

We would like to thank the reviewers *B.2020.0158E*, *B.2020.01571* and *B.2020.01586* for their time and positive appraisal of our project entitled *'Monthly monitoring of seroprevalence of SARS-CoV-2 antibodies in relation to lockdown and open-up measures in The Netherlands.'* Below we clarify the main points from the reviewers. We used reference numbers as referred in the original proposal except for the new references 1 to 3 that are listed below.

Both reviewers *B.2020.0158E* and *B.2020.01571* mention the unique opportunity we have upfront having the availability to determine SARS-CoV-2 antibodies in stored residual samples of a large proportion of all pregnant women in the Netherlands. Reviewer *B.2020.01571* mentions this is an elegant way of using this material, that can offer a quick insight on seroprevalence of SARS-CoV-2 antibodies, but also give relevant insight on its change over time in the Netherlands. Reviewer *B.2020.01571* also acknowledges the relevance at international level, as there is a unique opportunity for other (also low resource) countries to follow this example of efficient use of residual pregnancy samples.

Reviewer *B.2020.0158E* acknowledges the fact that most of our national policy has been based on models, and that these models depend data of seroprevalence in the Dutch population. If these model assumptions are not correct, this directly has impact on these models and therefore the decisions made at national level.

Reviewer *B.2020.0158E* however questioned why our seroprevalence data would be of added value to the existing seroprevalence studies in the Netherlands (blood donor and Pienter-Corona study). This is an important issue indeed, and exactly stresses out the urgent need for this project. It has to do with the relevance of more and less biased data to better inform the models. More data, from different sources that are complementary to each other are crucial to reduce biased information. In the Netherlands we currently have one study that aims to give an estimation of the seroprevalence of SARS-CoV-2 antibodies over different time periods: the blood donor. It is well known that blood donor cohorts tend to have very healthy, biased samples, and experience from other countries suggests lower seroprevalence in blood donors than other datasets.^{4,5,8,9} The serosurvey we propose here will not only provide more data at different crucial time points in this pandemic (1000 samples each month) but has many advantages compared to the blood donor study (broad representation of all subpopulations - ethnic, social and economic-, people with comorbidities and an independent cohort over time). More, and less biased data is absolutely critical to increase the confidence in the models, and therefore more reliably informs national policy during this pandemic.

Reviewer *B.2020.0158E* questions why our data would be more reliable compared to the blood donor and Pienter-Corona study.

This pregnancy serosurvey is the solution to the missing pieces in the existing two serosurveys (blood-donor and Pienter-Corona): 1) sampling of participants living in all municipalities in the Netherlands; 2) sampling all layers of society and therefore including low social-economic-status (SES) and non-Western populations. These missing pieces have become more relevant due to the fact that 1) infection with SARS-CoV-2 is not evenly distributed in all municipalities and 2) SES and ethnicity are known to be highly associated with an increased chance of SARS-CoV-2 infection (up to four-fold)¹⁻³. Not, or minimally including these populations in seroprevalence data, could mean that the current seroprevalence data potentially underestimate the real seroprevalence several-fold.

Reviewer *B.2020.0158E* also questions why pregnant women can be a representative sample from the Dutch population.

In sero-surveys outside COVID-19 we have examples of Hepatitis-B and HIV-pandemic pregnancy serosurveys that have already successfully been used a proxy for the general population.^{9,19} Besides the support from current existing literature there is also a clear rationale why the pregnancy population can be specifically used as a serosurvey for the COVID-19 pandemic. There is no question that pregnant women are different from the general population, as they consist of one single gender with one specific age range (15-45 years). These distinctive factors are however only relevant if they (substantially) contribute to a risk difference to get infected with SARS-CoV-2. Literature published so far on SARS-CoV-2 and age/gender differences in infection risk strongly suggest that these factors do not have major impact on seroprevalence estimates. Among the 23 global serosurvey studies published, no consistent major age and sex differences were found. One other factor that could have an impact on

results of antibodies is the potential different immune reaction in pregnant women, although this should be less prominent in the second trimester (the moment the blood samples is taken, being the most symbiotic immunologic stage between mother, placenta and fetus with a slight anti-inflammatory state). No other data have been published that suggest that pregnant woman have different SARS-CoV-2 seroprevalence.

Reviewer B.2020.0158E asks for clarification how this pregnancy serosurvey project plans to collaborate with the different monitoring systems (Blood donor and Pienter-Corona).

First, Pienter-Corona has not the intention to provide monthly seroprevalence data (labor intensive and costly design of asking repeated blood samples in the same pool of participants) and is therefore not at the same level of acting as a monitoring system when compared to the blood donor study and pregnancy seroprevalence study. To our knowledge, both Pienter-Corona (coordinated by RIVM) and blood donor study (coordinated by Sanquin, in collaboration with RIVM) provide data directly to RIVM key modelers (10)(2e). We plan to do the same. We have approached the PI's of the blood donor study (10)(2e) and Pienter-Corona (10)(2e) in April 2020 with the message of collaboration, and have been in direct contact with (10)(2e) who acknowledged the importance of this data source for their models due to the above explained arguments: More data, another valuable sample with a broad representation of SES, ethnicity and comorbidities for the Netherlands.

Where both reviewers B.2020.01571 and B.2020.01586 stress out the urgency of this project and the need to have accurate predictions of the seroprevalence and its inferred infection fatality rate (IFR), reviewer B.2020.0158E seems to be doubtful about the urgency of this project. We acknowledge that the direct urgency of this project is difficult to assess when we cannot predict the course of this pandemic. In the scenario of an absence of a second wave of this pandemic, knowing the seroprevalence every month might be too frequent. In that case, our project has the unique opportunity to scale down the frequency of sampling with the advantage of not losing budget (the samples are residual material, and if they are not analyzed, no money is wasted) but instead reserving the budget for moments in which a second wave is expected. In the scenario of a second wave, the precision of the assumptions made in the models are even more critical than before. Having only one (potentially biased) serosurvey, fitting these models would not be wise. Complimentary monitoring/surveillance sources are then extremely urgent to calibrate the models, and more reliably inform national policy during this pandemic.

Reviewer B.2020.01586 asks for clarification on the feasibility of 1000 samples/months also in case there is a lower participation rate than expected and how we will respond to specific questions (e.g. in case of a positive test). In this project we will only use anonymized residual samples. So we will not be able to communicate antibody test results to the pregnant women. However, to increase transparency about this project we intend to make a maximum effort to inform the professionals (general practitioners, gynecologists and midwives) to ensure they can provide appropriate information for the questions pregnant woman might have regarding this study (we will make sure there will be an official phone number that can be used). This will also give pregnant women the possibility to actively retract their sample in case they don't want their material to be used for this purpose. However, due to the anonymized nature of the data analyses, we don't think this will have impact on the anticipated samples. Especially because Sanquin receives a fourfold number of samples each month (56000 samples/year, >4000 samples/month) and the high screening compliance (>99%) of this screening program.

Budget.

Reviewer B.2020.0158E state the budget being potentially too high, reviewer B.2020.01571 states potentially too low, and reviewer B.2020.01586 states reasonable. Sanquin is a not-for profit organization and has given a fair estimate on the labor and material to perform the serology, knowing the importance and urgency of this project. We have also reserved budget for an epidemiologist with statistical experience for accurate analysis, coordination of data sharing with RIVM modelling team, and writing of publications in open access scientific journals.

New reference:

1. Niedzwiedz C, O'Donnell CA, Jani BD, et al. Ethnic and socioeconomic differences in SARS-CoV-2 infection: prospective cohort study using UK Biobank. MedRxiv April 30. <https://www.medrxiv.org/content/10.1101/2020.04.22.20075663v2.full.pdf>
2. Shittle RS, Diaz-Artiles A. An ecological study of socioeconomic predictors in detection of COVID-19 cases across neighborhoods in New York City. MedRxiv April 22. <https://www.medrxiv.org/content/10.1101/2020.04.17.20069823v1>
3. Prats-Urbe A, Paredes R, Prieto-Alhambra D. Ethnicity, comorbidity, socioeconomic status and their associations with COVID-19 infection in England: a cohort analysis of UK Biobank data. MedRxiv 11 June. <https://www.medrxiv.org/content/10.1101/2020.05.06.20092676v3.full.pdf>