STUDY PROTOCOL

Study protocol for the SeMaCo study: A longitudinal regional cohort study to assess COVID-19 seroprevalence in blood donors [version 1; peer review: 2 approved with reservations]

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Abstract

Introduction: Serologic studies are crucial for clarifying the regional dynamics of the SARS-CoV-2 coronavirus pandemic as well as the success of a vaccination campaign against COVID-19. We describe a cohort study investigating the seroprevalence of antibodies against SARS-CoV-2 in Magdeburg (Saxony-Anhalt, Germany).

Protocol and study design: The SeMaCo study (Serologische Untersuchungen bei Blutspendern des Großraums Magdeburg auf Antikörper gegen SARS-CoV-2) is a longitudinal, regional cohort study to assess the seroprevalence of COVID-19 in blood donors from Magdeburg (Capital of Saxony-Anhalt) and surrounding areas. We consider blood donors as a surrogate for the healthy, working-age population of Saxony-Anhalt. The study primarily aims to measure the prevalence and kinetics of IgG antibodies against SARS-CoV-2 in first time and repeat blood donors over a period of 21 months. The study explores four survey periods of three to four months each (January–April 21, July–October 21, February–April 22, July–October 22). At each visit, we will assess the attitude towards vaccination, the antibody response following vaccination, as well as undesired vaccination effects. Furthermore, we will collect data on occupational activities, housing conditions and the frequency of family and other social contacts.

Discussion: The SeMaCo study extends the spectrum of seroepidemiological investigations in Germany. A longitudinal

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Any reports and responses or comments on the article can be found at the end of the article.

observation with repeated testing and serial interviews can provide a more accurate view on the dynamics of COVID-19 prevalence and spread than repeated cross-sectional studies. Based on interim results from similar studies, we expect a seroprevalence of SARS-CoV-2 antibodies below 5% in the first survey period. SeMaCo will influence policy decisions and preventative measures.

Keywords

SeMaCo study protocol, COVID-19, SARS-CoV-2 antibodies, seroprevalence, repeat blood donors, COVID-vaccination, epidemiology

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Introduction

The SARS-CoV-2 virus (severe acute respiratory syndrome coronavirus 2) has been circulating since December 2019. It is the causative agent for COVID-19 (coronavirus disease 2019). Transmission is facilitated through infectivity in pre- and asymptomatic disease (Robert Koch-Institut – SARS-CoV-2 virus – profile). In Germany, more than 3.5 million people have contracted COVID-19 and more than 84,000 people have died as of 8th May 2021 (Robert Koch-Institut – SARS-CoV-2 virus – report).

At the beginning of the pandemic, the federal state of Saxony-Anhalt (FSA) was considered a COVID-19 low prevalence area within Germany (Robert Koch-Institut SARS-CoV-2 virus – report). Meanwhile, the FSA has a seven day incidence of COVID-19 in 103 per 100,000 inhabitants, which is in line with the nationwide average (as of 14th May 2021) (Robert Koch-Institut – SARS-CoV-2 virus – case numbers). Data from Japan and Italy show that approximately 18–23 % of all individuals infected with SARS-CoV-2 are asymptomatic.^{1,2} Therefore, the number of COVID-19 infections in the FSA may still be substantially underestimated.

Patients suffering from COVID-19 develop a cellular and humoral immune response. Detailed data on the long-term kinetics of the immune response are currently not available. Neutralizing antibodies³ and memory T-cells⁴ have been shown to persist for at least several months. By vaccination, high neutralizing antibody titers can be induced with vaccine efficacies of up to 95% in clinical studies.⁵ However, reports show that reinfections occur⁶ and vaccines do not offer 100% protection.⁷ During the course of the pandemic, new variants of the virus may lead to immune escape.

Epidemics become self-limiting when herd immunity is reached through natural infection or mass vaccination. The threshold when herd immunity can be expected is influenced by various factors such as the basic reproduction number, occurrence of immune escape variants, and waning immunity. Monitoring seroprevalence and circulating variants can help to understand these mechanisms.

Due to the temporary successful containment of SARS-CoV-2 in summer 2020 and despite the current exponential viral spread only a small proportion of the German population has experienced a SARS-CoV-2 infection. In March 2021, the seroprevalence of specific SARS-CoV-2 antibodies in a German population sample (93,000 blood donors) was reported to be a small proportion 7–8% (Robert Koch-Institut – Project RKI/SeBluCo Report). The use of safe and effective vaccines should protect individuals and the population from SARS-CoV-2 infection and/or COVID-19 disease. The vaccination start date in Germany was 27th December 2020. Several effective vaccines are currently available. However, a third wave with exponential growth, with variants of SARS-CoV-2, is currently being observed in Germany.

The detection of SARS-CoV-2-specific IgG antibodies in serum is a relatively reliable indicator of infection. About 90 % of patients with mild symptoms develop SARS-CoV-2 –specific IgG antibodies in serum whereas IgG is formed by all patients with severe symptoms.⁸ IgM and IgG antibodies are formed approximately simultaneously, 7–14 days after infection.⁹

Most commercially available serological tests detect SARS-CoV-2 antibodies against either the spike protein or the nucleocapsid protein. The spike protein is essential for binding to and fusion of the virus with the target cell. It can elicit a protective immune response and is also used as an antigen in vaccines.

The detection of specific antibodies to SARS-CoV-2 in a representative group will provide a better estimate of the true extent of the COVID-19 epidemic in the FSA. The SeMaCo study (Serologische Untersuchungen bei Blutspendern des Großraums Magdeburg auf Antikörper gegen SARS-CoV-2) will observe blood donors in the city of Magdeburg (capital of the FSA with 240,000 inhabitants) and surrounding areas.

Objectives

The primary objective of the study is to determine the dynamics of the antibody response to the spike protein of SARS-CoV-2 on a population level. Important secondary objectives are:

1. To investigate the influence of age, gender, occupational activities, domestic conditions, and the frequency of family and other social contacts, on the incidence of SARS-CoV2 antibodies.
2. To analyse differences between participants with symptomatic and asymptomatic COVID19 disease courses.
3. To assess vaccination preparedness and the effect of a vaccination campaign on vaccination preparedness.

4. If a new vaccine becomes available, to analyse the influence of vaccination on the antibody detection rate.
5. To determine test characteristics of other serological tests for antibodies against SARS-CoV-2 spike and nucleocapsid antigens, other coronaviruses like SARS, MERS, 229E NL63, and HKU1, as well as influenza A and B antigen subtypes.

Protocol

Study design and setting

This prospective, longitudinal cohort study will recruit donors at the blood donation service of the University Hospital Magdeburg in the FSA. Donors of blood, plasma, and thrombocytes will be asked to participate during four survey periods. Existing blood samples from 2019 will also be tested (negative controls):

BS-0: ca. 2,000 existing samples from 2019 (Q3/Q4, 2019)

BS-1: ca. 2,000 donors, January–April 2021

BS-2: ca. 2,000 donors, July–October 2021

BS-3: ca. 2,000 donors, January–April 2022

BS-4: ca. 2,000 donors, July–October 2022

We aim to test the same participants during all four survey periods. Donors who do not attend subsequent survey periods will be replaced by new donors until the sample size of 2,000 donors for each planned collection period has been reached. The first survey period (BS-1) is three and a half months (20th January 2021 – 30th April 2021).

The study will be conducted for 21 months so that vaccination effects can be reliably assessed (e.g., first approval for vaccine in the EU was on 27th December 2020).

Prior to the start of the SeMaCo study, we assessed demographic factors of the blood donors at the University Hospital Magdeburg. In addition to blood sampling, the study participants will be asked to fill out two questionnaires (Q1–2) and, from the start of the second survey period, a follow-up questionnaire (Q3): Q1 for possible contacts and contact frequencies in their educational, professional and private contexts, Q2 for their attitude towards vaccination (in general and towards COVID-19) as well as recording the timing, vaccine and undesired effects of vaccination. Different questionnaires will be used at the initial and the follow-up examinations. At follow-up, the answers regarding current educational, professional, and private contact frequencies (Q3) and the current vaccination status will be updated. To ensure compatibility with other studies in Germany, questions were adapted from other COVID studies and vaccination surveys with permission of the authors^{10–11} (<https://hzi-c19-antikoerperstudie.de/> and <https://methodcov.de/>). One aim was to be able to compare the results of our study with other COVID studies in Germany. The questions we used were therefore taken from other COVID and vaccination surveys conducted in Germany. Questions on socio-demographics are based on the demographic standards of the Federal Statistical Office. In addition, some questions from questionnaire 2 (vaccination attitudes) were developed by ourselves.¹² All questionnaires were pretested and slightly revised for final use.

Study population

The study population are blood donors at the University Hospital Magdeburg. In 2019, 4,724 donors attended, 2,317 (49.0%) of whom were women. A total of 3,931 (83.2%) were multiple donors. The multiple donors all age groups, from 18 years upward, were rather equally represented with an increase of donors in the higher age groups older than 45 years. This resembles the general age distribution of the FSA where the average age was 47.9 years and the majority of inhabitants were older than 40 years in 2019 (<https://de.statista.com/>). Residents of Magdeburg represent 68% of the Magdeburg University Hospital blood donors and 32% are residents of the surrounding area. Overall, the blood donors essentially represent a cross-section of the healthy working population. It is expected that a high proportion of the blood donors will participate in the study due to their intrinsic motivation.

Criteria for patient inclusion

Participants must be a minimum of 18 years old and must provide written informed consent. Consent can be given stepwise for each study module: testing of blood samples, sociodemographic/contact survey, and the attitude towards vaccination survey.

Criteria for patient exclusion

The exclusion criteria are based on the donor exclusion criteria of the [German Medical Association](#). There are numerous reasons that can lead to temporary or even permanent exclusion from blood donation. Typical reasons for temporary deferral are medical interventions, taking medication or travelling abroad, especially to areas in which mosquitoes can transmit malaria or viruses (e.g., Chikungunya virus, Zika virus). Reasons for temporal deferral do not result in exclusion from this study. Serious diseases are the most common reasons for a permanent ban and do result in an exclusion from this study.

Sample size calculation

Sample size was calculated using the [G*Power](#) program (version 3.1.9.7, Heinrich-Heine-University Düsseldorf, Düsseldorf, Germany) (G*Power, RRID:SCR_013726).¹³ Based on interim results of a similar study ([Robert Koch-Institut – Project RKI/SeBluCo Report](#)), there was an assumption that 1% of our study population was undetected infected. The sample calculation resulted in a sample size of $n = 1,719$ ($\alpha = 0.05$, $\beta = 0.80$, with a power of 80%). Therefore, our goal was to recruit at least 1,719 subjects.

Based on the donor numbers from the blood bank, we assumed 2,000 participants during the planning. We aim to test the same participants during survey periods. Donors who do not attend subsequent survey periods will be replaced by new donors until the sample size of 2,000 donors for each planned collection period has been reached.

Laboratory processing

Sample collection and transport

Blood samples (serum tubes, 8.5 ml) are collected during blood donation. Samples are pseudonymized in the Institute for Transfusion Medicine and Immunohematology with blood bank (ITIB). A label with the ITIB blood donation identification number (INR) is printed and attached to the serum tube. The samples are then registered using the laboratory information and management system (LIMS) of the Institute of Medical Microbiology and Hospital Hygiene (IMMB) and assigned an order number for every sample. The samples are transported from the ITIB to the IMMB with a pneumatic tube system.

Serological testing

Specifically, IgG antibodies are serially measured in first time and repeat blood donors over a period of 21 months. Upon arrival at the laboratory (IMMB), the serum tube is centrifuged and stored at 4°C for a maximum of 72 hours before being analysed. The test system ensures comparability of IgG values over all four survey periods by internal quality control procedures and assay calibration as prescribed in the analysers instruction manual and the IMMB Standard Operating Procedure. IgG antibody testing is performed according to the IMMB Standard Operating Procedure using an automated, CE-marked, accredited procedure. A uniform test system will be used throughout the study (LIAISON® SARS-CoV-2 TrimericS IgG, Diasorin).

Several retention samples are frozen at –80°C. These samples serve for retesting, neutralization tests, and testing in case new test methods become available.

The test results are stored in the IMMB's laboratory information and management system (LIMS) and are accessible through the order number. The test results can be accessed by the ITIB. The pseudonymized results will be stored for 30 years in the LIMS. If a test result is positive for antibodies, the participant will be informed by the ITIB.

Neutralizing antibodies

Neutralizing antibodies will be determined for a random portion of the samples at the IMMB. Additionally, samples from individuals who reported a COVID-19 infection or vaccination but do not exhibit IgG-antibodies in the serological test will be tested for neutralizing antibodies. A sample from the time prior to the infection is included in the analysis for comparison.

Specimen storage

The samples will be stored for at least two years at –80°C at the IMMB.

Data management and data protection

The study participant's survey will be pseudonymized during the participant's blood donation using five-digit participant pseudonyms (ID-P) by the ITIB. Ideally, the questionnaires will be completed online using the Otto-von-Guericke University's survey system, [LimeSurvey](#) (version 3.23.1+200825, LimeSurvey GmbH/LimeSurvey: An open-source survey tool. LimeSurvey GmbH, Hamburg, Germany). A paper version of the questionnaire will be available

to participants who do not wish to complete it online. The subsequent electronic recording of the paper questionnaires will be done by the Institute of Social Medicine and Health Systems Research (ISMHSR). The ISMHSR and the IMMB will not have access to the study participants' personal data at any time.

The data processing (collection, storage, use) in the SeMaCo study is based on the University Hospital Magdeburg's and the ISMHSR's data protection concepts. The data collection in the context of the (online) survey is carried out using the LimeSurvey server at the OvGU University Computing Center (UCC). The data protection concepts are in accordance with the EU General Data Protection Regulation (EU-GDPR) and the Federal Data Protection Act.

Data flow

1. The participant management at the ITIB uses five-digit participant pseudonyms (ID-P) for each of the study participants, which remain unchanged for each participant for the duration of the study. In addition, an eight-digit identification number (INR) is generated for each blood donation.
2. The online questionnaires are generated by the ISMHSR on OvGU's LimeSurvey server and made available to the study participants for completion.
3. The study participants fill in the online questionnaires, indicating their ID-P. Alternatively, a paper version of the questionnaire will be provided to participants who do not wish to complete the questionnaire online, or in the event that the survey system has a malfunction. The ID-P is also recorded on the paper version.
4. The survey data is stored pseudonymously in the LimeSurvey survey system in the OvGU Computing Centre for the duration of the respective collection period (BS-1 to BS-4).
5. At the end of the respective sampling period (BS-1 to BS-4), the survey data will be exported from the survey system to the ISMHSR. Intermediate data backups will also be made.
6. The survey data will be stored, long-term, pseudonymously in the ISMHSR.
7. Blood samples are taken from the study participants. The sample tubes are marked with the specific INR of the ITIB, assigned an order number for every sample in the IMMB's LIMS by ITIB and sent to the IMMB.
8. The IMMB performs the blood analysis and stores the results, together with the corresponding INR.
9. The antibody test-result is sent to the ITIB, together with the INR in the IMMB's LIMS.
10. The serological test results will be exported into a [Microsoft Excel](#) (version 2016) (RRID:SCR_016137) spreadsheet (An open-access alternative that can provide an equivalent function is [Google sheets](#) (RRID:SCR_017679)) in the ITIB computer system (Excel spreadsheet) and stored there for the long-term. The Excel file will contain the INR, the ID-P and the antibody result.
11. The antibody findings are assigned to the corresponding ID-P in the ITIB.
12. A positive antibody status (test result) is extracted from the antibody findings and stored separately, together with the INR.
13. The antibody status is transmitted to the ISMHSR together with the corresponding ID-P.
14. The antibody status and ID-P are stored, long-term, in the ISMHSR.
15. The survey data is linked to the antibody status data via the ID-P at the ISMHSR. The dataset is stored as an analysis dataset.
16. This is followed by the analysis of the data by the SeMaCo researchers.

Data storage locations

- Person identifying data: ITIB Donor Information System, Excel Data Sheet ITIB
- Pseudonymized blood analysis results: LIMS of the University Hospital Magdeburg
- Pseudonymized survey results: Temporary storage on the LimeSurvey server of the UCC; permanent storage in the ISMHSR
- Pseudonymized antibody status: permanent storage in the ITIB and ISMHSR

Data analysis and statistical plan

The main analyses will be descriptive using e.g., counts and percentages. Missing values will be excluded. We will compare groups (for example: vaccinated and non-vaccinated subjects) with the Wilcoxon test (for continuous parameters). Analyses of covariance (ANCOVA) are also included. P-values of 0.05 or less are deemed significant. All statistical analyses will be performed using Statistical Package for the Social Sciences (SPSS, version 26.0, Armonk, NY: IBM Corp (IBM SPSS Statistics, RRID:SCR_019096)) An open-access alternative that can provide an equivalent function is the R *stats* package (R Project for Statistical Computing, RRID:SCR_001905).

Patient confidentiality

Participants can revoke consent for each module of the study in writing. If the participant revokes consent to participate in the study, the questionnaire survey data will be deleted, and the results of the antibody tests will be anonymized. The study participants will be informed of the deletion and anonymization.

Ethics and dissemination

The written informed consent includes information about the study objectives and content, the measuring instruments, the type and content of data collection and storage, the voluntary nature of their participation, and the option to revoke consent at any time. The blood donors also have the option not to participate in individual study modules (partial consent) and are not disadvantaged by non-participation. The blood donors will have sufficient time to consider their decision before giving their consent/refusal. The blood donation staff will be always available to answer questions. The study has been approved by the Otto-von-Guericke University Magdeburg ethics committee (No. 163/20). The study is registered in the DRKS (German Clinical Trials Register): DRKS00023263.

The results of the study will be published in peer-reviewed journals and presented to the public at a press event. In addition, social media (e.g., Instagram, Facebook, Twitter, LinkedIn) will be used to inform the public about news from the study.

Study status

The study started on 20th January 2021. At the end of the initial survey period (30th April 2021), 2237 subjects were recruited. The next survey period started on 1st July 2021.

Conclusions

Seroepidemiological studies can be an important component for better estimation and classification of the prevalence of infection during the COVID-19 pandemic.¹⁰ The SeMaCo study expands the spectrum of German sero-epidemiological studies by investigating the prevalence of antibodies to SARS-CoV-2 in blood donors from Magdeburg and the surrounding areas of the capital of Saxony-Anhalt in a prospective manner. Both genders equally contribute to blood donation and the donors' age distribution reflects the age distribution in the general population of the FSA. Moreover, older donors (60–72 years of age) are also included. For donors over 60 years of age, this is possible in accordance with criteria of the German Medical Association after an individual medical decision. Therefore, we consider blood donors as a suitable surrogate from the healthy working age until pension age population of the FSA.

Longitudinal sampling in repeat donors will allow for an estimate of how the virus spreads in the general population and/or the success of a vaccination campaign during the study period of 21 months (January 2021 to October 2022). In addition to the serological examination, information about daily individual face-to-face contacts in the context of the donors' normal professional and social activities are collected and correlated with a future COVID infection.

Furthermore, the SeMaCo study assesses blood donors' attitude towards vaccination and their COVID-19 vaccination status. A special feature of the study is that both the antibody tests and the questionnaires are conducted among repeat donors at four different time periods. This allows a more accurate view on the dynamics and course of SARS-CoV-2 antibody prevalence, contact intensities and patterns and attitudes towards vaccination over time in northern Saxony-Anhalt. Depending on the further course of the epidemic, the efficacy of containment measures and the vaccination frequency within the study population, COVID-19 antibody levels are expected to increase significantly in the three subsequent survey periods. Moreover, SeMaCo will deliver data on the persistence of the SARS-CoV-2 antibody response in a large group of healthy individuals over a study period of 21 months. We expect that the results of the SeMaCo study can influence policy decisions and prevention efforts.

Data availability

Extended data

Figshare: Extended data for 'Study protocol for the SeMaCo study: A longitudinal regional cohort study to assess COVID-19 seroprevalence in blood donors'.

<https://doi.org/10.6084/m9.figshare.16546215.v2>.¹²

This project contains the following extended data:

- SeMaCo – Self-formulated questions.docx

(Questionnaire 2 (Attitude towards vaccination))

(Questionnaire 1 (Contact Information) and Questionnaire 3 (Follow-up):

Questions about sociodemographic data (Information about the person, school degree, occupational activities); Questions about contacts with COVID-19 infected persons and (occupational and private) contacts; questions about nursing activities; questions about participation in events (during pandemic); questions about commuting to work, housing conditions, household, family and travel used with permission from Robert Koch-Institute.¹⁰

Questions about testing for COVID-19 and physician diagnosis of COVID-19 and symptoms if test/diagnosis is positive used with permission from Robert Koch-Institute¹⁰ and Helmholtz Center for Infection Research (<https://hzi-c19-antikoerperstudie.de/>). Questions about marital status based on MethodCOV project (<https://methodcov.de/>).¹¹

Questionnaire 2 (Attitude towards vaccination): Questions about attitudes toward vaccination for COVID-19 used with permission from KUNO Kids Health Study. University of Regensburg.¹¹

Data are available under the terms of the [Creative Commons Zero "No rights reserved" data waiver](#) (CC0 1.0 Public domain dedication).

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Gannon C.K. Mak

Public Health Laboratory Services Branch, Hong Kong, China

The study protocol written by Pohl *et al.* described the plan to investigate SARS-CoV-2 seroprevalence in the city of Magdeburg and surrounding areas. Overall, the study protocol was clear and well written. It covered different aspects, (1) objectives, (2) study population including inclusion and exclusion criteria, and (3) time frames of sampling and targeted sample size. The technical parts were described in detail from pre-examination, examination, and post-examination procedures. The study protocol correlated well with the primary objective (i.e. determination of the dynamics of the antibody response). The secondary objectives 1 to 3 (page 3) should be able to be covered by Questionnaire 1 and Questionnaire 2 (page 8). However, I do have several comments for the remaining two secondary objectives and the corresponding examination procedures.

It is unlikely that the SARS-CoV-2 will vanish as evidenced by the SARS-CoV-1 between 2003 and 2004. On the contrary, SARS-CoV-2 will circulate among us just like other respiratory viruses. Due to the antigenic drift/shift, the vaccines for influenza viruses have to update annually. The currently available SARS-CoV-2 vaccines are based on the prototype strain detected in late December 2019, either Wuhan-Hu-1 or WIV04. With the emergence of Omicron in late November 2021, it is reasonable to suspect that the effectiveness of COVID-19 vaccines is affected due to the unusually high number of spike protein substitutions/changes. Although Omicron was only detected after the authors completed this protocol (i.e. September 2021), the new vaccine that you mentioned in the secondary objective 4 should be referring to the new COVID-19 vaccines based on the BA.1 Omicron available later this year¹.

Omicron evolves continuously, several sub-lineages/descendent lineages, BA.2 to BA.5, BA.2.12.1 were noted. The new variants usually replace the old variants with competitive advantages (e.g. higher transmissibility, mismatched vaccines). The latest findings showed that among participants who had been infected with the BA.1 or BA.2, the neutralizing antibody titer against BA.2.12.1, BA.4, and BA.5 was lower than the old variants. It means that neutralization escape was found for the emerging variants^{2,3}. Undoubtedly, the incidences of COVID-19 are increased due to the relaxation of COVID-19 control policies worldwide and emerging variants. As the disease

progresses, it is not an easy task to interpret the SARS-CoV-2 seroprevalence, different variables should be taken into account. To ensure a valid study, it is therefore important to rule out all sources of bias and confounding factors.

The test results of SARS-CoV-2 antibodies vary between assays⁴ and also the targets used⁵. Only one assay was used to assess the SARS-CoV-2 IgG antibody in this study protocol. Unless there are strong justifications, the authors should consider using another assay for assessing the SARS-CoV-2 antibodies and also the seroconversion. Although the authors will assess the neutralizing antibodies in a partial portion of the samples, the assay used was not known. The use of nucleocapsid (N) as the vaccine antigen target is in a dilemma. The downside of this target is that the results may be overestimated since N protein is conserved among other coronaviruses. Solving this issue should not be a concern since samples were obtained prior to SARS-CoV-2 being detected in late December 2019. However, it can help to differentiate if the results are due to vaccination or past infection⁴. In addition, it can help to confirm the responses from the questionnaires, and the outcomes of the study will be more convincing. Careful and comprehensive planning is important so that secondary objective 5 could be addressed.

The strength of the study is the overlapping between pre- and post-omicron circulation. I am not sure if the study has generated results yet. I hope the authors may find the comments useful and design the way forward for this ongoing study. Early identification of potential deficiencies should enable the authors to overcome these flaws so that positive results are generated and concordant with the authors' objectives.

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Is the rationale for, and objectives of, the study clearly described?

Partly

Is the study design appropriate for the research question?

Partly

Are sufficient details of the methods provided to allow replication by others?

Partly

Are the datasets clearly presented in a useable and accessible format?

Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Virology

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Reviewer Report 29 June 2022

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In the present study protocol, the authors aim to address the seroprevalence of SARS-CoV2 or/and SARS-CoV2 vaccination in the Saxony-Anhalt area population in Germany. In addition, the authors will also assess social behaviors and the subject's attitude towards vaccination via questionnaires. The sample population representing people from the Saxony-Anhalt area are blood donors at the University Hospital Magdeburg.

The rationale and objectives of the study are clearly described. The authors established an appropriate study design to address the study's objectives, including four follow-up visits and existing samples for 2019 as control (for antibody response/titration).

Information is missing to clearly understand the planned statistics and be able to repeat the study, i.e. :

- The authors indicate that they « aim to test the same participant during all four survey periods .» How missing data will be handled, e.g., data of a subject are present for BS-1, BS-4 but not for BS-2 and BS-3 (missing visits due to medical condition (COVID-19 or not) or not related to medical condition).
- Are BS-0 subjects' specific samples needed? If yes, how are data from a new donor (no BS-0) analyzed?
- Are only subjects analyzed if all visits are completed (if yes, please explain how generated bias is handled)?
- How are handled data of patients who die during the study period (COVID-19 related or not)?

- Are alternatives to obtain information if patients are not presenting to a study visit (proactive contact, at least for questionnaires)?
- Exclusion criteria that could affect the sample population should be listed e.g. if any, according to German regulations: restriction on BMI, sexual behavior, age... (not all readers are aware of German blood donation regulations).

Is the rationale for, and objectives of, the study clearly described?

Yes

Is the study design appropriate for the research question?

Yes

Are sufficient details of the methods provided to allow replication by others?

No

Are the datasets clearly presented in a useable and accessible format?

Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: immunology,

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

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