results were found in 6% (n = 4) of the SUB1 group, 7.50% (n =3) of the SUB2 group, and 5% of the SUB3 group. The percentage of participants without work interruption from the beginning of the pandemic was 54% of dentists and 60% of chairside assistants.	Serum IgG prevalence with the use of a semi-quantitative test was low, and further research on the biobanked samples should follow to determine the levels of IgG with quantitative methods and/or to evaluate the presence of neutralising antibodies in dental personnel. Because of the low representation of seropositivity studies in this group, it will be crucial to confirm the risk of COVID-19 transmission in dental offices.

Table 9. Continues

Author	Objective	Methods	Results	Conclusion
(Inchingolo et al., 2022)	The aim of the present investigation was to evaluate the immune reaction in health workers of the Polyclinic of Bari to identify the relationship of antispike titers with blood type, sex, age, and comorbidities.	This prospective observational study (RENAISSANCE) had as its primary endpoint the assessment of serologic response to BNT162b2 at three blood titers: the first at 60 days after the second dose (3 February 2021); the second titer at 75 days after the first titer; and the third titer at 130 days after the second titer.	Out of 230 enrolled staff members, all responded excellently to the mRna Pfizer (BNT162b) vaccine. Only one patient, 40 days after the second dose (3 February 2021), was positive on the swab control performed on 15 March 2021, although completely asymptomatic, and was negative on the subsequent molecular swab performed on 30 March 2021. All the patients responded to the mRNA Pfizer (BNT162b) vaccine with an antispike IgG level above 500 BAU/mL at the first antispike protein essay (60 days after the second dose on 3 April 2021); at the second titer (75 days after the first titer on 20 June 2021), 4 (1.7% of 230 enrolled) patients showed an antispike IgG level under 500 BAU/mL; at the third titer (130 days after the second titer on 30 June 2021, which means 9 months after the second dose), 37 (16.1% of 230 enrolled) patients showed an antispike IgG level under 500 BAU/mL.	The data analysis demonstrated that patients belonging to blood group 0, regardless of their rhesus factor, showed the strongest level of antibodies compared to the other groups. No dependency was found between low antibodies level and sex or age. Molecular swab controls were performed every 15th of the month continuously. However, the enrolled patients' activity was at high risk because they carried out medical activities such as dental and surgical as well with droplets of water vaporized by the effect of turbines, piezosurgery. The vaccination campaign among health workers of the Policlinico of the University of Bari "Aldo Moro" led to an excellent serological response and the complete absence of COVID-19 incident cases, so the antibody response was excellent. The COVID-19 vaccine booster shot should be administered after 9 months and not without prompt antispike titer detection to assess if any sign of waning immunity is present in that specific patient.
(Mksoud et al., 2022)	During the corona pandemic, dental practices temporarily closed their doors to patients except for emergency treatments. Due to the daily occupational exposure, the risk of SARS-CoV-2 transmission among dentists and their team is presumed to be higher than that in the general population. This study examined this issue among dental teams across Germany.	Intotal,2784participants providedusablequestionnairesanddrybloodsamples.Drybloodsamples were used to detect IgG antibodies against SARS-CoV-2. The questionnaires were analyzed to investigate demographic data and working conditions during the pandemic. Multivariable logistic mixed-effects models were applied.	We observed 146 participants with positive SARS-CoV-2 IgG antibodies (5.2%) and 30 subjects with a borderline finding (1.1%). Seventy-four out of the 146 participants with SARS-CoV-2 IgG antibodies did not report a positive SARS- CoV-2 PCR test (50.7%), while 27 participants without SARS-CoV-2 IgG antibodies reported a positive SARS-CoV-2 PCR test (1.1%). Combining the laboratory and self-reported information, the number of participants with a SARS-CoV-2 infection was 179 (6.5%). Though after adjustment for region, mixed-effects models indicated associations of use of rubber dams (OR 1.65; 95% CI: 1.01–2.72) and the number of protective measures (OR 1.16; 95% CI: 1.01–1.34) with increased risk for positive SARS-CoV-2 status, none of those variables was significantly associated with a SARS-CoV-2 status in fully adjusted models.	The risk of SARS-CoV-2 transmission was not higher among the dental team compared to the general population. Clinical relevance. Following hygienic regulations and infection control measures ensures the safety of the dental team and their patients.

Table 9. Continues

Author	Objective	Methods	Results	Conclusion
(Ribeiro et al., 2022)	This cross-sectional study aimed to determine the seroprevalence of SARS-CoV-2 infection among Brazilian dentists and its associated factors.	Stratified random sampling of dentists from 33 administrative regions of the Federal District (Brazil) was performed. The presence of antibodies was verified by the OnSite COVID-19 IgG/IgM Rapid Test. Participants answered a survey about sociodemographic characteristics, exposure to COVID-19, and professional practice. A chi-square test was performed between serostatus and exposure variables. Mann-Whitney tests were carried out for quantitative variables. Odds ratio (OR) and 95% confidence intervals (95%CI) were calculated. A series of binomial logistic regression models was performed.	The seroprevalence of SARS-CoV-2 infection among 324 selected dentists was 19.1%. There was a statistically significant association between seropositivity and previous confirmed diagnosis of COVID-19, loss of taste or smell, diagnosis of COVID-19 in a household member, and treatment of a patient with fever. Dentists with a previous confirmed diagnosis of COVID-19 had 29.5 [12.7–68.4] higher odds to exhibit positive serology test results. Dentists with confirmed diagnosis of COVID-19 in a household member had 2.5 [1.1–5.3] times higher odds to exhibit positive serology test results. Professionals with loss of taste or smell in the last 15 days had 5.24 [1.1–24.1] times higher odds to exhibit positive serology test results, and, for those who had treated patients with fever, there were 2.99 [1.03–8.7] times higher odds to exhibit negative serology test results.	There was a similar prevalence rate of infection among dentists and in the general population. Nevertheless, this finding applies to the epidemiological situation in 2020, before the development of vaccines and the emergence of SARS-CoV-2 Delta variant.
(Souan et al., 2022)	We aim to determine seroprevalence rates and neutralizing IgG antibody response to various immunizations among HCWs.	This study was conducted between July and September 2021, in which blood samples were obtained from HCWs and SARS-CoV-2 IgG neutralizing antibodies were measured. Data regarding vaccination status with Pfizer/BioNTech, Sinopharm, or AstraZeneca vaccines, occu- pation, and prior COVID-19 infection were analyzed.	COVID-19 infection post-vaccination was associated with higher mean antibody titers, regardless of vaccine type. Pfizer/BioNTech vacci- nation produced higher mean antibody titers for HCWs with prior COVID-19 infection ($p < 0.00001$) than other types of vaccines. Although 96% of HCWs were vaccinated, 3% were seronegative. For HCWs who were seropositive, there were no significant differences between the mean antibody titers when comparing occupations and blood indices.	Awareness of the immunity status of HCWs is key to protecting this important group against SARS-CoV-2, especially those without prior COVID-19 infection. Further public health efforts regarding booster vaccination for HCWs are crucial to provide necessary antibody protection.

Table 9. Continues

Author	Objective	Methods	Results	Conclusion
(Gallus et al., 2021)	The aim of this study is to quantify the SARS-CoV-2 antibody prevalence and determinants in a sample of dentists, dental hygienists, and other personnel employed among the dental staff in Lombardy region.	We used an accurate rapid diagnostic test kit detecting immunoglobulins (Ig) in 504 adults	Of the 499 participants who obtained a valid antibody test, 54 (10.8%) had a SARS-CoV-2 positive test (0.4% IgM+, 1.8% both IgM+ and IgG+, and 8.6% IgG+). A statistically significant association with infection was found for geographic area (compared to Milan, adjusted odds ratio was 2.79, 95% confidence interval, CI: 1.01–7.68 for eastern and 2.82, 95% CI: 1.34–5.94, for southern Lombardy). The clinical staff did not result positive to SARS-CoV-2 more frequently than the administrative staff.	This is the first study using antibody test in the dental staff personnel. It shows that the prevalence of SARS-CoV-2 infection in Lombardy region was around 10%, in line with estimates on other healthcare professionals. Despite the close physical contact with the patient, dentists have been able to scrupulously manage and effectively use protective devices.
(Nishida et al., 2021)	To evaluate the effectiveness of our hospital's current nosocomial infection control measures, we conducted a serological survey of anti-SARS-CoV-2 antibodies (immunoglobulin [Ig] G) among the staff of our hospital, which is treating coronavirus disease 2019 (COVID-19) patients.	The study design was cross-sectional. We measured anti-SARS-CoV-2 IgG in the participants using a laboratory-based quantitative test (Abbott immunoassay), which has a sensitivity and specificity of 100% and 99.6%, respectively. To investigate the factors associated with seropositivity, we also obtained some information from the participants with an anonymous questionnaire.	We invited 1133 staff members in our hospital, and 925 (82%) participated. The mean age of the participants was 40.0 ± 11.8 years, and most were women (80.0%). According to job title, there were 149 medical doctors or dentists (16.0%), 489 nurses (52.9%), 140 medical technologists (14.2%), 49 healthcare providers (5.3%), and 98 administrative staff (10.5%). The overall prevalence of seropositivity for anti-SARS-CoV-2 IgG was 0.43% (4/925), which was similar to the control seroprevalence of 0.54% (16/2970) in the general population in Osaka during the same period according to a government survey conducted with the same assay. Seropositive rates did not significantly differ according to job title, exposure to suspected or confirmed COVID-19 patients, or any other investigated factors.	The subclinical SARS-CoV-2 infection rate in our hospital was not higher than that in the general population under our nosocomial infection control measures.

Table 9. Continues

Author	Objective	Methods	Results	Conclusion
(Shields et al., 2021)	We report a longitudinal seroprevalence analysis of antibodies to SARS-CoV-2 spike glycoprotein, with baseline sampling prior to large- scale practice reopening in July 2020 and follow-up postimplementation of new public health guidance on infection prevention control (IPC) and enhanced personal protective equipment (PPE).	In total, 1,507 West Midlands DCPs were recruited into this study in June 2020. Baseline seroprevalence was determined using a combined IgGAM enzyme-linked immunosorbent assay and the cohort followed longitudinally for 6mo until January/February 2021 through the second wave of the coronavirus disease 2019 pandemic in the United Kingdom and vaccination commencement.	Baseline seroprevalence was 16.3%, compared to estimates in the regional population of 6% to 7%. Seropositivity was retained in over 70% of participants at 3- and 6-mo follow-up and conferred a 75% reduced risk of infection. Nonwhite ethnicity and living in areas of greater deprivation were associated with increased baseline seroprevalence. During follow- up, no polymerase chain reaction–proven infections occurred in individuals with a baseline anti–SARS-CoV-2 IgG level greater than 147.6 IU/ml with respect to the World Health Organization international standard 20-136.	After vaccination, antibody responses were more rapid and of higher magnitude in those individuals who were seropositive at baseline. Natural infection with SARS-CoV-2 prior to enhanced PPE was significantly higher in DCPs than the regional population. Natural infection leads to a serological response that remains detectable in over 70% of individuals 6 mo after initial sampling and 9 mo from the peak of the first wave of the pandemic. This response is associated with protection from future infection. Even if serological responses wane, a single dose of the Pfizer-BioNTech 162b vaccine is associated with an antibody response indicative of immunological memory.