Factors associated with COVID-19 infection and infection severity in Dutch health care workers during the COVID-19 epidemic in the Netherlands

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Abstract

Background: The BCG-Corona trial began in March 2020 and followed 1511 healthcare workers in the Netherlands for a year: 753 participants received BCG vaccine and 758 placebo vaccine. The trial found no impact of BCG vaccination on SARS-CoV-2 infection incidence or infection severity. As a secondary analysis, we examined factors associated with cumulative SARS-CoV-2 infection and infection severity.

Methods: Participants completed a baseline and endline questionnaire. Additionally, they completed daily/weekly diaries within a mobile phone application. Blood sample collection for SARS-CoV-2 serology testing occurred twice during follow up; serology results could distinguish natural infections from COVID-19 vaccination responses. Infections were classified as proven (by participant-reported positive test with or without seroconversion), possible (seroconverted but no participant-reported positive test), unlikely (due to inconsistent data), or unknown (due to insufficient data). The 55 participants in the latter two categories were excluded from the analyses. Furthermore, only first infection episodes were included. Infection severity was classified as: 1) no infection; 2) asymptomatic infection; 3) mild infection; and 4) moderate/severe infection. We used logistic regression to model cumulative infection and ordinal logistic regression to model infection severity. Each covariate of interest was first modelled in univariate models, followed by stepwise forward multivariable models using a cut-off of p=0.05 for retention in the model.

Results: During follow-up, 277 infections occurred in 273 participants of 16.6% were asymptomatic, 61.0% mild, and 22.4% moderate/severe; only four participants acquired a second infection. In univariate models, taking hypertension medication, having a higher number of patient contact hours per week, having had COVID ward duty, working in internal medicine departments (compared to urgent or intensive/medium care or other hospital departments) and being female were associated with higher risks of infection as well as severe infection. In the multivariable models, the increased risk associations with hypertension medication and the work-related variables persisted.

Conclusions: During the first year of the COVID-19 epidemic in the Netherlands, healthcare workers were exposed to SARS-CoV-2 at work and their levels of risk for both infection acquisition as well as infection severity were associated with work-related conditions.

Layman's Summary

When the coronavirus pandemic began, there was global concern for how to combat the virus. The tuberculosis vaccine (BCG) had been reported to provide some protection against other respiratory tract infections. At that time, coronavirus vaccines were not yet available but the BCG vaccine was available, and it was thought to be worthwhile to see if the BCG vaccine would indeed reduce coronavirus infections or infection severity. With this in mind, a clinical trial in healthcare workers across the Netherlands was initiated in March 2020: 753 healthcare workers received the BCG vaccine and 758 received a placebo vaccine. Unfortunately, the trial showed that BCG vaccination could not protect healthcare workers from coronavirus infection. We used the dataset from this trial to determine risk factors for acquiring coronavirus infection or for developing more severe illness after infection in healthcare workers.

The participants completed a questionnaire at the time of their vaccination and again about one year later. Throughout the year of follow-up, they also completed daily/weekly diaries using a mobile phone application and donated blood samples for coronavirus antibody testing twice. We determined for each participant if they had coronavirus infection during the year of follow-up, and if yes, how severe that infection was. We could not use the data of 55 participants because the data were either inconsistent or incomplete.

During follow-up, 277 coronavirus infections occurred in 275 participants of which 16.6% were asymptomatic, 61.0% mild, and 22.4% moderate/severe; only four participants experienced a second coronavirus infection. Taking hypertension medication, having a higher number of patient contact hours per week, having had coronavirus ward duty, working in internal medicine departments (compared to urgent or intensive/medium care or other hospital departments) and being female were associated with higher risks of infection as well as severe infection.

To conclude, during the first year of the coronavirus epidemic in the Netherlands, healthcare workers were exposed to coronavirus at work and their levels of risk for both infection acquisition as well as infection severity were associated with work-related conditions.

Introduction

Coronavirus disease 2019 (COVID-19) is an infectious disease, caused by severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2), which has immensely impacted the health of global societies. More than two years after the identification of the virus, it remains a large-scale global issue with which the world is attempting to transition to endemicity.

SARS-CoV-2 is a positive-sense, single-stranded RNA virus. Viral transmission can occur through direct or indirect contact with an infected individual. Once infected, the virus receptor binding domain binds with high affinity to the host ACE2 receptor (1,2). Following an asymptomatic incubation period lasting on average 5 days, most – but not all – infected individuals begin to experience symptoms like dry cough, fever, and shortness of breath (1,3). The severity of the disease is observed to be much higher in the elderly, individuals with comorbidities, and immunocompromised individuals (3,4).

The first laboratory-confirmed COVID-19 case in the Netherlands was on 27 February 2020 (5). At these initial stages in the pandemic there was no-pre-existing immunity within the community, and it was thought that it would take quite some time before SARS-CoV-2 specific vaccines would be available. Therefore, there was a need for interventions to protect vulnerable people and the healthcare workers (HCW) who would have to take care of them. The Bacillus Calmette Guerin (BCG) vaccine, developed in the early 1900s, provides protection against tuberculosis and contains live attenuated virus (6). It was observed that young infants who received the BCG vaccine, compared to those who did not, were less likely to die in the first 5 years of life. This reduction in infant mortality appeared to be due to protection from infectious agents in general and not just tuberculosis (7). Other studies in adults and animals have shown protective effects of the BCG vaccine against respiratory tract infections other than tuberculosis (8,9,10,11,12,13).

Scientists believe that this reduced vulnerability to respiratory tract infections is due to trained innate immunity (14). While it was originally thought that only the adaptive immune system has a memory, it has now been hypothesised that the innate immunity also has a memory-like aspect to it as a result of epigenetic changes directed by histone modification (12,15). Immune cells included in trained innate immunity include monocytes, macrophages, and natural killer cells. For example, a humans vaccinated with BCG followed by the yellow fever vaccine showed epigenetic modifications of monocytes, and these altered monocytes produced increased cytokine levels after in vitro stimulation (16).

While BCG vaccines are available in the Netherlands, most people have not been vaccinated. Current guidelines do not recommend vaccination of the general population due to low tuberculosis incidence. To assess the potential impact of BCG vaccination on COVID-19 incidence, severity, and duration in HCWs, a randomized controlled trial (the BCG-Corona trial) was initiated in March 2020 in nine hospitals across the Netherlands. It was hypothesized that BCG vaccination would reduce incidence, severity, and duration of infection in HCWs, but unfortunately, the primary results of the trial showed that this was not the case. In the current paper, we used data from the BCG-Corona trial to determine factors other than BCG-vaccination associated with cumulative infection incidence and infection severity in HCWs during the first year of the COVID-19 epidemic.

Methods

Study design, products, and population

All the participant data used within this study was obtained from participants in the BCG-Corona trial, a multisite randomized placebo-controlled clinical trial. Participants were randomised in a 1:1 ratio to BCG vaccination (Danish strain 1331, Statens Serum Insitut, Copenhagen, Denmark) or placebo vaccination (0.9% NaCl). 1511 HCW from 9 Dutch hospitals participated in the trial: 753 in the BCG arm and 758 in the placebo arm. The participants were vaccinated at the start of the first epidemic wave in the Netherlands (March-April 2020) and were followed-up for one year.

Data and sample collection

At the time of randomisation and vaccination, participants completed an online baseline questionnaire in Research Online (Julius Center, UMC Utrecht, Netherlands) about sociodemographic and job-related characteristics, past BCG vaccination and tuberculosis testing, recent influenza and other vaccinations, and comorbidities. From that day onwards, participants were asked to complete a diary in a mobile phone application (ResearchFollowApp, Your Research BV, Huizen, Netherlands) about daily symptoms and their severity, and work-related absenteeism. Participants were initially asked to complete the diary on a daily basis but about 6 months into the trial were asked to do this weekly to ease the burden. In addition to the symptom data, participants were also asked to complete a weekly questionnaire within the app about any SARS-CoV-2 testing and exposures as well as healthcare visits. Almost a year after the first case was detected, on 6 January 2021, the Dutch COVID-19 vaccination programme was initiated. Individuals were able to receive Moderna (Spikevax), Pfizer/BioNTech (Comirnaty), AstraZeneca (Vaxzeveria), and Janssen vaccines. HCW were among the first individuals to be vaccinated. From January 2021 onwards, questions about COVID-19 vaccination (vaccination dates and types) were added to the weekly diary questionnaire in the app.

Each participant was asked to provide a blood sample for SARS-CoV-2 antibody testing twice during follow-up: participants in the three academic hospitals UMCU, RADN and LUMC provided a serum sample by venepuncture about three (M3) and 12 months (M12) post vaccination and participants in the other 6 hospitals about 6 (M6) and 12 months (M12) post-vaccination via a fingerprick at home. Furthermore, participants in the three academic hospitals who could not attend a venepuncture visit were also offered the possibility to collect a fingerprick sample at home. The venepuncture samples were stored frozen until shipment to the Dutch National Institute of Public Health and the Environment (Rijksinstituut voor Volksgezondheid en Milieu (RIVM) in Dutch) for testing, and the fingerprick samples were sent to the RIVM on the day of collection using pre-addressed and prepaid envelopes provided to participants by the study team. In the first sampling round (M3 or M6), when COVID-19 vaccination had not yet started, the RIVM determined SARS-CoV-2 anti-S1 antibodies. In the second sampling round (M12), the RIVM determined both anti-S1 and anti-N antibodies to allow for the differentiation between natural infections and COVID-19 vaccination responses.

Diary completion ended on 27 March 2021 for all participants. However, the M12 fingerprick sampling took place between April and June 2021. We therefore asked all fingerprick participants to complete an online questionnaire at the time of fingerprick collection about any SARS-CoV-2 symptoms, positive tests, or vaccinations

between the end of March and the time of sample collection. Participants who did not complete the online form were approached by email.

Outcomes

The study consists of two analysis periods, defined by the blood sampling rounds. Period 1 was from BCG/placebo vaccination date to the first sampling round. Period 2 was from the first to the second sampling round. The antibody results at the end of periods 1 and 2, in combination with the diary information, were used to classify infection episodes into proven (with or without seroconversion), possible, unknown and unlikely episodes as well as asymptomatic, mild, or moderate/severe episodes. The full definitions for each episode type and severity are present in the Appendix. Briefly, a proven episode was defined as any participant-reported positive SARS-CoV-2 test with or without evidence of a natural infection via seroconversion (a positive test for anti-S1 at the end of period 1 or a positive test for anti-S1 in an unvaccinated individual or anti-S1 and anti-N in a vaccinated individual) (Appendix: Table S1). Episodes were classified as unknown if we did not have sufficient data for classification. Unlikely episodes were cases who had anti-N but no anti-S1 antibodies at the end of Period 2. Episode severity definitions were determined based on the self-reported symptoms, their respective symptom severity scores, and duration reported by the participants in the diary app (see Appendix: Table S2).

Statistical Analysis

Previous analyses of the BCG-Corona trial data had shown that there were no significant differences in participant-reported infections (17) nor in infections based on both participant reports and serology (unpublished data) between the BCG and placebo arms. We therefore analysed the BCG and placebo arms as one dataset and ignored the randomisation. In the analyses reported here, all cases with unknown or unlikely episodes were excluded.

The main outcomes were SARS-CoV-2 infection (proven and probably cases combined) or infection severity (no infection, asymptomatic, mild, or moderate/severe infection; there were only three severe cases and these were therefore pooled with the moderate cases). Predictors included most variables from the baseline questionnaire. The 9 recruitment hospitals were located in different regions of the Netherlands and the epidemic circumstances fluctuated over time and by region. However, we did not include enrolment week and recruitment site as predictors in the current analyses because previous analyses had shown that adjustment for these variables did not change the results (unpublished data). The categories of some predictors were pooled to optimize statistical power (job-related variables, prior tuberculosis exposure defined by Mantoux or TB Quantiferon testing, and chronic respiratory illness).

Outcome groups were compared by Chi-square tests for categorical variables and ANOVA (one-sample) tests for continuous variables. We used logistic regression for models with SARS-CoV-2 infection as the outcome and ordinal logistic regression for models with infection severity as the outcome. We first conducted univariate analyses, followed by forward stepwise modelling to arrive at multivariable models. All variables that were statistically significant in the univariate models were considered for inclusion in the multivariable models. A Kaplan- Meir survival curve was used to generate a time to first SARS-CoV-2 vaccination graph, to check if SARS-CoV-2 vaccination over time did not differ between the various outcome groups.

Results

A total of 753 HCWs were randomised to the BCG arm and 758 to the placebo arm (Figure 1). However, 57 HCWs had an unknown or unlikely infection and were therefore excluded from the analyses. The final analysis population consisted of 1454 HCWs.

The demographic and clinical characteristics of the analysis population are depicted by randomisation group in Table 1 and by infection severity in Table 2. Most of the participants were female (1074/1454; 73.9%) and the mean age was 41,9 years (range: 18-67). Most of them (1268/1454; 87.2%) had patient care functions, such as nurses, doctors, or paramedics, more than half had patient contact hours of more than 75% per week (722/1454; 53.1%), and more than half was (scheduled to) work in a COVID-ward (928/1454; 63.8%). Eight percent were current smokers, and comorbidities were uncommon except for hay fever (Table 1).

During the winter season of 2019/2020, just prior to the start of the trial, 835/1456 (57.4%) of the participants received an influenza vaccine. During the winter season of 2020/2021, during the data collection period, 667/1456 (45.9%) of the cohort received an influenza vaccine. From 6 January 2021, participants begun receiving COVID-19 vaccines; 814/1454 (56%) of the participants received a vaccine during the data collection period. The most received vaccine was Comirnaty (Pfizer), which was received by 391/1454 (26.9%) of the participants. The time to first vaccine graph (Figure 2) is reflective of the COVID-19 vaccine rollout policy in HCWs in the Netherlands. From 6 January 2021, the first group of HCWs to be vaccinated were the HCWs with direct patient contact, followed a few months later by support personnel. The curve therefore has a steep increase from 6 January 2021 onwards, then plateaus for some time, and then increases again.

During the data collection period, 19.1% (N=277) individuals had a proven or possible SARS-CoV-2 infection. These infections were asymptomatic (46/277; 16.6%), mild (169/277; 61.0%) or moderate/severe (62/277; 23.4%). There were four cases of multiple infections in any one individual participant.

Predictors of SARS-CoV-2 infection

In univariate logistic regression models, having COVID-19 ward duty, percentage of work hours with patient contact, department of work, and taking hypertension medication were statistically significantly associated with acquiring SARS-CoV-2 infection during follow-up and sex showed a trend towards association (Table 3). After adjustment in the final multivariate model, a lower percentage of work hours with patient contact (OR=0.40, 95% confidence interval (CI) 0.25-0.63, p<0.001 for ≤25% versus ≥75%; reduced risks were also seen for 26-74%) and not taking hypertension medication (OR=0.59, 95% CI 0.36-0.95; p=0.029) were associated with reduced infection risk, and working in an internal medicine department compared to urgent, intensive, or immediate care or another department (OR=1.63, 95% CI 1.16-2.30; p=0.005) was associated with an increased infection risk.

Predictors of SARS-CoV-2 infection severity

In univariate ordinal logistic regression analyses, sex, having COVID-19 ward duty, percentage of work hours with patient contact, department of work, and taking hypertension medication were statistically significantly associated with SARS-CoV-2 infection severity (Table 4). After adjustment in the final multivariate model, a lower percentage of work hours with patient contact (OR=0.40, 95% confidence interval (CI) 0.25-0.63, p<0.001 for ≤25% versus ≥75%; reduced risks were also seen for 26-74%) and not taking hypertension medication (OR=0.59, 95% CI 0.37-0.95; p=0.030) were associated with reduced infection severity, and working in an internal medicine department compared to urgent, intensive, or immediate care or another department (OR=1.60, 95% CI 1.14-2.24; p=0.007) was associated with an increased infection severity.

Tests for multicollinearity between female sex and the work-related variables (department, function, patient contact, and COVID-ward duty) revealed that some collinearity is present (Appendix: Table S3). However, it is minimal and within an acceptable range as the variance inflation factor are < 2. Similarly, tests for multicollinearity between the work-related variables produced VIF values <2.

Discussion

This multicentre study examined the possible predictors for COVID-19 infection risk and severity in HCWs. The unadjusted results from this study indicate that women had a higher SARS-CoV-2 infection risk and infection severity than men but these differences disappeared after adjustment for job-related characteristics. Studies have shown that, on average, men have higher morbidity and mortality from COVID-19 than their female counterparts (18,19). We hypothesize that we did not see this in our study because female HCWs were more likely to be in jobs with close patient contact than male HCWs. Therefore, they may have been more likely to be exposed. In addition, they likely kept less distance from infected patients due to their job responsibilities (e.g. having to measure vital signs, wash patients, etc.) and may therefore have been exposed to higher viral loads. However, we cannot rule out that female staff may have been less likely to use preventative measures than male staff.

Age is a recognized risk factor for respiratory infections, and especially infection severity, including COVID-19 (20). However, in our analyses, age was not associated with SARS-CoV-2 infection risk or severity. The BCG-Corona trial did not include vulnerable individuals. The age range of the study population was 18-67 and all participants were fit to work.

In a HCW cohort, work-related factors are essential to consider (21,22). Indeed, working in a COVID-ward, department of work, and the percentage of work hours with direct patient contact were associated with both infection risk and severity in univariate models. We anticipated that these variables might be collinear, and also collinear with sex, but multicollinearity tests indicated a low level of collinearity. However, in the multivariate models, only department of work and the percentage of work hours with direct patient contact remained statistically significant after adjustment for the other work-related factors. HCWs employed in internal medicine departments (including pulmonology and infectious diseases) had higher infection and infection severity risks than HCWs employed in urgent, intensive, or medium care or other hospital departments. We hypothesise that personal protective equipment was used more extensively in urgent, intensive and medium care than on the internal medicine

wards, but differences in numbers and types of patients, and levels of sickness of those patients, may also have played roles. As expected, HCWs with a higher percentage of patient contact hours had higher risks of infection and infection severity.

Strengths of this study were the large sample size, the fact that we captured the first year of the Dutch SARS-CoV-2 epidemic when the population was still immune naïve, and the addition of serology to determine SARS-CoV-2 endpoints. The serology enabled us to identify asymptomatic and mild infections for which participants did not seek testing. More than half of the participants received a COVID-19 vaccine during follow-up, and some even completed their primary vaccination series, but the serology that we did could differentiate between natural infections and immune responses due to vaccination.

The analyses presented in this paper also had some limitations. One limitation is that we used cumulative infection (or infection severity) as the outcome rather than infection as a time-dependent variable. We did not have infection dates for infections that were only uncovered by serology (all asymptomatic and some of the mild infections), limiting our ability to do time-dependent analyses. Moreover, epidemic waves, SARS-CoV-2 variants-of-concern, and governmental measures to control epidemic waves were also not considered. However, adjustment for enrolment week and recruitment site did not affect our results (data not shown). Finally, HCWs are not only exposed to SARS-CoV-2 in their work place but also at home and in society-at-large while our analyses focused on work-related characteristics. However, we did consider the number of household members and it was not associated with infection and infection severity risks.

In conclusion, during the first year of the COVID-19 epidemic in the Netherlands, HCWs were exposed to SARS-CoV-2 at work and their levels of risk for both infection acquisition as well as infection severity were associated with work-related conditions.

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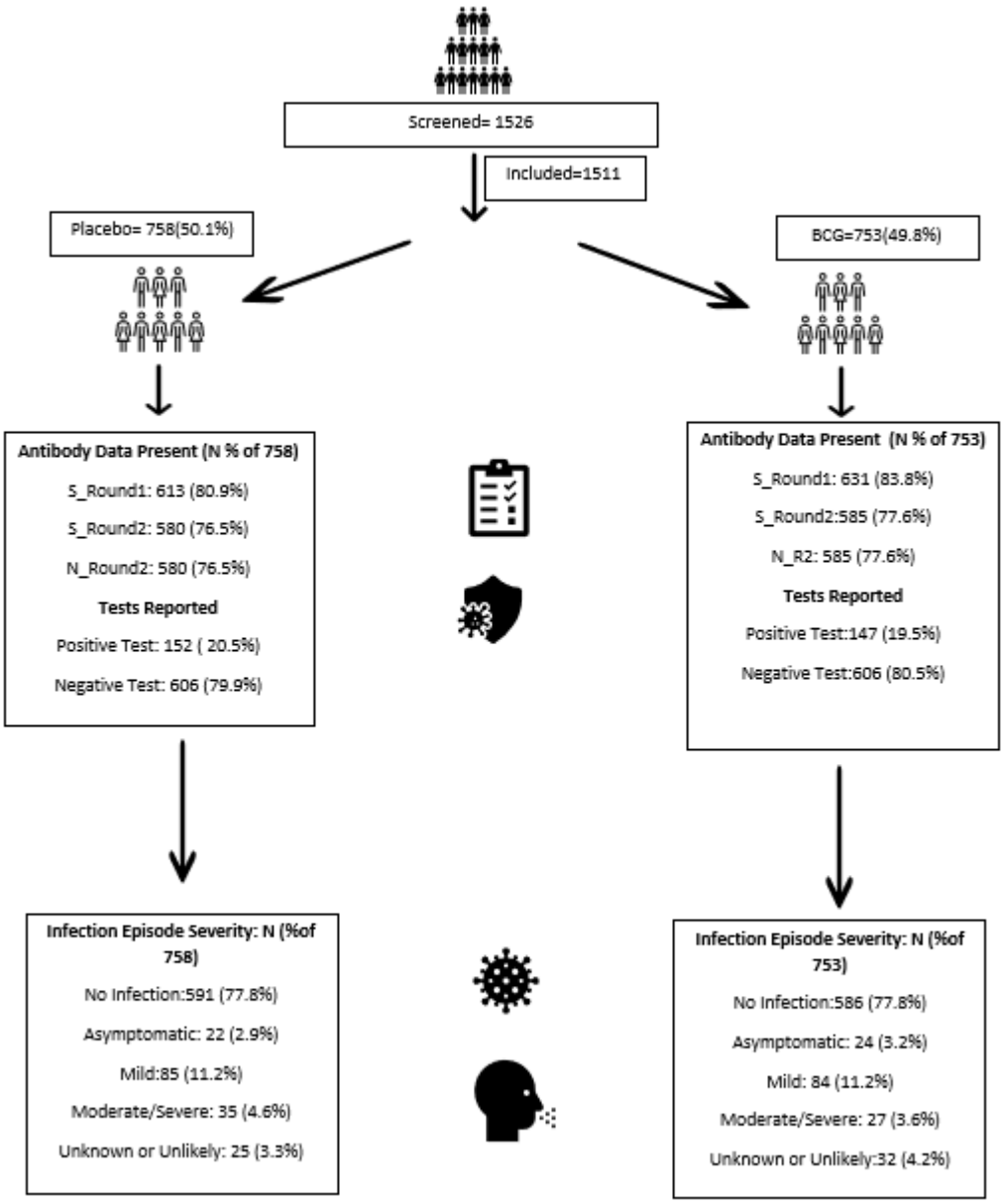
Figure 1: Study flow of the BCG-Corona trial



BCG Corona trial participant flow. In the first layer (randomization layer), the percentage (%) is the percentage of the total number of 1511 included participants. In all subsequent layers, the percentage refers to the percentage of that randomization arm. 57 participants had infections that were classified as unlikely or unknown and were excluded from all data analyses.

Table 1: Baseline and clinical characteristics of BCG-Corona participants by infection status

n (%) unless stated otherwise		No infection N=1177	Infection N=277	Total N=1454
Intervention	BCG	586 (49.8%)	135 (48.7%)	721 (49.6%)
	Placebo	591 (50.2%)	142 (51.3%)	733 (50.4%)
Sex	Female	856 (72.7%)	218 (78.7%)	1074 (73.9%)
	Male	321 (27.2%)	59 (21.3%)	380 (26.1%)
Age, mean (range)		42.1 (18-67)	40.9 (20-64)	42(18-67)
Household members[1], mean (range)		2.9 (1-18)	3.0 (1-13)	3(1-18)
Recruitment site[2]	CWZN	58 (4.9%)	16 (5.8%)	74 (5.1%)
	ERMC	31 (2.6%)	7 (2.5%)	38 (2.6%)
	HZDH	81 (6.9%)	20 (7.2%)	101 (6.9%)
	JBZD	40 (3.4%)	9 (3.2%)	49 (3.4%)
	LUMC	46 (3.9%)	7 (2.5%)	53 (3.6%)
	NWZA	234 (19.9%)	72 (26.0%)	306 (21.0%)
	RADN	342 (29.1%)	60 (21.7%)	402 (27.6%)
	STMA	52 (4.4%)	13 (4.7%)	65 (4.5%)
	UMCU	293 (24.9%)	73 (26.4%)	366 (25.2%)
Smoking status	Current smoker	99 (8.4%)	19 (6.9%)	118 (8.1%)
	Former smoker	329 (28.0%)	90 (32.5%)	419 (28.8%)
	Never smoked	749 (63.6%)	168 (60.6%)	917 (63.1%)
Past TB exposure[3]	No	1076 (91.4%)	252 (91.0%)	1328 (91.3%)
	Yes	101 (8.6%)	25 (9.0%)	126 (8.7%)
Comorbidities	Hay fever	341 (29.0%)	83 (30.0%)	424 (29.2%)
	Other respiratory[4]	95 (8.1%)	26 (9.4%)	121 (8.3%)
	On diabetes meds	7 (0.6%)	2 (0.7%)	9 (0.6%)
	On hypertension meds	71 (6.0%)	26 (9.4%)	97 (6.7%)
Place of work[5]	Intensive/medium care	114 (9.7%)	20 (7.2%)	134 (9.2%)
	Internal medicine	169 (14.4%)	59 (21.3%)	228 (15.7%)
	Urgent care	66 (5.6%)	21 (7.6%)	87 (6.0%)
	Other	828 (70.3%)	177 (63.9%)	1005 (69.1%)
Work function[6]	Patient care	1020 (86.7%)	248 (89.5%)	1268 (87.2%)
	Administrative	157 (13.3%)	29 (10.5%)	186 (12.8%)
Patient contact in hours per week (n %)				
	0-25	208 (17.7%)	25 (9.0%)	233 (16.0%)
	26-50	169 (14.4%)	36 (13.0%)	205 (14.1%)
	51-75	203 (17.2%)	41 (14.8%)	244 (16.8%)
	75+	597 (50.7%)	175 (63.2%)	772 (53.1%)
Covid ward duty	Yes	728 (61.9%)	200 (72.2%)	928 (63.8%)
	No	371 (31.5%)	59 (21.3%)	430 (29.6%)
	Unknown	78 (6.6%)	18 (6.5%)	96 (6.6%)
Had respiratory infection in winter 2019/2020				
	Yes, with fever	107 (9.1%)	14 (5.1%)	121 (8.3%)
	Yes, without fever	239 (20.3%)	45 (16.2%)	284 (19.5%)
Flu vaccine in winter 2019/2020		683 (58.0%)	152 (54.9%)	835 (57.4%)
Other vaccine in year prior to enrolment		128 (10.9%)	29 (10.5%)	157 (10.8%)
Flu vaccine during follow-up		552 (46.9%)	115 (41.5%)	667 (45.9%)
COVID-19 vaccine during follow-up				
	Pfizer	313 (26.6%)	78 (28.2%)	391 (26.9%)
	Moderna	112 (9.5%)	33 (11.9%)	145 (10.0%)
	AstraZeneca	67 (5.7%)	15 (5.4%)	82 (5.6%)
	Janssen	11 (0.9%)	2 (0.7%)	13 (0.9%)
	CureVac/unknown	8 (0.7%)	1 (0.4%)	9 (0.7%)
	None	667 (56.6%)	147 (53.5%)	814 (56.0%)

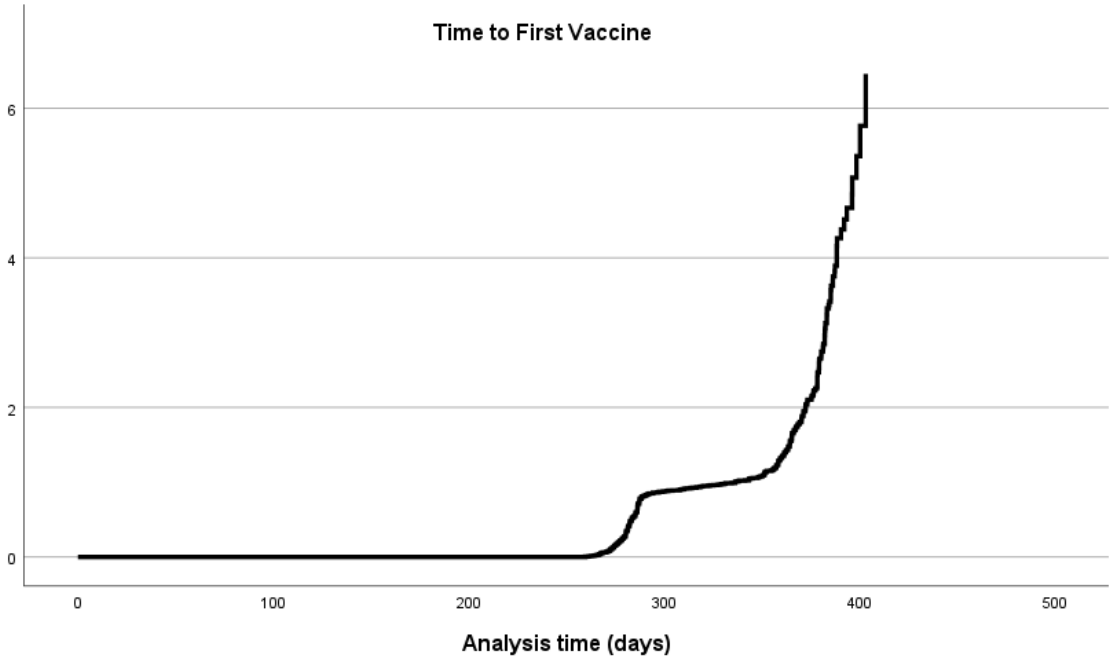
Baseline demographic statistics of BCG-Corona participants by infection status (proven or possible infection during follow-up or no infection during follow-up). Statistical tests used to evaluate variables: Chi-square test used to test categorical variables. Independent-Sample t-test used to evaluate used for the continuous variables (age and household number). [1]Household variable refers to all the members in the household (including the participants). [2]The sites in the study are Canisius Wilhelmina Ziekenhuis, Nijmegen (CWZN), Erasmus Medical Centre, Rotterdam (ERMC), Hagaziekenhuis, The Hague (HZDH), Jeroen Bosch Ziekenhuis, 's Hertogenbosch, Leiden University Medical Center, Leiden (LUMC), Noordwest Ziekenhuis, Alkmaar (NWZA), Sint Maartenskliniek, Woerden (STMA), Utrecht Medical Center, Utrecht (UMUC). [3]Tuberculosis (TB) exposure refers to participants who had a positive Mantoux test and/or a positive TB QuantiFERON test. [4]Respiratory illness are all those individuals who had asthma and/ or other lung diseases. [5]Place of work: Internal medicine includes the lung disease and infectious diseases departments. [6]Work function "patient care" refers to all the participants who were working as doctors, nurses, or paramedics during the study.

Table 2: Baseline and clinical characteristics of BCG-Corona Participants by Episode Severity

N (%) unless stated otherwise		No infection N=1177	Asymp[1] N=46	Mild N=169	Moderate/Severe[2] N=62	Total N=1454
Intervention	BCG	586 (49.8%)	24 (52.2%)	84 (49.7%)	27 (43.5%)	721 (49.6%)
	Placebo	591 (50.2%)	22 (47.8%)	85 (50.3%)	35 (56.5%)	733 (50.4%)
Sex	Female	856 (72.7%)	38(82.6%)	128 (75.7%)	52 (83.9%)	1074 (73.9%)
	Male	321 (27.3%)	8(17.4%)	41 (24.3%)	10 (16.1%)	380 (26.1%)
Age mean(range)		42.14 (18-67)	42.17 (21-62)	39.51 (20-63)	43.98 (22-64)	42(18-67)
Household mean(range)[3]		2.9 (1-18)	2.7 (1-13)	3.0 (1-6)	3.1 (1-7)	3(1-18)
Recruitment Site[4]	CWZN	58 (4.9%)	1 (2.2%)	8 (4.7%)	7 (11.3%)	74 (5.1%)
	ERMC	31 (2.6%)	1 (2.2%)	5 (3.0%)	1 (1.6%)	38 (2.6%)
	HZDH	81 (6.9%)	3 (6.5%)	10 (5.9%)	7 (11.3%)	101 (6.9%)
	JBZD	40 (3.4%)	1 (2.2%)	8 (4.7%)	0 (0.0%)	49 (3.4%)
	LUMC	46 (3.9%)	1 (2.2%)	6 (3.6%)	0 (0.0%)	53 (3.6%)
	NWZA	234 (19.9%)	10 (21.7%)	46 (27.2%)	16 (25.8%)	306 (21.0%)
	RADN	342 (29.1%)	12(26.1%)	35 (20.7%)	13 (21.0%)	402 (27.6%)
	STMA	52 (4.4%)	1 (2.2%)	10 (5.9%)	2 (3.2%)	65 (4.5%)
	UMCU	293 (24.9%)	16 (34.8%)	41 (24.3%)	16 (25.8%)	366 (25.2%)
Smoke Status	Current smoker	99 (8.4%)	3 (6.5%)	12 (7.1%)	4 (6.5%)	118 (8.1%)
	Former smoker	329 (28.0%)	8 (17.4%)	54 (32.0%)	28 (45.2%)	419 (28.8%)
	Never smoked	749 (63.6%)	35 (76.1%)	103 (60.9%)	30 (48.4%)	917 (63.1%)
Past TB Exposure[5]	No	1076 (91.4%)	41 (89.1%)	154 (91.1%)	57 (91.9%)	1328 (91.3%)
	Yes	101 (8.6%)	5 (10.9%)	15 (8.9%)	5 (8.1%)	126 (8.7%)
Comorbidities	Hay fever	341 (29.0%)	9 (19.6%)	58 (34.3%)	16 (25.8%)	424 (29.2%)
	Other Respiratory [6]	95 (8.1%)	2 (4.3%)	18 (10.7%)	6 (9.7%)	121 (8.3%)
	On diabetes meds	7 (0.6%)	0 (0.0%)	2 (1.2%)	0 (0.0%)	9 (0.6%)
	On hypertension meds	71 (6.0%)	3 (6.5%)	16 (9.5%)	7 (11.3%)	97 (6.7%)
Place of Work[7]	Intensive/Medium Care	114 (9.7%)	7(15.2%)	6 (3.6%)	7 (11.3%)	134 (9.2%)
	Internal Medicine	169 (14.4%)	9(19.6%)	36 (21.3%)	14 (22.6%)	228 (15.7%)
	Urgent Care	66 (5.6%)	4(8.7%)	16 (9.5%)	1 (1.6%)	87 (6.0%)
	Other	828 (70.3%)	26(56.5%)	111 (65.7%)	40 (64.5%)	1005 (69.1%)
Work Function[8]	Patient Care	1020 (86.7%)	40(87.0%)	154 (91.1%)	54 (87.1%)	1268 (87.2%)
	Administrative	157 (13.3%)	6(13.0%)	15 (8.9%)	8 (12.9%)	186 (12.8%)
Patient contact hours per week	0-25	208 (17.7%)	6 (13.0%)	12 (71. %)	7 (11.3%)	233 (16.0%)
	26-50	169 (14.4%)	5 (10.9%)	26 (15.4%)	5 (8.1%)	205 (14.1%)
	51-75	203 (17.2%)	7 (15.2%)	26 (15.4%)	8 (12.9%)	244 (16.8%)
	75+	597 (50.7%)	28 (60.9%)	105(62.1%)	42(67.7%)	772 (53.1%)
COVID-ward duty	Yes	728 (61.9%)	33 (71.7%)	118 (69.8%)	49 (79.0%)	928 (63.8%)
	No	371 (31.5%)	10 (21.7%)	39 (23.1%)	10 (16.1%)	430 (29.6%)
	Unknown	78 (6.6%)	3 (6.5%)	12 (7.1%)	3 (4.8%)	96 (6.6%)
Had Respiratory infection (2019/2020)						
	Yes, with fever	107 (9.1%)	4 (8.7%)	8 (4.7%)	2 (3.2%)	121 (8.3%)
	Yes, without fever	239 (20.3%)	7 (15.2%)	32 (18.9%)	6 (9.7%)	284 (19.5%)
	Other Vaccine (before baseline)	128 (10.9%)	6 (13.0%)	19 (11.2%)	4 (6.5%)	157 (10.8%)
Flu vaccine in winter 2019/2020		683 (58.0%)	19 (41.3%)	98 (58.0%)	35 (56.5%)	835 (57.4%)
Other vaccine in year prior to enrolment		128 (10.9%)	6 (13.0%)	19 (11.2%)	4 (6.5%)	157 (10.8%)
Flu vaccine during follow-up		552 (46.9%)	12 (26.1%)	80 (47.3%)	23 (37.1%)	667 (45.9%)
COVID-19 vaccine received during follow-up						
	Pfizer	313 (26.6%)	14 (30.4%)	49 (29.0%)	15 (24.2%)	391 (26.9%)
	Moderna	112 (9.5%)	5 (10.9%)	16 (9.5%)	12 (19.4%)	145 (10.0%)
	AstraZeneca	67 (5.7%)	2 (4.3%)	10 (5.9%)	3 (4.8%)	82 (5.6%)
	Janssen	11 (0.9%)	0 (0.0%)	1 (0.6%)	1 (1.6%)	13 (0.9%)
	CureVac/Unknown	8 (0.7%)	0 (0.0%)	1 (0.0%)	0 (0.0%)	9(0.7%)
	None	666 (56.6%)	25 (54.3%)	92 (54.4%)	31 (50.0%)	814 (56.0%)

Baseline demographic statistics of BCG-Corona participants by infection severity status. Statistical tests used to evaluate variables: Chi-square test used to test categorical variables. One-way ANOVA used to evaluate used for the continuous variables (age and household number).[1]Asymp refers to asymptomatic infections. [2]Moderate/Severe refers to all participants that were classified as moderate and severe for the infection episode severity; there were only three severe cases. [3]Household variable refers to all the members in the household (including the participants).[4]The sites in the study are Canisius Wilhelmina Ziekenhuis, Nijmegen (CWZN), Erasmus Medical Centre, Rotterdam (ERMC), Hagaziekenhuis, The Hague (HZDH), Jeroen Bosch Ziekenhuis, 's Hertogenbosch, Leiden University Medical Center, Leiden (LUMC), Noordwest Ziekenhuis, Alkmaar (NWZA), Sint Maartenskliniek, Woerden (STMA), Utrecht Medical Center, Utrecht (UMUC).[5]Tuberculosis (TB) exposure refers to participants who had a positive Mantoux test and/or a positive TB QuantiFERON test. [6]Respiratory illness are all those individuals who had asthma and/ or other lung diseases. [7]Place of work: internal medicine includes the lung diseases and infectious diseases departments. [8]Work Function "patient care" refers to all the participants who were doctors, nurses, or paramedics during the study.

Figure 2: Time to first COVID-19 vaccine



Time to first COVID-19 vaccine received by participants in BCG-Corona trial. Kaplan-Meier graph showing time to first vaccination as a survival analysis. X-axis depicts the analysis time, beginning at first participant enrolment to the end of the study. Y-axis depicts the hazard ratios.

Table 3: Univariate and multivariable multinomial logistic regression models with infection status as outcome

Covariates	Unadjusted OR (95% CI)	Unadjusted p	Adjusted OR (95% CI)	Adjusted p
Randomised to BCG (reference placebo)	0.98 (0.75-1.27)	0.855		
Female sex (reference male)	1.370 (1.00-1.88)	**0.050**		
Age in years (per year)	0.99 (0.98,1.00)	0.171		
Household (per member)	1.03 (0.95,1.13)	0.171		
Has covid ward duty (reference: COVID-ward duty)	Reference			
No duty	0.57(0.42-0.98)	**<0.001**		
% of hours patient contact:				
≤25	0.41 (0.26,0.65)	**<0.001**	0.40(0.24-0.63)	**<0.001**
26-50	0.73(0.49,1.09)	0.124	0.69(0.46-1.03)	0.068
51-75	0.67(0.46,0.98)	**0.041**	0.67(0.46-0.98)	**0.040**
≥75 (reference)	Reference			
Department				
Intensive/medium care	0.83 (0.50,1.37)	0.457	0.75(0.45-1.25)	0.274
Internal medicine (including lung and infectious diseases)	1.64 (1.17,2.31)	**0.004**	1.63(1.16-2.30)	**0.005**
Urgent care	1.41 (0.83,2.38)	0.203	1.17(0.69-2.00)	0.557
Other (reference)	Reference			
Function				
Patient Contact Function	1.30(0.856,1.983)	0.217		
Support staff (reference)	Reference			
Smoker (reference never)	Reference			
Current	0.87 (0.52,1.46)	0.594		
Former	1.24 (0.93,1.65)	0.146		
Prior TB Exposure	Reference			
No prior TB exposure	0.99(0.62,1.58)	0.968		
Chronic lung disease (reference: has lung disease)	0.84 (0.53,1.32)	0.451		
Chronic hay fever (reference: has hay fever)	0.94 (0.71,1.25)	0.679		
Hypertension medication (reference: taking hypertension medication)	0.61 (0.38,0.98)	**0.042**	0.59(0.36-0.95)	**0.029**
Diabetes medication (reference: taking diabetes medication)	0.82 (0.17,3.95)	0.800		

Table 4: Univariate and ordinal logistic regression models with infection severity as the outcome

Covariates	Unadjusted OR (95% CI)	Unadjusted p	Adjusted OR (95% CI)	Adjusted p
Randomized to BCG (reference placebo)	0.95 (0.730-1.23)	0.680		
Female sex (reference male)	1.38 (1.02-1.90)	**0.040**		
Age in years (per year)	0.99 (0.98-1.00)	0.197		
Household (per member)	1.04 (0.95-1.13)	0.422		
Has covid ward duty (reference: COVID-ward duty)				
No duty	0.57 (0.42,0.79)	**<0.001**		
% Of hours patient contact:				
≤25	0.41(0.26-0.64)	**<0.001**	0.40 (0.25,0.63)	**<0.001**
26-50	0.72 (0.48-1.07)	0.101	0.68 (0.45,1.00)	0.054
51-75	0.69 (0.47-1.00)	**0.047**	0.69(0.47,1.00)	**0.049**
≥75(reference)				
Department				
Intensive/medium care	0.81 (0.49,1.34)	0.418	0.74(0.45-1.22)	0.240
Internal medicine (incl. lung and infectious diseases)	1.63 (1.16,2.27)	**0.004**	1.60(1.14-2.24)	**0.007**
Urgent care	1.40 (0.84,2.33)	0.194	1.16(0.69-1.94)	0.577
Other (reference)	Reference			
Function				
Patient Contact Function	1.31 (0.86-1.99)	0.206		

Support staff (reference)	Reference			
Smoker (reference never) Current Former	Reference 0.87 (0.52-1.46) 1.28 (0.96-1.71)	 0.595 0.089		
Prior TB Exposure No prior exposure	Reference 0.96(0.61,1.51)	 0.855		
Chronic lung disease (reference has lung disease)	0.83(0.523-1.31)	0.422		
Chronic hay fever (reference: has hay fever)	0.95 (0.53-1.31)	0.712		
Hypertension medication (reference: taking hypertension medication)	0.61 (0.38-0.97)	**0.036**	0.59 (0.37,0.95)	**0.030**
Diabetes medication (reference: taking diabetes medication)	0.84 (0.18,3.99)	0.825		