

High amounts of SARS-CoV-2 precede sickness among asymptomatic healthcare workers

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Summary: Detection of high amounts of SARS-CoV-2 virus, as determined using PCR Ct values, associated with development of sickness in the next few weeks. The Ct value in the PCR may be informative to distinguish pre-symptomatic from post-symptomatic infection.

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ABSTRACT

Background: Whether SARS-CoV-2 positivity among symptomatic subjects reflects past or future disease may be difficult to ascertain.

Methods: We tested a cohort of 9449 employees at work at the Karolinska University Hospital, Stockholm, Sweden for SARS-CoV-2 RNA and antibodies, linked the testing results to sick leave records and determined associations with past or future sick leave using multinomial logistic regression. ClinicalTrials.gov NCT04411576.

Results: Subjects with high amounts of SARS-CoV-2 virus, as indicated by the Cycle threshold (Ct) value in the PCR, had the highest risk for sick leave in the two weeks after testing (OR 11.97 (CI 95% 6.29-22.80)) whereas subjects with low amounts of virus had the highest risk for sick leave in the past three weeks before testing (OR 6.31 (4.38-9.08)). Only 2.5% of employees were SARS-CoV-2 positive while 10.5% were positive by serology and 1.2% were positive in both tests. Serology-positive subjects were not at excess risk for future sick leave (OR 1.06 (95% CI, 0.71-1.57)).

Conclusions: High amounts of SARS-CoV-2 virus, as determined using PCR Ct values, associates with development of sickness in the next few weeks. The results support the concept that PCR Ct may be informative when testing for SARS-CoV-2 is performed.

Key words: SARS-CoV-2; Coronavirus; antibodies; sick leave; healthcare workers

INTRODUCTION

The current epidemic of SARS-CoV-2 is largely driven by asymptomatic individuals [1, 2]. To design strategies for SARS-CoV-2 control, effective identification of infectious subjects in defined communities is critical [3]. The incubation time from exposure to onset of symptoms has been estimated to last a median of six days [1], with peak infectiousness occurring zero to two days before onset of symptoms and pre-symptomatic spread estimated to account for a substantial proportion of disease transmission [1, 2]. While infectiousness decreases with increasing time after onset of symptoms, viral nucleic acids can still be detected after resolution of symptoms, in one study even six weeks after symptom resolution [4, 5]. If the virus is still present after symptom resolution it is usually only in low amounts and appears to not be viable [4, 5]. Screen-detected positivity may mark subjects who are symptomatic, pre-symptomatic (will develop symptoms later), post-symptomatic (symptoms have resolved), or asymptomatic (will never develop symptomatic disease) [6].

To identify potentially contagious subjects among asymptomatic healthcare workers (HCWs) is particularly important for SARS-CoV-2 control as various healthcare-related outbreaks have been observed [3, 7, 8] and it could be useful for adequate healthcare-seeking behavior [9] if the ability of the tests to predict past or future disease were more precisely known.

Antibodies to SARS-CoV-2 develop rather slowly, commonly concomitantly with symptom resolution and increases in subsequent weeks [10]. The PCR test, in addition to providing a dichotomous positive or negative result, will also provide a semiquantitative measure of the amount of virus present, the Cycle Threshold value (Ct) [5]. The Ct value is the number of sample amplification cycles needed before the virus was detectable. For example, a sample with a Ct value of 3 contains >30 billion times more virus than a sample that is positive with a Ct value of 38 and the case has been made that contact tracing should focus on the subjects with a large amount of virus [5].

It is particularly important to obtain data on how the SARS CoV-2 testing results relate to pre-symptomatic disease or post-symptomatic disease in a manner that is free from recall bias. To address this, we invited all employees currently on duty at the Karolinska University Hospital, Stockholm, Sweden to participate in a study that concomitantly measured presence of SARS-CoV-2 viral nucleic acid in throat samples and presence of antibodies to the virus in serum samples, in relation to the sick leave records of the participants.

MATERIALS AND METHOD

The Karolinska University Hospital has about 15,300 employees. The hospital announced that all HCWs on duty were welcome to participate in a study that evaluated the concomitant presence of viral nucleic acids in throat swabs and presence of antibodies to the virus in serum. Participants were recruited between April 23rd, 2020 and June 24th, 2020. All enrolled participants signed a written informed consent that also included permission to extract data from the employer's administrative databases that included data on sick leave. The study was approved by the National Ethical Review Agency of Sweden (Decision number 2020-01620). Trial registration number: ClinicalTrials.gov NCT04411576.

Viral Nucleic Acid Detection

Throat swab samples were obtained using the Beaver Specimen Collection kit (stratech.co.uk/wp-content/uploads/2020/04/BEAVER-IFU-43903-Sample-Collection-Kit19324.pdf) as described in the users' manual. Sample preparation followed safety routines according to BSL2 requirements including negative pressure in the room, biosafety cabinets, and installed HEPA filters. Samples were heat inactivated for 50 minutes at 75 degrees C. Extraction of viral RNA was performed using the MGISP-960 automated extraction standard workflow, according to the manufacturer's protocol (Wuhan MGI Tech Co, Ltd) using the MGIEasy Magnetic Beads Virus DNA/RNA extraction kit. The BGI 2019-

nCov Detection kit (BGI Real-Time RT-PCR for detecting 2019 nCoV) was used according to the manufacturer's instructions, including internal parameters to monitor sampling quality and testing process. RT-PCR was performed on QuantStudio5 instruments and software (Design and Analysis Software v1.5.1, Thermo Scientific). All steps in the diagnostic pipeline followed standard operating protocol validated for reproducibility, sensitivity, and specificity, including lack of cross-reactivity with other Coronavirus strains. The assay had a sensitivity of 12 molecules at a Ct of 38 (Ct 27 thus corresponds to approximately 25,000 molecules).

Serological analyses of antibodies

Whole blood was collected in serum-separating tubes and centrifuged at 2000 x g for 10 minutes. Serum samples were inactivated by heat-treatment at 56 degrees C for 30 minutes and then stored at -20 degrees C until further analysis.

Serological reactivity was measured towards three different virus protein variants, (i) Spike trimers comprising the prefusion-stabilized spike glycoprotein ectodomain [11] expressed in HEK-cells and purified using a C-terminal Strep II tag), (ii) Spike S1 domain, expressed in CHO-cells and purified using C-terminal HPC4-tag, and (iii) Nucleocapsid protein, expressed in *E.coli* and purified using a C-terminal His-tag. The sera were analyzed using a multiplex antigen bead array in a 384-plate format using a FlexMap3D instrument (Luminex Corp) with IgG detection [12]. The serology assay was then evaluated based on the analyses of 154 samples from Covid-19 subjects (defined as PCR-positive individuals sampled more than 16 days after disease onset) and 321 negative samples (defined as samples collected 2019 or earlier in the same region, including 26 individuals with confirmed infections of other Coronaviruses than SARS-CoV-2). The assay had a 99.4% sensitivity and 99.1% specificity. The cut-off for seropositivity was defined for each antigen as mean +6SD of 12 negative control samples included in each analysis batch. To be assigned as IgG positive, a sample

was required to show reactivity against at least two of the three included viral antigens.

Serum IgG bound to antigen coated beads was detected by fluorescent anti-hIgG (Invitrogen, H10104) and recorded as relative fluorescence intensity (AU).

Data analyses

Screening test results were examined separately and as a combined categorical variable. PCR positivity was dichotomized into strongly (<27.0) and weakly positive (greater than or equal to 27.0) based on the median Ct value among PCR positive/serology negative participants, rounded down to the nearest whole integer. Antibody positivity modified the risk for sick leave associated with PCR positivity ($p=0.0008$). Therefore, a combined variable of PCR and serology results was used to examine the association between SARS-CoV-2 status and sick leave. A combined variable with four categories was used to simultaneously examine serology and PCR test results.

Descriptive statistics were used to examine test results by age and sick leave. A multinomial logistic regression examined the association between test results and sick leave measured as a categorical variable, adjusted for age in 10-year categories and sex. Sick leave in the six weeks prior to testing and two weeks after testing was categorized as either no sick leave during the period of interest (reference category), sick leave in the 4-6 weeks before testing, sick leave in the 1-3 weeks before testing and sick leave in the two weeks after testing. For subjects with sick leave in more than one category, the period with the highest number of sick leave days was chosen. If two periods had an equal number of sick leave days, the period further back in time was chosen. With conventional statistical power and confidence while assuming a cumulative proportion of sick leave among non-exposed persons of 30% and that 10% of the cohort might be exposed, about 3,800 subjects would need to be enrolled to be able to detect associations of 1.4 or greater. Analyses used SAS 9.4, Cary, NC.

RESULTS

The Karolinska University Hospital had approximately 15,300 employees in the spring of 2020. Of these, 14,201 were enrolled in this study. After exclusion of HCWs not formally employed (e.g. medical students) and those without valid results on both the PCR and serology tests, the final cohort consisted of 9,449 subjects with complete data on sick leave and valid results on both tests (Figure 1), well over the estimated number needed for sufficient statistical power.

The overall number and proportion of employees that tested positive or negative in the two tests are shown by age in 10-year spans in Table 1. Seropositivity was most common in the youngest age group (14.9% were positive among subjects under the age of 29) and decreased with age (p-value for trend <0.0001). In total, 88.2% (87.5-88.9) of subjects were negative on both tests, 9.3% (8.7-9.9) were serology positive only, 1.3% (1.1-1.5) were positive for the virus, and 1.2% (1.0-1.5) were positive for both antibodies and the SARS-CoV-2 virus.

Overall, 54.5% (38.3% in weeks 1-3 before testing and 16.2% in weeks 4-6) of PCR-positive subjects had a history of sick leave during the past six weeks (post-symptomatic), whereas 63% of seropositive subjects had such history (29.3% in weeks 1-3 before testing and 33.7% in weeks 4-6) (Table 2). In the two weeks after testing, 15.3% of PCR positive subjects had sick leave reported, compared to only 3.4% of the seropositives. By comparison, 5.2% of the double negative subjects had sick leave after the sampling. Among PCR positive subjects, 30.2% did not have any sick leave recorded, neither before nor after testing (asymptomatic). Positivity in serology was significantly associated with past history of sick leave (Table 3) but did not confer any risk for future sick leave for the coming two weeks after testing (OR 1.06 (95% CI, 0.71 to 1.57)) (Table 2). By contrast, subjects with viral nucleic acids in the absence of antibodies had very little excess risk for past sick leave (similar to the sick leave history of test-negative subjects), but had a strongly increased risk for imminent sick leave in

the two weeks after testing (OR 7.23 (95% CI 4.52-11.57)) (Table 3). Positivity for both virus and for antibodies tended to be most strongly associated with sick leave during the past three weeks (OR 16.51 (95% CI 10.13-26.90)) (Table 3). Compared to PCR negative subjects, strong PCR positivity was in particular associated with future sick leave (OR 11.97 (95% CI 6.29-22.80)) while weak PCR positivity was most strongly associated with sick leave in the 1-3 weeks before testing (OR 6.31 (95% CI 4.38-9.08)). In the multivariate model, male sex and over 50 years of age were associated with lower risk for sick leave (data not shown). The mutual adjustments in the multivariate model had only minor effects on the estimates (Supplementary Table 1).

Examining test results and sick leave week by week in the six weeks before test and two weeks after testing highlights these patterns. Sick leave peaked for subjects that tested PCR positive/serology positive two weeks before testing while sick leave increased in the two weeks after testing for PCR positive/serology negative subjects (Figure 2). The amounts of virus as defined by the Ct values revealed a clear pattern of sick leave prior to testing for subjects with low amounts of virus and a sharp increase in sick leave after testing for subjects with a high amount of virus (Figure 3).

DISCUSSION

We found a limited number of SARS-CoV-2-positive subjects among asymptomatic HCWs (235/9449 subjects). Among these, more than half were only positive for low amounts of virus (had high Ct values) and had mainly already had disease (post-symptomatic subjects). Systematic reviews have not identified any reports of shedding of live virus for more than 9 days after debut of symptoms, whereas low amounts of virus may be detectable for many weeks after resolution of symptoms [13]. Our large-scale study confirms that the amounts of virus (the Ct value) is useful for distinguishing between post-symptomatic and pre-symptomatic subjects, that may be a risk group for transmission.

As it is established that subjects who have recovered from symptomatic disease are no longer infectious, it seems appropriate to focus infection control on the subjects with the pattern of pre-symptomatic disease. Positivity in serology is also primarily associated with past sick leave and presence of antibodies may also be useful to identify the subjects with post-symptomatic positivity.

Many studies have reported testing of HCWs [7, 14]. For example, 3% of HCWs were PCR positive in a major London hospital [15]. Another study reported on an outbreak in a skilled nursing facility, where a large proportion of HCWs tested positive.⁷ Although many studies have screened HCWs with PCR, the amount of virus (the cycle threshold value) has commonly not been taken into account, although this value is obtained when a real-time PCR reaction is performed.

Studies comparing detection of viral nucleic acids and antibodies have mostly been focusing on COVID-19 patients, whereas not on combined PCR/serology testing of asymptomatic HCWs. This enabled us to provide unique insights on delineation of post-symptomatic and pre-symptomatic subjects. There also appears to exist a group of entirely asymptomatic subjects who had no sick leave either before or after sampling.

Strengths of our study include the fact that it was a large and systematically enrolled cohort that used routinely collected administrative sick leave data and was therefore not hampered by recall bias to which studies sourcing information from participants can be subjected.

Weaknesses of our study include that we were not able to study the relation of biomarkers to infections occurring more than 6-7 weeks before testing, as community transmission of SARS-CoV-2 started in our region only about 6-7 weeks before the study. Also, employees who were not at work were not eligible for inclusion which is likely to have resulted in an underestimation of the spread of the infection at the hospital as employees may have been absent because of COVID-19. The fact that some participants did not have both tests

completed is not likely to have affected results, as lack of analysis results was a random phenomenon and the study was still substantially overpowered. Finally, participants were not questioned about present or prior symptoms. The hospital rules were clear that employees with symptoms should not be at work and we had, by design, decided to use only sick leave data to avoid possible recall bias. Subjects may of course have sick leave for many other reasons than Covid-19, but the increases of total sick leave associated with SARS-CoV-2 test positivity was greatly increased compared to the sick leave rates for SARS-CoV-2 negative subjects.

We conclude that the amount of virus as determined by the Ct value of the PCR test and also the serology status is useful for distinction between post-symptomatic, asymptomatic, and pre-symptomatic subjects. This is essential for understanding of the natural history of the infection, particularly in a phase of the epidemic where many exposed and still positive subjects may have recovered quite some time ago. Prior evidence seems clear that pre-symptomatic subjects are indeed infectious 0-2 days before onset of symptoms and that pre-symptomatic subjects significantly contribute to the spread of the infection [2]. As infectivity declines rapidly after the debut of symptoms, it seems more useful to detect infected subjects before the debut of symptoms, rather than after the symptoms have already been present for some time. When the epidemic has been ongoing for some time, testing strategies need to ascertain whether a test positivity reflects a post-symptomatic infection or whether it may reflect a high risk for a pre-symptomatic infection.

In summary, we find that high amounts of SARS-CoV-2 virus may predict pre-symptomatic disease also in a phase of the epidemic where many positive subjects have had previous disease.

NOTES

Conflicts of interest

None of the authors have any conflicts of interest to declare.

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ETHICAL APPROVAL

The study was approved by the Swedish Ethical Review Authority (approval number 2020-01620).

DATA SHARING STATEMENT

The data constitutes sensitive data about health of human research subjects. However, pseudonymised, individual-level data that allow full replication of the results in this article will be made freely available from joakim.dillner@sll.se. The study protocol is available at [clinicaltrials.gov NCT04411576](https://clinicaltrials.gov/NCT04411576)

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TABLES AND FIGURES

Table 1. Detection of SARS CoV-2 virus and antibodies to the virus among 9,449 employees of the Karolinska University Hospital, by age

Age	Serology positive n (%)*	PCR negative & serology negative n (%)	PCR negative & serology positive n (%)	PCR positive & serology negative n (%)	PCR positive & serology positive n (%)	Total
<29	170 (14.9)	956 (83.6)	157 (13.7)	17 (1.5)	13 (1.1)	1,143
30-39	259 (11.0)	2,055 (87.6)	217 (9.3)	33 (1.4)	42 (1.8)	2,347
40-49	251 (10.8)	2050 (87.8)	219 (9.4)	33 (1.4)	32 (1.4)	2,334
50-59	209 (9.4)	1,985 (89.6)	188 (8.5)	21 (1.0)	21 (1.0)	2,215
60+	106 (1.1)	1,289 (91.4)	98 (7.0)	15 (1.1)	8 (0.6)	1,410
Total (n, % (95% CI)	995, 10.5 (9.9-11.2)	8,335, 88.2 (87.5- 88.9)	879, 9.3 (8.7-9.9)	119, 1.3 (1.1-1.5)	116, 1.2 (1.0-1.5)	9,449

*Serology positive, regardless of PCR result, Cochran-Armitage Trend Test p-value <0.0001

Table 2. Distribution of background characteristics and screening results, by sick leave

	n, % (95% CI)	Sick leave			
		No sick leave n (%)	1-2 weeks after testing n (%)	1-3 weeks before testing n (%)	4-6 weeks before testing n (%)
Age					
20-29	1,143 (12.1)	648 (56.7)	77 (6.7)	180 (15.8)	238 (20.8)
30-39	2,347 (24.8)	1,270 (54.1)	162 (6.9)	376 (16.0)	539 (23.0)
40-49	2,334 (24.7)	1,403 (60.1)	104 (4.5)	344 (14.7)	483 (20.7)
50-59	2,215 (23.4)	1,359 (61.4)	105 (4.7)	296 (13.4)	455 (20.5)
60+	1,410 (14.9)	934 (66.2)	52 (3.7)	160 (11.4)	264 (18.7)
Sex					
Female	7,488 (79.3)	4,252 (56.8)	420 (5.6)	1,156 (15.4)	1,660 (22.2)
Male	1,961 (20.8)	1,362 (69.5)	80 (4.1)	200 (10.2)	319 (16.3)
SARS-CoV-2 test results					
PCR neg/Serology neg	8,335 (88.2)	5,230 (62.8)	436 (5.2)	1,046 (12.6)	1,623 (19.5)
PCR neg/Serology pos	879 (9.3)	313 (35.6)	28 (3.2)	220 (25.0)	318 (36.2)
PCR pos/Serology neg	119 (1.3)	49 (41.2)	30 (25.2)	19 (16.0)	21 (17.7)
PCR pos/Serology pos	116 (1.2)	22 (19.0)	6 (5.2)	71 (61.2)	17 (14.7)
SARS-CoV-2 PCR test results					
PCR negative	9,214 (97.5)	5,543 (60.2)	464 (5.0)	1,266 (13.7)	1,941 (21.1)
PCR positive	235 (2.5)	71 (30.2)	36	90 (38.3)	38 (16.2)

			(15.3)		
PCR weakly positive	168 (1.8)	52 (31.0)	16 (9.5)	74 (44.1)	26 (15.5)
PCR strongly positive	67 (0.7)	19 (28.4)	20 (29.9)	16 (23.9)	12 (17.9)
SARS-CoV-2 serology test results					
Serology negative	8,485 (89.5)	5,279 (62.4)	466 (5.5)	1,065 (12.6)	1,644 (19.5)
Serology positive	995 (10.5)	335 (33.7)	34 (3.4)	291 (29.3)	335 (33.7)

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Table 3. Association between testing results and sick leave*			
	1-2 weeks after testing vs No sick leave OR (95% CI)	1-3 weeks before testing vs No sick leave OR (95% CI)	4-6 weeks before testing vs No sick leave OR (95% CI)
SARS-CoV-2 test results			
PCR neg/Serology neg	1.00	1.00	1.00
PCR neg/Serology pos	1.06 (0.71-1.57)	3.52 (2.92-4.25)	3.31 (2.80-3.91)
PCR pos/Serology neg	7.23 (4.52-11.57)	1.92 (1.12-3.28)	1.38 (0.82-2.31)
PCR pos/Serology pos	3.24 (1.30-8.06)	16.51 (10.13-26.90)	2.54 (1.34-4.81)
SARS-CoV-2 PCR test results			
PCR negative	1.00	1.00	1.00
PCR weakly positive	3.61 (2.04-6.40)	6.31 (4.38-9.08)	1.45 (0.90-2.34)
PCR strongly positive	11.97 (6.29-22.80)	3.61 (1.84-7.09)	1.80 (0.87-3.73)

*Model 1 with testing results in four categories, adjusted for age and sex. Model 2 with PCR test results in three categories, adjusted for age and sex.

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Figure Legends.

Figure 1. Study flow chart according to the Standard Reporting of Observational studies (STROBE) guidelines.

Figure 2. Reported sick leave before and after testing, in relation to PCR and serology results. Testing results are plotted as percent study participants with reported sick leave by week before and after testing, stratified by testing result in PCR (Positive or negative) and in serology (positive or negative). Dotted lines around the curves represent the boundaries of the 95% Confidence Limits.

Figure 3. Reported sick leave before and after testing, in relation to amounts of virus detected by the PCR test.

Testing results are plotted as percent study participants with reported sick leave by week before and after testing, stratified by testing result in PCR (strongly positive (Ct, weakly positive (Ct) or negative).

Dotted lines around the curves represent the boundaries of the 95% Confidence Limits.

Figure 1. STROBE flowchart of study subjects

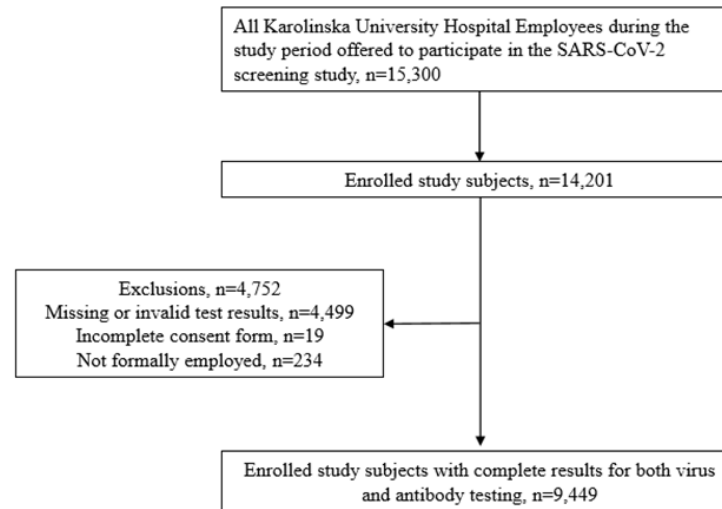


Figure 2. SARS-CoV-2 screening results by sick leave before and after testing

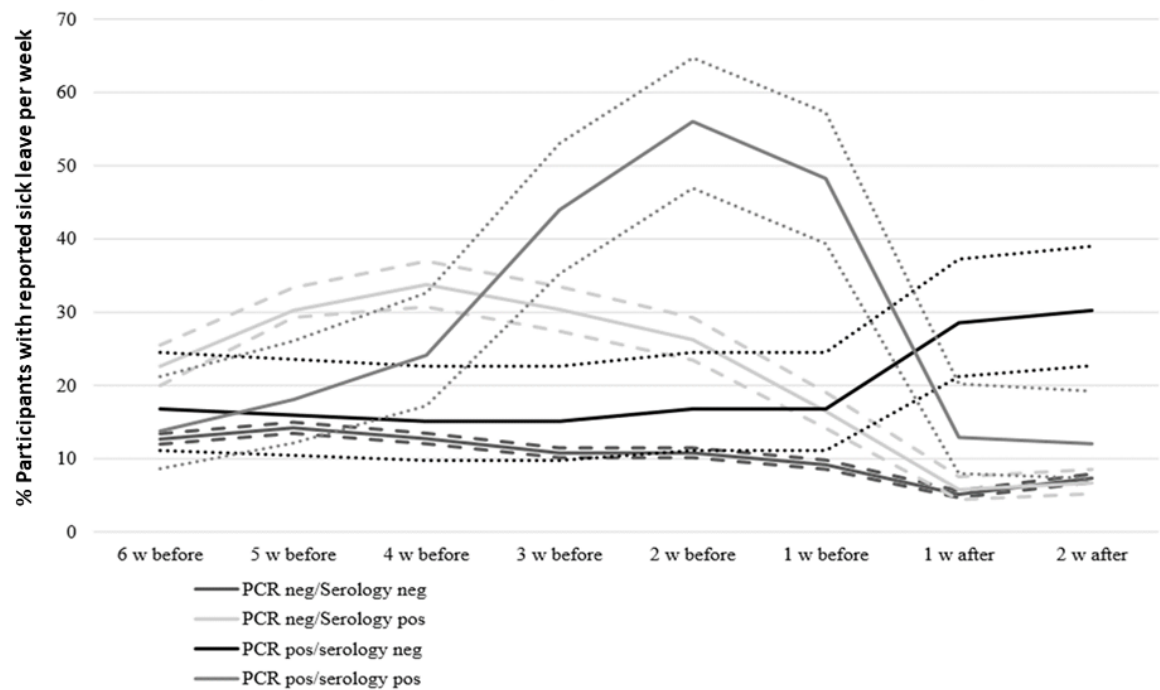


Figure 3. Sick leave among healthcare workers by PCR screening results, stratified by strongly or weakly positive

