Cover page

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BCG to Reduce Absenteeism Among Health Care Workers During the COVID-19 Pandemic

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Statistical Analysis Plan

Title BCG vaccine to reduce unplanned absenteeism due to illness of health care workers during the COVID-19 pandemic. A multi-center randomized controlled trial (BCG-COVID-RCT)

Sponsor

Version 4.0

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Table of contents

1. Summary of the study

Background and Rationale

The COVID-19 pandemic challenges available hospital capacity. This is augmented by absenteeism of health care workers (HCW). Bacille Calmette-Guérin (BCG) has protective non-specific effects against other infections; a plausible immunological mechanism has been identified in terms of "trained innate immunity". European and North American trials to study if BCG can reduce the incidence and/or severity of COVID-19 have now been initiated. African studies are needed. Even with the availability of specific COVID-19 vaccines, it is relevant to study if BCG can reduce the risk of infectious diseases.

Hypothesis

Based on the capacity of BCG to: 1) reduce the incidence of respiratory tract infections and mortality in children and perhaps in the elderly; 2) exert antiviral effects and reduce viremia in an experimental human model of viral infection, we hypothesize that BCG vaccination may induce partial protection against susceptibility to and/or severity of COVID-19 and other infections which might result in a reduction in the number of days of unplanned absenteeism from work for HCW. The underlying hypothesis for this study is that BCG vaccination of HCW reduces unplanned absenteeism due to illness by 20%.

Objectives

Primary: Test the capability of BCG to reduce absenteeism due to illness among HCW working at a health care facility that treats patients who could suffer from COVID during the COVID-19 pandemic. Secondary: reduce number of HCW that develop COVID-19; ii) reduce number of hospital admissions due to illness of HCW during the COVID-19 pandemic.

Trial design

Single-blind, parallel-group placebo-controlled multi-centre block randomized trial including a total of 1050 HCW. The study sites were the Manhiça District Hospital and Mavalane General Hospital in Mozambique, and Hospital Nacional Simão Mendes and other hospitals in the capital Bissau in Guinea-Bissau.

Unfortunately, Cape Verde was not authorized to conduct the study, because there is no existing legislation regulating clinical research in the country. As so, the number of the sample size in Guinea Bissau and in Mozambique was increased from 350 to 525 to guarantee the inclusion of the 1050 participants.

Study population. Health Care Workers (HCW) defined as a person who delivers care and services to the sick and ailing either directly as doctors and nurses or indirectly as aides, helpers, laboratory technicians, or even medical waste handlers.

Exclusion criteria

Known allergy to (components of) BCG or serious adverse events to prior BCG administration; known previous, active or latent infection with Mycobacterium tuberculosis or other mycobacterial species, fever (>38 C) within past 24 hours; previous confirmed COVID-19 (positive test by PCR or antibody) until inception of COVID-19 vaccination of HCW; suspicion of active viral or bacterial infection, severely immunocompromised subjects, self-reported HIV infection (Guinea: HIV-rapid test), self-reported pregnancy; active solid or non-solid malignancy or lymphoma within the last two years; any other contraindications for live-attenuated vaccine administration, not having a telephone.

Randomization

All participants who give consent for participation and who fulfil the inclusion criteria will be randomly assigned to either placebo or BCG group with a 1:1 (treatment:placebo) allocation in varying block sizes of 4 or 6 per block within strata defined by gender (male/female) and occupational group (doctors/ nurses/other).

Blinding

The BCG vaccine was administered by study physicians/nurses, who are not blinded but also not involved in the data collection. Participants and follow-up assistants will be blinded to the treatment allocation. In case of serious adverse events, the participant can be unblinded after consultation with the investigator or the vaccinating physician/nurse. When the study has ended, all participants will receive information about the intervention that they received.

Intervention

The intervention consists of the administration of an intradermal injection of a standard 0.1 ml adult dose of attenuated *Mycobacterium bovis* BCG (Bacillus Calmette-Guerin), Danish strain 1331, 2-8 × 105 CFU or the placebo comparator: intradermal standard 0.1 ml saline solution (NaCl 0.9%). Both BCG and saline solution will be injected in the skin over the upper deltoid muscle.

Outcomes

Primary outcome measure: Total numbers of days of unplanned absenteeism from work due to illness.

Secondary outcome measures: Days of unplanned absenteeism because of documented COVID-19 and cumulative incidence of hospital admissions due to illness (minus accidents).

Other Outcomes Measures: Hospitalisation for COVID-19; hospitalisation for respiratory infections; COVID-19 infection episodes; Furthermore, we will study the effect on Death for any reason, Death due to documented COVID infection. Cumulative incidence of infectious disease episodes, in particular respiratory infections. Cumulative incidence of infectious hospital admissions, in particular respiratory infections. Cumulative incidence of hospital admission due to documented COVID-19. Cumulative incidence of all-cause and infectious intensive care admission. Cumulative incidence of intensive care admission due to documented COVID infection.

Baseline data collection

Enrolment data regarding chronic illnesses and treatment, lifestyle (family structure, socioeconomic factors, smoking), vaccination history including previous BCG vaccination. Blood sample for SARS-CoV-2 serology.

Follow-up

Follow-up will last for 6 months (182 days). Telephone interviews every second week, regarding symptoms, absenteeism and causes, COVID-19 testing (if done) and their results. Supplemented by daily workplace presence registry information (where present).

End of follow-up

At the end of follow-up, participants will be invited back to the room of the healthcare facility where they were recruited to have another SARS-COV-2 antibody test and to complete the final questionnaire; also, at this time, the research officer will be asked to inspect and report how scarification is in the deltoid area of the right upper limb of the HCW, which may occur due to the BCG vaccine. Information regarding the treatment (BCG or placebo) will be disclosed to the participant at this time.

Sample size

The sample size was calculated on the basis of the primary hypothesis. A total of 1050 HCW randomized with an estimated loss to follow-up of 5%, and a mean number of days off work due to illness in the control group of 5 days (SD=5) over a 6-month period will demonstrate a reduction among BCG vaccinated of 20% for a mean absence of 4 days (80% power and alpha 0.05). The estimated loss to follow-up (5%) was based on past telephone-based surveys conducted in Bissau.

Statistical analysis.

Data will be reported quantitatively. All analyses will be performed from the intention-to-treat principle. Missing data on background variables will be dealt with by multiple imputation. Final data analysis will begin when the last participant in the multicentric RCT has completed the follow-up period. The primary endpoint, work absenteeism due to illness, will be reported as the total number of sick days with standard deviation. Continuous baseline characteristics will be reported as means with the standard deviation or medians with the inter-quartile range, as appropriate. Categorical baseline characteristics will be reported as count and percentage. Statistical testing for baseline characteristics will be performed. Days of absenteeism will be analysed using a Bayesian negative binomial regression with a fixed effect for BCG, hospital, professional category, age, enrolment week and number of average workdays per week. Incidence data will be analysed in Cox proportional hazards models. Monthly, data on absenteeism by randomization group will be reported to the DSMB.

Trial registration

The trial is registered at clinicaltrials.gov. https://clinicaltrials.gov/ct2/show/NCT04641858)

Funding

EDCTP is funding the run-in costs for the BCG-COVID-RCT, including trials in the respective countries and for training and management.

Study management, monitoring and quality control

The project is led by an International Steering Committee (ISC) consisting of PIs in each of the five countries involved: Christine Stabell Benn (international coordinator), PI from Denmark; Amabelia Rodrigues, PI from Guinea-Bissau; Inês Fronteira, PI from Portugal; Isabel Inês Araújo, PI from Cape Verde; and Pedro Aide, PI from Mozambique. The overall coordination is the responsibility of the Danish partner. The leader has extensive leadership experience from running a Center of Excellence in Denmark and the research group of the Bandim Health Project in Bissau for many years. The Bandim Health Project has a history of past collaboration with the Portuguese partner. The research group will hold teleconferences at least once a week with a formal pre-established agenda on training, enrollment, follow-up, losses to follow-up, staff turnover, vaccine logistics, quality control of data collection, data entry and database management, interim analysis, communication and dissemination activities, other risks. Decisions from each meeting are recorded by the coordinator.

2. Definitions

2.1. Treatment groups

Single-blind, parallel-group placebo-controlled adaptive multi-center trial, with block randomisation 1:1 to intradermal standard 0.1 ml dose of BCG vaccine or placebo (saline) including a total of 1050 HCW (BCG arm and placebo arm). The intervention will consist of the administration of an intradermal injection of a standard 0.1 ml adult dose of attenuated *Mycobacterium bovis* BCG (Bacillus Calmette-Guerin), Danish strain 1331, 2-8 × 105 CFU or the placebo comparator: intradermal standard 0.1 ml saline solution (NaCl 0.9%).

Both BCG and saline solution will be injected in the skin over the upper deltoid muscle. The BCG vaccine is being administered by healthcare professionals who are not blinded to the intervention administered, but who will also not be involved in data collection during follow-up. Participants, research assistants and analysts are blinded to the intervention received. In the event of serious adverse effects, the participant may be revealed the intervention they received, after consultation with the investigator or physician/nurse. When the study ends, all participants are informed about the intervention they received.

2.2. Analyzed populations

The clinical trial participants are 1,050 HCW (definition below) recruited from hospitals in two different African countries.

The Guinea-Bissau arm of the BCG-COVID-RCT study is conducted in Bissau, the country capital, by the Bandim Health Project (BHP). The team is led by Amabelia Rodrigues. Inclusions commenced in Guinea-Bissau on December 3rd, 2020, in the Hospital Nacional Simão Mendes. After concluding inclusions at Simão Mendes, inclusions were commenced at other hospitals and health centers.

In Mozambique, this study is being conducted at Manhiça District Hospital (MDH) and Mavalane General Hospital (MGH) by the Centro de Investigação em Saúde de Manhiça (CISM) through the team led by Dr. Pedro Aide. Manhiça District Hospital is located on the main National Road One, in the capital of the Manhiça district, Maputo Province, southern Mozambique. Manhiça is a rural area located approximately 80km away from the capital, Maputo city; has a total population close to two hundred thousand people. MDH is the referral hospital with more than 100 beds and absorbs the largest proportion of HCW within the district. MGH (260 beds) is located in the district of neighborhood of Mavalane, in Maputo city (Southern Mozambique). The MGH is part of the three general hospitals of the city of Maputo. The health

area of Mavalane is the largest in the city and serves an estimated population of 609.889 inhabitants, about 50% of the health population of the capital of nation capital.

2.3. Study definitions

- ***Health Care Workers (HCW)*** defined as a person who provides service and/or care to patients/users attending the health care facilities participating in the study, either directly (nurses, nursing assistants, physicians, and medical students), or indirectly as aides, lab technicians, cleaning staff, or even medical waste handlers.
- ***SARS-CoV-2* (“*Severe Acute Respiratory Syndrome Coronavirus 2*”)** defined as a virus associated with or responsible for COVID-19.
- ***COVID-19*** is a disease caused by the coronavirus (a large family of viruses common in many different animal species, including camels, cattle, cats and bats), called SARS-CoV-2, which has a clinical spectrum ranging from asymptomatic to severe infections. The symptoms of COVID-19 can range from a cold to a Gripal Syndrome-SG (presence of an acute respiratory condition characterized by at least two of the following symptoms: febrile feeling or fever associated with sore throat, headache, cough, runny nose) to severe pneumonia.
- ***BCG (Bacillus Calmette-Guérin)*** vaccine is composed of Bacillus Calmette & Guérin, obtained by attenuating *Mycobacterium bovis*, one of the bacteria that transmit tuberculosis. This vaccine prevents tuberculosis, an infectious disease that most commonly attacks the lungs, but can also cause infections in the bones, kidneys and meninges (the membranes that surround the brain).
- ***Placebo*** is a simulated drug that does not contain any chemical or medicinal substance and can only influence the individual taking it psychologically. In a clinical trial, a placebo is a pharmaceutical form without any activity, taken by the patients in the control group, and identical in appearance to the pharmacologically active pharmaceutical form(s) taken by the subjects in the other treatment group(s) of the trial.
- ***Clinical Trial (Clinical Study or Clinical Research)*** is a method of scientific investigation applied to human beings in order to prove the efficacy of treatments or drugs, the probable benefits and adverse events, as well as to make possible the offer of treatments not yet applied in clinical practice.
- ***Randomized ("chosen at random")*:** This is any randomization procedure (in our study we will use a computer program - REDCap - for the randomization of participants. In this way, all subjects participating in the trial will have strictly the same probability of receiving the BCG vaccine or the one corresponding to the study control (placebo).

- ***Absenteeism*** is referred to as the total number of absences (in days) of the health worker care due mainly to some illness.

3. Sample size

Our sample size was defined based on the calculations made by the Dutch group which computed in 1000 the minimum sample size. We decided include 350 participants per site(Cape Verde, Guinea Bissau and Mozambique) which adds 1050 participants. This participants number is near enough to show significance for the primary outcome - expected absenteeism reduction from 5% to 4%.

Based on current experience, the investigators consider that this a feasible sample size, which well balances burden of participants against public interest. As this is an adaptive study, the final follow-up duration is subject to the percentage of absenteeism during the study period, variation in absenteeism between participants, and the true effect of BCG vaccine.

4. Recruitment and follow-up

The RCT involves healthy, volunteer human participants able to give informed consent to participate in an interventional trial consisting in the intradermal administration of BCG vaccine standard dose or placebo (saline).

The participants in this research are HCW. Prior to the initiation of the trial, the hospital director will inform the department heads about the trial. For recruitment we performed a rapid test (POC test) for antibodies against SARS-CoV2 using the COVID-19 IgG/IgM CTK OnSite COVID-19 IgG/IgM Rapid Test (https://ctkbiotech.com/covid-19/). The test is performed by collecting a drop of blood (maximum 0.4 ml of blood) from a fingerstick. The participant was informed about the POC test result and the interpretation of what it means to having or not having IgM and/or IgG antibodies. If the result is positive for IgM antibodies, we recommend that the HCP be tested for SARS-CoV2 with a swab in the throat (PCR test), according to the recommendations of local health authorities. The BCG vaccine was administered by people trained to administer vaccines by the intradermal technique. The injection site should be clean and dry. The vaccine was injected intradermally on the outer side of the upper arm, corresponding to the area of the distal insertion of the deltoid muscle (about one-third down the upper arm).

Follow-up will last for 6 months (182 days). Every second week, participants will be contacted over telephone and interviewed for symptoms and absenteeism from work. By the end of follow-up,

participants will be invited for another POC test for COVID-19 serology. The study relies on bi-weekly telephone follow-up. Participants have indicated whether they prefer to be contacted during the morning, the afternoon or at any time during the day. The responsible assistant conducts the telephone follow-up every day and introduces the data on absenteeism and causes, COVID-19 testing (if done) and their results on the WiFi-connected tablet during the interview. This data can be supplemented by daily workplace presence registry information (where present). An explicit permission for this procedure will be requested from the participant during informed consent procedures at enrolment.

5. Endpoint variables

The endpoint variables are described in Table 1

Table 1 – Definition of end-points variables

Variable	Definition	Type	Scale	Domain
Absenteeism	Refers to the total number of days absent from work due to illness	Quantitative	Numeric	In days
Absenteeism for COVID-19	Refers to the number of days absent from work due to COVID-19	Quantitative	Numeric	In days
Absenteeism besides COVID-19	Refers to the number of days absent from work due to illness besides COVID-19	Quantitative	Numeric	In days
Absenteeism for infections	Refers to the number of days (unplanned) absent from work due to infections	Quantitative	Numeric	In days
Absenteeism for respiratory infections	Refers to the number of days (unplanned) absent from work due to respiratory infections	Quantitative	Numeric	In days
COVID-19 infection	Describes if the participant is positive for SARS-CoV2 or has had COVID-19	Qualitative	Nominal	No Yes
Death	Whether the participant died during follow-up	Qualitative	Nominal	No Yes
Cumulative incidence of infectious disease episodes	Cumulative incidence of infectious disease episodes	Quantitative	Numeric	Episodes
Cumulative incidence of respiratory infectious disease episodes	Cumulative incidence of respiratory infectious disease episodes	Quantitative	Numeric	Episodes
Cumulative incidence of hospital admissions	Cumulative incidence of hospital admissions	Quantitative	Numeric	Admissions
Cumulative incidence of infectious disease hospital admissions	Cumulative incidence of infectious hospital admissions	Quantitative	Numeric	Admissions

Variable	Definition	Type	Scale	Domain
Cumulative incidence of respiratory infectious hospital admissions	Cumulative incidence of respiratory infectious hospital admissions	Quantitative	Numeric	Admissions
Cumulative incidence of hospital admissions due to documented COVID-19	Cumulative incidence of hospital admissions due to documented COVID-19	Quantitative	Numeric	Admissions
Cumulative incidence all-cause and infectious intensive care admission	Cumulative incidence all-cause and infectious intensive care admission	Quantitative	Numeric	Nights
Cumulative incidence of intensive care admission due to documented COVID-19 infection	Cumulative incidence all-cause and infectious intensive care admission	Quantitative	Numeric	Nights

6. General Statistical considerations

6.1. General statistical methodology

The database system for both inclusion procedures and follow-up is REDCap (www.project-redcap.org), and the instruments have been developed by the Institute of Hygiene and Tropical Medicine at NOVA University.

Data entry for both inclusion and follow-up procedures is conducted online using the browser version, which means that no participant data is stored locally and that the study responsible(s) can monitor the data collection in real-time.

The randomization code was developed by the trial statistician, Sebastian Nielsen. This code produces an allocation table for all the stratification layers and all the sites, with block sizes varying randomly between 4 and 6 within each individual stratum. The allocation table used for the study has not been seen and is not available to any of the researchers involved in the study and it was implemented by an independent statistician, Andreas Møller Jensen, in Bissau.

From the databases of the trials in Guinea-Bissau and Mozambique, their analysis will be performed by either STATA version 17 software (Stata, College Station, TX) or SPSS version 26.

The combined data analysis will begin when the last participant in the multicentric RCT has completed the follow-up period or after the 182 day of the study and data has been cleaned.

Descriptive statistical techniques (absolute and relative frequency distribution) will be used to analyze the quality of the database through the evaluation of two aspects: completeness (field filling) and consistency (consistency between the categories marked in two related fields). The completeness indicator will be calculated as the proportion of filled fields in relation to the total of records, in percentage. Regarding completeness, the results will be categorized as the percentage of records without filling out as follows: excellent (<10% of records without filling out), regular (11 to 30%) and low (>30% of records without filling out).

Primarily a descriptive analysis will be performed of all information contained in the two study groups (BCG and placebo). All variables will be analysed, one by one, to know their distribution. Background factors will be summarised by counts (percentages), means (standard deviation) or medians (interquartile range) as appropriate. Proportions will be compared using the chi-square test - χ^2 test or Fisher's Exact test (categorial variable) or Student's t-test *or* Mann-Whitney test (quantitative variable) according to the distribution of variables. Statistical significance was set at the 5% level (two-tailed tests) and 95% confidence intervals (95%CI) for the estimates.

The endpoints variables (table 1) will be analyzed using univariate analysis (Logrank test) and Multivariate analysis (Cox Proportional Hazard Regression, or Cox Regression), stratified by the block randomization variables gender (male/female) and occupational group (doctors/ nurses/other) in addition to site. Covariates will be tested in the model univariate, and only those that were associated with the outcome at a significance level of at least 20% will be retained in a possible multivariate model. A significance level (p-value) of less than 0.05 and its respective confidence intervals (CI) will be used.

6.2. Missing Data

Information about the proportion with missing information will be provided, informing about the variations of the "n" (sample size), investigating and describing the reasons that generated the omission.

Variables with more than 10% of data missing are not suitable for techniques for imputation of values, and retention of the subject or variable in the study will be questioned and decided by the steering commitee. Imputation of missing data can be considered after analysis of the type of mechanism that led to it.

RCT should preferably analyze all participants by intention to treat (ITT), so that all of those randomized and allocated to a group should be analyzed at the end of the study, irrespective of diversions from the therapeutic protocol or of dropouts. We will use Last Observation Carried Forward (LOCF), a single

imputation technique that imputes the last measured outcome value for participants who either drop out of a clinical trial or for whom the final outcome measurement is missing. LOCF is usually used in the longitudinal study design where the outcome is measured repeatedly at pre-specified intervals. LOCF usually requires there is at least one post-baseline measure.

We will perform imputation of missing entries from incomplete data sets *m* times; the imputed values are drawn from a distribution. The random draw simulation does not include the uncertainty in the model parameters. A better approach is to use Markov Chain Monte Carlo (MCMC) simulation. This step results in complete data sets. We will analyze each of the complete data sets and finally integrate the results of the *m* analysis into a final result. For data imputation on categorical variables, the missing values will be treated as a separate category by themselves. We can create another category for the missing values and use it as a different level. After this procedure we will use multiple imputation.

6.3. Descriptive statistics

We will describe participant flow and reasons for non-participation by group allocation in a flowchart.

For HCW included in the analysis, we will describe background factors. Distribution of background factors will be presented by group allocation overall and by gender (male/female) and occupational group (doctors/ nurses/other).

In the exploratory data analysis, all variables will be analysed to know their distribution. Background factors will be summarised by counts (percentages), means (standard deviation) or medians (interquartile range) as appropriate. Information on the proportion with missing information will be provided.

For qualitative variables, absolute and relative frequencies will be used to understand the distribution, and from there, to define if there is a need to group some categories in order to make a statistical comparison possible.

In the case of quantitative variables, the analysis of their distribution will be done by observing measures of central tendency, measures of position, and measures of variation. In this step, if the quantitative variable is continuous, we will study its distribution that will determined the type of statistical tests to apply in the bivariate step. If the variable has normal distribution the appropriate measure for representation is the mean with its respective standard deviation and the line of parametric tests, otherwise the appropriate measure is the median accompanied by the information of the interquartile range (first and third quartile) and the tests to be applied are the non-parametric tests. To test the normality of the data we will use the Kolmogorov-Smirnov tests.

6.4. Inferential statistics

The comparison between the intervention versus placebo groups will be done using the chi-square test (-χ^2 test or Fisher's Exact test (categorial variable) or Student's t-test *or* Mann-Whitney test (quantitative variable) according to the distribution of variables.

Fisher's test is useful for categorical data, which result from classifying objects in two different ways and when considering the sample number low; it is used to examine the significance of the association (contingency) between the two types of classification. It is used because the approximation is inadequate when the sample size is small, or if the data are very unevenly distributed among the cells of the table, resulting in the cell count predicted by the null hypothesis (the "expected values") being low. Although considered conservative, we can - for its use - use the usual rule for deciding whether the chi-square approximation test is good enough, where the chi-square test is not appropriate when the expected values in the cells of the contingency table are below 5, or below 10 when there is only one degree of freedom. In fact, for small, sparse, or unbalanced data, the exact and asymptotic p-value can be very different and can lead to opposite conclusions about the hypothesis of interest. Fisher's exact test keeps the row and column totals fixed, and can therefore be used regardless of the sample characteristics. It becomes difficult to calculate with large samples or well-balanced tables; under these conditions, the χ^2 test is appropriate.

When you have a small sample and the numerical variable is not known to have a normal distribution (or cannot be verified satisfactorily), or when there is no homogeneity of variances, Student's t-test is not appropriate. In this situation, the nonparametric Mann-Whitney test (Wilcoxon rank-sum test, U-test) can be used. Unlike the t-test, which tests for equality of means, the Mann-Whitney test tests for equality of medians. The U values calculated by the test assess the degree of intermingling of the data of the two groups after sorting. The greater separation of the data together indicates that the samples are distinct, rejecting the hypothesis of equality of the medians. Total days of absenteeism will be analyzed using a Bayesian negative binomial regression with a fixed effect for BCG, hospital, professional category, age, enrolment week and number of average workdays per week. The excess absence of the event of interest can lead to data overdispersion (a phenomenon that occurs when the variance of the response variable is greater than the value of the mean). To check the overdispersion of the data we will use the deviance, which is also a statistic used to check the goodness of fit of the model.

The Kaplan-Meier method consists of dividing the follow-up time into intervals, whose limits correspond to the follow-up time when events occurred. The measure of association used in survival analysis to

compare groups is the Hazard Ratio (HR), with similar meaning to Relative Risk; HR is the probability that some participant who did not have the outcome event by a certain time, will have it at that time. HR therefore compares the instantaneous incidence with which events occur in the different groups (BCG and Placebo).

For the univariate analysis to check the difference between the BCG versus Placebo groups we will use the Logrank test of significance by means of its p-value or confidence interval. For the univariate analysis to check the difference between the BCG versus Placebo groups we will use the Logrank test of significance by means of its p-value or confidence interval. In the multivariate analysis for the comparison of the two analyzed groups, we will use the Cox Proportional Hazard Regression, or Cox Regression. This allows us to obtain results adjusted for possible confounding variables. Cumulative incidence data will be analysed in Cox proportional hazards models. The Cox Model, which is semi-parametric, assumes that failure rates are proportional, that is, the risk of failure of the variables is constant over time. Survival analysis will allow us to correctly assess the rate at which events (outcomes) are occurring in the different groups in our study.

7. Demographics and other baseline characteristics

Baseline characteristics

Table 2 – Baseline characteristics of the participants

Variable	Type	BCG vaccine	Placebo	Statistical (P-value)
Age (years)	Quantitative	$\bar{X}$ ± SD *or* Md (IQR)	$\bar{X}$ ± SD *or* Md (IQR)	Student's t-test *or* Mann-Whitney test
Gender				
Female	Categorical	% (n/N)	% (n/N)	χ^2 test or Fisher's exact test (P-value)
Male		% (n/N)	% (n/N)	
Number adults (> 18 years) living in the household	Quantitative	$\bar{X}$ ± SD *or* Md (IQR)	$\bar{X}$ ± SD *or* Md (IQR)	Student's t-test *or* Mann-Whitney test
Adult living at home and also healthcare worker	Quantitative	$\bar{X}$ ± SD *or* Md (IQR)	$\bar{X}$ ± SD *or* Md (IQR)	Student's t-test *or* Mann-Whitney test
Number children (<18 years) living in the household	Quantitative	$\bar{X}$ ± SD *or* Md (IQR)	$\bar{X}$ ± SD *or* Md (IQR)	Student's t-test *or* Mann-Whitney test
Age of the youngest child living in the household (years)	Quantitative	$\bar{X}$ ± SD *or* Md (IQR)	$\bar{X}$ ± SD *or* Md (IQR)	Student's t-test *or* Mann-Whitney test
Animals living in the household				
Dogs	Categorical	% (n/N)	% (n/N)	
Cats		% (n/N)	% (n/N)	χ^2 test or Fisher's exact test (P-value)
Pigs		% (n/N)	% (n/N)	

Variable	Type	BCG vaccine	Placebo	Statistical (P-value)
Birds		% (n/N)	% (n/N)	
Sheep		% (n/N)	% (n/N)	
Other		% (n/N)	% (n/N)	
Person living in the household diagnosed with COVID-19	Categorical			
No		% (n/N)	% (n/N)	χ^2 test or Fisher's exact test (P-value)
Yes		% (n/N)	% (n/N)	
Occupation				
Doctor	Categorical	% (n/N)	% (n/N)	χ^2 test or Fisher's exact test (P-value)
Nurse		% (n/N)	% (n/N)	
Other		% (n/N)	% (n/N)	
Unit / Department with the highest frequency at work				
Urgency center		% (n/N)	% (n/N)	
Medicine		% (n/N)	% (n/N)	
Surgery	Categorical	% (n/N)	% (n/N)	χ^2 test or Fisher's exact test (P-value)
Consultation / outpatient		% (n/N)	% (n/N)	
Maternity		% (n/N)	% (n/N)	
Pediatric		% (n/N)	% (n/N)	
Other		% (n/N)	% (n/N)	
Hours worked per week at the hospital or health center (on a typical work week)	Quantitative	$\bar{X}$ ± SD *or* Md (IQR)	$\bar{X}$ ± SD *or* Md (IQR	Student's t-test *or* Mann-Whitney test
Work in another place				
No		% (n/N)	% (n/N)	
Yes		% (n/N)	% (n/N)	
Yes, another public hospital/ health institution/ clinic /private practice	Categorical	% (n/N)	% (n/N)	χ^2 test or Fisher's exact test (P-value)
Yes, another private hospital/ health institution/ clinic / consulting rooms		% (n/N)	% (n/N)	
Yes, another place that it is not a hospital/ health institution/ clinic/ private practice		% (n/N)	% (n/N)	
Provide direct care patients infected with COVID-19 or patients that are suspected to be infected	Categorical			χ^2 test or Fisher's exact test (P-value)
No		% (n/N)	% (n/N)	
Yes		% (n/N)	% (n/N)	
Contact with areas where COVID-19 patients are treated	Categorical			
No		% (n/N)	% (n/N)	χ^2 test or Fisher's exact test (P-value)
Yes		% (n/N)	% (n/N)	
Access to personal protection equipment available at your	Categorical			

Variable	Type	BCG vaccine	Placebo	Statistical (P-value)
workplace to prevent COVID-19 and other infectious diseases				χ^2 test or Fisher's exact test (P-value)
No		% (n/N)	% (n/N)	
Yes		% (n/N)	% (n/N)	
Use of mask by the patient during the interview				
Correct use	Categorical	% (n/N)	% (n/N)	χ^2 test or Fisher's exact test (P-value)
Incorrect use		% (n/N)	% (n/N)	
Does not wear a mask		% (n/N)	% (n/N)	
Absent from work for the past 2 weeks due to illness	Categorical			χ^2 test or Fisher's exact test (P-value)
No		% (n/N)	% (n/N)	
Yes		% (n/N)	% (n/N)	
Days absent from work for the past 2 weeks	Quantitative	$\bar{X}$ ± SD *or* Md (IQR)	$\bar{X}$ ± SD *or* Md (IQR)	Student's t-test *or* Mann-Whitney test
Hospitalization for the past 2 weeks due to illness	Categorical			χ^2 test or Fisher's exact test (P-value)
No		% (n/N)	% (n/N)	
Yes		% (n/N)	% (n/N)	
Days hospitalization for the past 2 weeks	Quantitative	$\bar{X}$ ± SD *or* Md (IQR)	$\bar{X}$ ± SD *or* Md (IQR)	Student's t-test *or* Mann-Whitney test
Symptoms in the past 2 weeks	Categorical			
Fever (> 38 C)		% (n/N)	% (n/N)	
Cough		% (n/N)	% (n/N)	
Respiratory problem		% (n/N)	% (n/N)	
Fatigue		% (n/N)	% (n/N)	
Headache		% (n/N)	% (n/N)	
Muscle pain		% (n/N)	% (n/N)	χ^2 test or Fisher's exact test (P-value)
Sore throat		% (n/N)	% (n/N)	
Diarrhea		% (n/N)	% (n/N)	
Loss of smell / taste		% (n/N)	% (n/N)	
Other		% (n/N)	% (n/N)	
Body structure				
1		% (n/N)	% (n/N)	
2		% (n/N)	% (n/N)	
3		% (n/N)	% (n/N)	
4	Categorical	% (n/N)	% (n/N)	χ^2 test or Fisher's exact test (P-value)
5		% (n/N)	% (n/N)	
6		% (n/N)	% (n/N)	
7		% (n/N)	% (n/N)	
8		% (n/N)	% (n/N)	
9		% (n/N)	% (n/N)	
Chronic disease				
No	Categorical	% (n/N)	% (n/N)	χ^2 test or Fisher's exact test (P-value)
Yes		% (n/N)	% (n/N)	
Type of chronic disease				
Diabetes		% (n/N)	% (n/N)	
Chronic obstructive pulmonary disease	Categorical	% (n/N)	% (n/N)	
Other respiratory disease		% (n/N)	% (n/N)	
Hypertension		% (n/N)	% (n/N)	

Variable	Type	BCG vaccine	Placebo	Statistical (P-value)
Other cardiovascular diseases		% (n/N)	% (n/N)	χ^2 test or Fisher's exact test (P-value)
Autoimmune disease		% (n/N)	% (n/N)	
Obesity		% (n/N)	% (n/N)	
Overweight		% (n/N)	% (n/N)	
Other		% (n/N)	% (n/N)	
Health scale				
1	Categorical	% (n/N)	% (n/N)	χ^2 test or Fisher's exact test (P-value)
2		% (n/N)	% (n/N)	
3		% (n/N)	% (n/N)	
4		% (n/N)	% (n/N)	
5		% (n/N)	% (n/N)	
6		% (n/N)	% (n/N)	
7		% (n/N)	% (n/N)	
8		% (n/N)	% (n/N)	
9		% (n/N)	% (n/N)	
10		% (n/N)	% (n/N)	
Use of medication				
No	Categorical	% (n/N)	% (n/N)	χ^2 test or Fisher's exact test (P-value)
Yes		% (n/N)	% (n/N)	
Do not know		% (n/N)	% (n/N)	
COVID-19 vaccine				χ^2 test or Fisher's exact test (P-value)
No	Categorical	% (n/N)	% (n/N)	
Yes		% (n/N)	% (n/N)	
COVID-19 vaccine type				χ^2 test or Fisher's exact test (P-value)
Astra Zeneca	Categorical	% (n/N)	% (n/N)	
Pfizer		% (n/N)	% (n/N)	
Moderna		% (n/N)	% (n/N)	
Sinopharm		% (n/N)	% (n/N)	
Other		% (n/N)	% (n/N)	
COVID-19 Vaccine dose				χ^2 test or Fisher's exact test (P-value)
First dose	Categorical	% (n/N)	% (n/N)	
Second dose		% (n/N)	% (n/N)	
BCG vaccine				χ^2 test or Fisher's exact test (P-value)
No	Categorical	% (n/N)	% (n/N)	
Yes		% (n/N)	% (n/N)	
Do not know		% (n/N)	% (n/N)	
BCG vaccination number				
One time	Categorical	% (n/N)	% (n/N)	χ^2 test or Fisher's exact test (P-value)
Two time		% (n/N)	% (n/N)	
Three or more time		% (n/N)	% (n/N)	
BCG scar				χ^2 test or Fisher's exact test (P-value)
No	Categorical	% (n/N)	% (n/N)	
Yes		% (n/N)	% (n/N)	
Previous vaccination scar				
No scar	Categorical	% (n/N)	% (n/N)	χ^2 test or Fisher's exact test (P-value)
BCG scar		% (n/N)	% (n/N)	
Smallpox scar		% (n/N)	% (n/N)	
Has not been examined		% (n/N)	% (n/N)	
BCG scar local	Categorical			
Right arm		% (n/N)	% (n/N)	

Variable	Type	BCG vaccine	Placebo	Statistical (P-value)
Left arm		% (n/N)	% (n/N)	χ^2 test or Fisher's
Both arms		% (n/N)	% (n/N)	exact test (P-value)
Smallpox scar local				χ^2 test or Fisher's
Right arm	Categorical	% (n/N)	% (n/N)	exact test (P-value)
Left arm		% (n/N)	% (n/N)	
Both arms		% (n/N)	% (n/N)	
BCG scar number				
1	Categorical	% (n/N)	% (n/N)	χ^2 test or Fisher's
2		% (n/N)	% (n/N)	exact test (P-value)
3 or more		% (n/N)	% (n/N)	
Smallpox scar number				
1	Categorical	% (n/N)	% (n/N)	χ^2 test or Fisher's
2		% (n/N)	% (n/N)	exact test (P-value)
3 or more		% (n/N)	% (n/N)	

Characteristics of the participants in the follow-up

Table 3 - Characteristics of the participants in the follow-up

Characteristics	Type	BCG vaccine	Placebo	Statistical (P-value)
Vaccine in the last 2 years				χ^2 test or Fisher's exact
No	Categorical	% (n/N)	% (n/N)	test (P-value)
Yes		% (n/N)	% (n/N)	
Received any vaccines in the last 2 years				
Oral Polio Vaccine		% (n/N)	% (n/N)	
Yellow Fever Vaccine		% (n/N)	% (n/N)	
Measles Vaccine	Categorical	% (n/N)	% (n/N)	
Rota virus vaccine		% (n/N)	% (n/N)	
Smallpox vaccine		% (n/N)	% (n/N)	χ^2 test or Fisher's exact
Oral Typhoid vaccine		% (n/N)	% (n/N)	test (P-value)
Varicella vaccine		% (n/N)	% (n/N)	
BCG vaccine		% (n/N)	% (n/N)	
Other vaccine		% (n/N)	% (n/N)	
Vaccine in the last two weeks				χ^2 test or Fisher's exact
No	Categorical	% (n/N)	% (n/N)	test (P-value)
Yes		% (n/N)	% (n/N)	
Vaccine type received in the last two weeks				
Oral Polio Vaccine		% (n/N)	% (n/N)	
Yellow Fever Vaccine		% (n/N)	% (n/N)	
Measles Vaccine		% (n/N)	% (n/N)	
Rota virus vaccine		% (n/N)	% (n/N)	
Smallpox vaccine		% (n/N)	% (n/N)	
Oral Typhoid vaccine		% (n/N)	% (n/N)	
Varicella vaccine		% (n/N)	% (n/N)	
BCG vaccine	Categorical	% (n/N)	% (n/N)	χ^2 test or Fisher's exact
Other vaccine		% (n/N)	% (n/N)	test (P-value)
Symptoms in the past 2 weeks		% (n/N)	% (n/N)	
Fever (> 38 C)		% (n/N)	% (n/N)	

Cough		% (n/N)	% (n/N)	
Respiratory problem		% (n/N)	% (n/N)	
Fatigue		% (n/N)	% (n/N)	χ^2 test or Fisher's exact
Headache		% (n/N)	% (n/N)	test (P-value)
Muscle pain		% (n/N)	% (n/N)	
Sore throat	Categorical	% (n/N)	% (n/N)	
Diarrhea		% (n/N)	% (n/N)	
Loss of smell / taste		% (n/N)	% (n/N)	
Other		% (n/N)	% (n/N)	
Health problem in the past 2 weeks				χ^2 test or Fisher's exact
No		% (n/N)	% (n/N)	test (P-value)
Yes	Categorical	% (n/N)	% (n/N)	
Absent from work for the past 2 weeks due to illness				χ^2 test or Fisher's exact test (P-value)
No	Categorical	% (n/N)	% (n/N)	
Yes		% (n/N)	% (n/N)	
Days absent from work for the past 2 weeks	Quantitative	$\bar{x}$ ± SD *or* Md (IQR)	$\bar{x}$ ± SD *or* Md (IQR)	Student's t-test *or* Mann-Whitney test
Absent from work in the last 2 weeks due to a quarantine				
No	Categorical	% (n/N)	% (n/N)	χ^2 test or Fisher's exact
Yes		% (n/N)	% (n/N)	test (P-value)
Days absent from work in the last 2 weeks due to a quarantine	Quantitative	$\bar{x}$ ± SD *or* Md (IQR)	$\bar{x}$ ± SD *or* Md (IQR)	Student's t-test *or* Mann-Whitney test
Absent from work in the last 2 weeks due to illness				
No	Categorical	% (n/N)	% (n/N)	
Yes		% (n/N)	% (n/N)	χ^2 test or Fisher's exact test (P-value)
Days absent from work in the last 2 weeks due to illness	Quantitative	$\bar{x}$ ± SD *or* Md (IQR)	$\bar{x}$ ± SD *or* Md (IQR)	Student's t-test *or* Mann-Whitney test
Absent from work in the last 2 weeks due to COVID-19				
No	Categorical	% (n/N)	% (n/N)	χ^2 test or Fisher's exact
Yes		% (n/N)	% (n/N)	test (P-value)
Days absent from work in the last 2 weeks due to COVID-19	Quantitative	$\bar{x}$ ± SD *or* Md (IQR)	$\bar{x}$ ± SD *or* Md (IQR)	Student's t-test *or* Mann-Whitney test
Hospitalisation in the last 2 weeks due to illness				
No		% (n/N)	% (n/N)	
Yes	Categorical	% (n/N)	% (n/N)	χ^2 test or Fisher's exact test (P-value)
Nights hospitalisation in the last 2 weeks due to illness	Quantitative	$\bar{x}$ ± SD *or* Md (IQR)	$\bar{x}$ ± SD *or* Md (IQR)	Student's t-test *or* Mann-Whitney test
Hospitalisation due to COVID-19				
No	Categorical	% (n/N)	% (n/N)	χ^2 test or Fisher's exact
Yes		% (n/N)	% (n/N)	test (P-value)
Nights hospitalisation due to COVID-19	Quantitative	$\bar{x}$ ± SD *or* Md (IQR)	$\bar{x}$ ± SD *or* Md (IQR)	Student's t-test *or* Mann-Whitney test
Hospitalisation due other causes				χ^2 test or Fisher's exact
No	Categorical	% (n/N)	% (n/N)	test (P-value)
Yes		% (n/N)	% (n/N)	

Person living in the household diagnosed with COVID-19 in the last 2 weeks				
No		% (n/N)	% (n/N)	χ^2 test or Fisher's exact test (P-value)
Yes	Categorical	% (n/N)	% (n/N)	
Suspected but not confirmed		% (n/N)	% (n/N)	χ^2 test or Fisher's exact test (P-value)
No	Categorical	% (n/N)	% (n/N)	
Yes		% (n/N)	% (n/N)	
COVID test in the last 2 weeks				
No	Categorical	% (n/N)	% (n/N)	χ^2 test or Fisher's exact test (P-value)
Yes		% (n/N)	% (n/N)	
COVID test type				
RT-PCR (swab in the throat or nose)		% (n/N)	% (n/N)	
Rapid test for the antibodies detection in the blood (finger prick)	Categorical	% (n/N)	% (n/N)	χ^2 test or Fisher's exact test (P-value)
RT-PCR result				
Positive	Categorical	% (n/N)	% (n/N)	χ^2 test or Fisher's exact test (P-value)
Negative		% (n/N)	% (n/N)	
Missing		% (n/N)	% (n/N)	
Rapid test result				
Positive	Categorical	% (n/N)	% (n/N)	χ^2 test or Fisher's exact test (P-value)
Negative		% (n/N)	% (n/N)	
Missing		% (n/N)	% (n/N)	

8. Analysis of endpoints

Table 4 – Analysis of endpoints from Bayesian analysis

Endpoint Variable	BCG	Placebo	Risk Ratio (95%CI) p-value
Absenteeism	$\bar{X}$ ± SD *or* Md (IQR)	$\bar{X}$ ± SD *or* Md (IQR)	RR (95%CI) p-Value
Absenteeism for COVID-19	$\bar{X}$ ± SD *or* Md (IQR)	$\bar{X}$ ± SD *or* Md (IQR)	RR (95%CI) p-Value
Absenteeism besides COVID-19	$\bar{X}$ ± SD *or* Md (IQR)	$\bar{X}$ ± SD *or* Md (IQR)	RR (95%CI) p-Value
Absenteeism for infections	$\bar{X}$ ± SD *or* Md (IQR)	$\bar{X}$ ± SD *or* Md (IQR)	RR (95%CI) p-Value
Absenteeism for respiratory infections	$\bar{X}$ ± SD *or* Md (IQR)	$\bar{X}$ ± SD *or* Md (IQR)	RR (95%CI) p-Value

Table 5 – Analysis of endpoints from Cox regression and Poisson regression

Endpoint Variable	BCG	Placebo	Hazard Ratio (95%CI) p-value
Cumulative incidence of infectious disease episodes	rate (events / risk time)	rate (events / risk time)	HR (95%CI) p-Value
Cumulative incidence of respiratory infectious disease episodes	rate (events / risk time)	rate (events / risk time)	HR (95%CI) p-Value
Cumulative incidence of hospital admissions	rate (events / risk time)	rate (events / risk time)	HR (95%CI) p-Value
Cumulative incidence of infectious disease hospital admissions	rate (events / risk time)	rate (events / risk time)	HR (95%CI) p-Value
Cumulative incidence of respiratory infectious hospital admissions	rate (events / risk time)	rate (events / risk time)	HR (95%CI) p-Value
Cumulative incidence of hospital admissions due to documented COVID-19	rate (events / risk time)	rate (events / risk time)	HR (95%CI) p-Value
Cumulative incidence all-cause and infectious intensive care admission	rate (events / risk time)	rate (events / risk time)	HR (95%CI) p-Value
Cumulative incidence of intensive care admission due to documented COVID-19 infection	rate (events / risk time)	rate (events / risk time)	HR (95%CI) p-Value
COVID-19 infection*	% (n/N)	% (n/N)	RR (95%CI)
Death*	% (n/N)	% (n/N)	RR (95%CI)

*Analysed in Poisson regression with robust variance estimation, including stratification variables, i.e. country, profession and sex, providing Risk Ratios (RR).

9. Analysis of exploratory endpoints

9.1. Safety endpoints: serious adverse events and suspected unexpected serious adverse reactions

The safety endpoints of this study are:

- Hospital admissions for any reason involves staying at a hospital for at least one night or more for medical reasons. It includes admissions to hospital wards and overnight stays in emergency departments.
- Intensive Care Unit admission for any reason involves staying at ICU for at least one night.
- Death for any reason while the participant is being followed during the clinical trial.

Based on previous experience and randomized controlled trials in adult and elderly individuals, the risks of BCG vaccination are considered low. The expected local reaction after successful vaccination with BCG

Vaccine "AJ Vaccines" is injection site swelling followed by a local lesion that can form an ulcer after 2-4 weeks and heal after a few months, leaving a small flat scar. Redness and tenderness may occur at the injection site. Regional swelling of the lymph node <1 cm may also occur. Not common (≥1/1,000 to <1/100) and rare (≥1/10,000 to 1/1,000) adverse reactions: blood and lymphatic system - regional swelling of lymph nodes> 1 cm; nervous system disorders – headache; bones, joints, muscles and connective tissue – osteitis; infections and parasitic diseases - suppurative lymphadenitis, osteomyelitis, BCGitis; abscess at the injection site. We will specifically enquire about adverse events at the biweekly interviews and in the end questionnaire. It is common and not treatment-demanding that, following BCG vaccination, redness, swelling and ulceration of the skin where the vaccine is given will occur. There may be swollen lymph nodes in the area some weeks after the vaccine is given, and in the longer term, a small ~5 mm diameter scar will appear where the vaccine was given. For the descriptive analysis of adverse events, we used counts (percentage) for categorical variables and mean (standard deviation) or median (interquartile range) for continuous variables. For the comparison of adverse events between the two groups studied proportions will be compared using the chi-square test (- χ^2 test (categorial variable) or Student's t-test *or* Mann-Whitney test (quantitative variable) according to the distribution of variables. Statistical significance was set at the 5% level (two-tailed tests) and 95% confidence intervals (95%CI) for the estimates.