Supplement to:

The BCG-PRIME investigators: Bacillus Calmette-Guérin vaccine for prevention of COVID-19 and other respiratory tract infections in older adults with comorbidities: a randomized controlled trial

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Supplementary methods

Table S1: Eligibility criteria

Inclusion criteria:

- Age >= 60 years
- Meeting at least one of the following risk factors:
    - Being hospitalized and planned to be discharged
    - Visiting the outpatient clinic within six weeks after hospital discharge
    - Having a chronic somatic comorbidity (not including risk factors such as hypertension unless medically treated)
    - Attending a thrombosis care service

Exclusion criteria:

- Suspicion of infection or fever within the past 24 hours at the time of evaluation for enrolment *
- Vaccination with a live vaccine in the past four weeks or planned vaccination with live vaccine during the next four weeks *
- Severely immunocompromised state, defined as meeting any of the following criteria:
    - Infection by the human immunodeficiency virus (HIV-1)
    - Neutropenic with less than 500 neutrophils/mm^3
    - Solid organ or bone marrow transplantation
    - Hematological malignancy
    - Chemo-, radio- or immunotherapy for solid organ malignancy in the past 6 months
    - Primary immunodeficiency
    - Severe lymphopenia with less than 400 lymphocytes/mm^3
    - Treatment with any immunosuppressant drugs such as anti-cytokine therapies
    - Treatment with oral or intravenous steroids defined as daily doses of >10 mg/day or a cumulative dose of >700 mg prednisone or equivalent for other corticosteroids in the three months prior to enrolment, or probable use of oral or intravenous steroids in the following four weeks
    - Receiving chronic renal replacement therapy
- Known history of a positive Mantoux or active TB
- Born in a country with high incidence of TB
- Participation in another study involving BCG administration
- History of documented COVID-19

* Patients could be re-screened for eligibility at a later stage

Sample size calculation

Given the unpredictability of the pandemic, a sample size calculation for COVID-19 was considered unreliable and therefore not performed. Given the urgent need for effectiveness data for BCG against COVID-19, we set the target power for this endpoint at 80%. For a 50% relative reduction of the primary endpoint, 67 (for COVID-19) and 90 episodes (for clinically relevant RTIs) were required to achieve 80 and 90% power, respectively, with a two-sided alpha of 0.05. We considered that a sample size of at least 5,200 was needed for 90 clinically relevant RTI episodes to occur within six months, taking into account an estimated loss-to-follow-up of 5%. We aimed for more inclusions to reduce the time needed to determine efficacy.

Participant follow-up

Participants were encouraged to use a mobile application (Research Follow App, Your Research, Huizen, the Netherlands) to fill in a weekly (from week 1-4) or bi-weekly (from week 4 onwards) questionnaire regarding clinical symptoms, hospital admissions, medical consultations, whether they were tested for SARS-CoV-2 (including test date and results) and local skin reactions (first four weeks). Adverse events (AEs) and serious adverse events (SAEs) were collected based on reported doctor visits. A centralized follow-up team contacted participants to collect information about the doctor visits and, if necessary, collected information from the general practitioner or hospital. If a participant was not willing or able to use the smartphone app, the participant received paper questionnaires as a memory aid and the information was collected bi-weekly by telephone calls. Follow-up of all reported AEs and SAEs was performed during the course of the study period until they were abated, or until a stable situation had been reached. All SAEs were reviewed individually by the medical monitor who applied coding according to the Medical Dictionary for Regulatory Activities (MedDRA). AEs were reviewed on aggregated level.

Table S2: Endpoint definitions

Endpoint	Definition
Candidate primary endpoints	

COVID-19 †	An episode meeting all of the following criteria:
	• Symptoms compatible with COVID-19 as judged by the adjudication based on the most recent knowledge of COVID-19*. Self-reported symptoms were verified with the participant in case of a positive SARS-CoV-2 test.
	• Confirmation of infection by any of the following methods:
	  ○ SARS-CoV-2 PCR-test
	  ○ SARS-CoV-2 antigen test
	  ○ CT-scan (CO-RADS score 4-5)

Clinically relevant RTI ‡	An episode meeting all of the following criteria:
	• RTI, defined as new onset or sudden aggravation of:
	  ○ At least one respiratory symptom (cough, sore throat, runny or congested nose, dyspnea, loss of smell or taste, signs at auscultation or percussions of the lungs)
	  ○ At least one systemic symptom (fever, headache, muscle ache, sweats or chills, tiredness, confusion)
	• Requirement of a medical intervention. A medical intervention was defined as the initiation of antibiotic, antiviral or corticosteroid treatment in primary or secondary care, adaptation in pulmonary maintenance medication, or hospitalization.

Secondary endpoints: Respiratory tract infections	
Asymptomatic SARS-CoV-2 infections	A positive SARS-CoV-2 PCR-test or antigen test in the absence of symptoms compatible with COVID-19.
Mild/moderate SARS-CoV-2 infections	COVID-19 (according to the primary endpoint definition) without the requirement of hospitalization.
Severe SARS-CoV-2 infections	COVID-19 (according to the primary endpoint definition) with the

	requirement of hospitalization.
Pneumonia	A physician diagnosis of pneumonia as recorded in the participants medical records.
Medically attended RTIs	An episode meeting the RTI definition for which the subject has consulted a medical doctor (i.e. not necessarily requiring an intervention).
RTI-related hospital admission	An episode meeting the criteria for clinically relevant RTI and being associated with hospitalization.

Secondary endpoints: mental, physical and social functioning

Katz-ADL questionnaire	Dependency in activities of daily living (ADL) score ranging from 0-6 and composed of the following elements: bathing, dressing, toileting, bed-transferring, continence, and feeding. A higher score indicates a higher degree of dependence. A score >= 2 is considered to reflect dependence.[1]
Lawton & Brody ADL questionnaire	Dependency in ADL score ranging from 0-8 for women and 0-5 for men and composed of the following elements: telephone use, shopping, food preparation, housekeeping activities, laundry, transportation, self-medication use, and management of finances. A higher score indicates a lower degree of dependence. A score <8 for women or <5 for men is considered to reflect dependence.[2]
EQ5D3L quality of life questionnaire	Quality of life score comprising five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has three levels: no problems, some problems, and extreme problems. (https://euroqol.org/eq-5d-instruments/eq-5d-3l-about/)
EQ- visual analogue scale (VAS) score	Self-rated health on a vertical visual analogue scale where the endpoints are labelled 'Best imaginable health state' and 'Worst imaginable health state'. (https://euroqol.org/eq-5d-instruments/eq-5d-3l-about/). In this study, to avoid differences between smartphone app and telephone follow-up, the EQ-VAS was implemented as a text box in which a score between 0 and 100 had to be provided.

Safety endpoints

All cause 6-month mortality	Mortality due to any cause occurring within 182 days from administration of BCG or placebo.
AEs	Adverse event: any undesirable experience occurring to a participant during the study, whether or not considered related to the investigational product or the trial procedures. Solicited adverse events are local reactions at the injection site at 7, 14, 21 and 28 days, and include swelling, redness, and pain. All adverse events reported spontaneously by the participant or observed by the investigator or his staff were recorded. Medical consultations were solicited for the entire follow-up duration and details were obtained to assess whether this concerned a (serious) adverse event.
SAEs	Serious adverse event: any adverse event that: - resulted in death; - was life threatening (at the time of the event); - required hospitalization or prolongation of existing inpatients' hospitalization; - resulted in persistent or significant disability or incapacity; or - any other important medical event that did not result in any of the outcomes listed above due to medical or surgical intervention but could have been based upon appropriate judgement by the investigator.

† Selected as primary endpoint. ‡ Selected as secondary endpoint.

* During follow-up of participants there were no new insights in COVID-19 symptoms.

Endpoint adjudication

Both primary endpoints were continuously monitored. An adjudication committee, blinded for randomization, determined primary endpoints, based on information provided in a standardized narrative using data reported by the participant and collected from general practitioners and hospital medical records when considered relevant. Primary endpoints were based on independent confirmations of possible events, provided by two adjudication members. If interpretation differed, the event was evaluated by a third member, unaware of the earlier votes.

COVID-19

All episodes with a positive COVID-19 test or medically suspected COVID-19 were considered for adjudication. Episodes were not adjudicated if both fever and coughing or at least three symptoms were reported by the participant and/or medical records (these were all considered a case as unanimously decided by the adjudication committee) or when no symptoms were reported at all (these were considered not a case per the protocol definition).

Clinically relevant RTI

All medically attended episodes with a clinically suspected or diagnosed respiratory infection were presented to the adjudication committee.

Supplementary results

Follow-up completeness

In total 90,649 questionnaires were completed, with a mean duration of follow-up of 179.6 days in the placebo group versus 179.9 days in de BCG group. Completion of the (bi)weekly questionnaires within 7, 14 and 28 days of the planned date was 77.1%, 88.1%, and 95.9% in the BCG group compared to 77.8%, 88.4% and 95.9% in the placebo group, respectively. In the placebo group 2,940 (96%) and in the BCG group 2,960 participants (97%) completed all questionnaires.

In 5,174 (bi-)weekly questionnaires participants indicated having had respiratory symptoms, of which 3,814 times (73.7%) a symptoms diary was completed during the related period. A symptoms diary was compared 1,830 times without reporting of respiratory symptoms in the subsequent (bi-)weekly questionnaire.

Table S3: Complete baseline characteristics of the randomized population

Characteristic	Placebo (n=3,054)	BCG (n=3,058)	Missing %
Demographics			
Female sex (%)	1150 (37.7)	1125 (36.8)	0.0
Age (median [IQR])	69.00 [65.00, 74.00]	69.00 [65.00, 74.00]	0.0
Age category (%)			0.0
60-69 years	1565 (51.2)	1576 (51.5)	
70-79 years	1260 (41.3)	1254 (41.0)	
80+ years	229 (7.5)	228 (7.5)	
Country/region of birth (%)			0.4
Africa	4 (0.1)	2 (0.1)	
Asia	10 (0.3)	21 (0.7)	
Australia	2 (0.1)	3 (0.1)	
Easthern Europe	4 (0.1)	8 (0.3)	
Netherlands	2944 (96.9)	2951 (96.8)	
North America	3 (0.1)	8 (0.3)	
Northern Europe	5 (0.2)	1 (0.0)	
South America	26 (0.9)	23 (0.8)	
Southern Europe	6 (0.2)	5 (0.2)	
Western Europe	34 (1.1)	26 (0.9)	
Highest education level (%)			0.4
Primary education	92 (3.0)	94 (3.1)	
Secondary education, lower or secondary vocational training	1855 (61.1)	1808 (59.3)	
University or higher vocational training	1091 (35.9)	1146 (37.6)	
Housing situation			
Housing situation (%)			0.4
Independent	2963 (97.5)	2973 (97.5)	
Sheltered home	72 (2.4)	71 (2.3)	
Elderly home	3 (0.1)	4 (0.1)	
Nursing home	0 (0.0)	0 (0.0)	
Has one or more household members (%)	2280 (75.0)	2348 (77.0)	0.4

Characteristic	Placebo (n=3,054)	BCG (n=3,058)	Missing %
Life-style factors			
Body mass index (median [IQR])	26.53 [24.15, 29.76]	26.51 [24.07, 29.63]	0.1
Smoking (%)			0.4
Never	816 (26.9)	840 (27.6)	
Stopped	1957 (64.4)	1955 (64.1)	
Current	265 (8.7)	253 (8.3)	
Alcohol consumption (%)			0.4
None	960 (31.6)	902 (29.6)	
<1 units a week	250 (8.2)	251 (8.2)	
1-3 units a week	484 (15.9)	538 (17.7)	
4-7 units a week	691 (22.7)	737 (24.2)	
>7 units a week	653 (21.5)	620 (20.3)	
Comorbidities			
Number of reported comorbidities (median [IQR])	2 [1-3]	2 [1-3]	0.3
Presence of comorbidities (%)			
Hypertension	1622 (53.1)	1600 (52.3)	0.0
Cardiovascular disease	1769 (58.0)	1708 (55.9)	0.1
Stroke	209 (6.8)	207 (6.8)	0.0
Diabetes mellitus	686 (22.5)	656 (21.5)	0.0
COPD	511 (16.7)	529 (17.3)	0.0
Asthma	412 (13.5)	449 (14.7)	0.0
Other pulmonary disease	151 (4.9)	166 (5.4)	0.1
Moderate to severe renal disease	240 (7.9)	224 (7.3)	0.0
Malignancy	162 (5.3)	152 (5.0)	0.0
Dementia	8 (0.3)	4 (0.1)	0.0
Vaccination history			
BCG vaccination ever (%)	413 (14.9)	495 (17.9)	9.5
Flu vaccination 2019-2020 season (%)	2211 (73.3)	2209 (73.0)	1.1
Flu vaccination 2020-2021 season (%)	1578 (51.8)	1592 (52.1)	0.2
Pneumococcal vaccination 2019-2020 season (%)	44 (1.5)	56 (1.8)	0.7

Characteristic	Placebo (n=3,054)	BCG (n=3,058)	Missing %
Pneumococcal vaccination 2020-2021 season (%)	394 (13.0)	409 (13.4)	0.4
Other vaccination in past 12 months (%)	68 (2.2)	79 (2.6)	0.5
Frailty, independence and quality of life			
Clinical Frailty Scale (%)			0.2
1 - Very fit	630 (20.7)	666 (21.8)	
2 - Well	1085 (35.6)	1078 (35.3)	
3 - Managing well	856 (28.1)	844 (27.7)	
4 - Vulnerable	321 (10.5)	324 (10.6)	
5 - Mildly frail	100 (3.3)	89 (2.9)	
6 - Moderately frail	42 (1.4)	40 (1.3)	
7 - Severely frail	15 (0.5)	10 (0.3)	
8 - Very severely frail	1 (0.0)	1 (0.0)	
9 - Terminally ill	0 (0.0)	0 (0.0)	
Dependent (Katz ADL score) (%)	39 (1.3)	25 (0.8)	0.4
Dependent (Lawton & Brody iADL score) (%)	270 (8.9)	281 (9.2)	0.4
EQ-5D-3L Quality of Life score (median [IQR])	0.93 [0.81, 0.93]	0.93 [0.81, 0.93]	0.4
base_EQ_VAS_num (median [IQR])	80 [70, 89]	80 [70, 90]	0.5
Medication use (number (%) of subjects)			
Medication use at enrolment (%)	2993 (98.0)	2990 (97.9)	0.0
Number of medication records (median [IQR])	5.00 [3.00, 8.00]	5.00 [3.00, 8.00]	0.4
Drugs used in diabetes (%)	631 (20.9)	589 (19.5)	1.3
Vitamin and mineral supplements (%)	746 (24.9)	756 (25.2)	1.7
Gastro-intestinal tract (%)	1494 (50.3)	1496 (50.0)	2.4
Antithrombotic agents (%)	1816 (60.0)	1819 (60.1)	1.0
Antianemic preparation (%)	201 (6.7)	189 (6.3)	1.4
Cardiac therapy (%)	484 (16.1)	494 (16.4)	1.3

Characteristic	Placebo (n=3,054)	BCG (n=3,058)	Missing %
Diuretics (%)	887 (29.4)	856 (28.3)	1.2
Beta blocking agents (%)	1207 (39.9)	1165 (38.6)	1.1
Calcium channel blockers (%)	701 (23.3)	672 (22.3)	1.3
Agents acting on the renin-angiotensin system (%)	1567 (51.9)	1515 (50.1)	1.2
Other antihypertensives (%)	49 (1.6)	40 (1.3)	1.7
Lipid modifying agents (%)	1586 (52.5)	1620 (53.5)	1.0
Dermatologicals (%)	254 (8.7)	265 (9.1)	4.4
Urologicals (%)	340 (11.4)	346 (11.5)	2.0
Genito urinary system and sex hormones (%)	51 (1.7)	56 (1.9)	1.5
Systemic hormonal preparations, excl. sex hormones and insulins (%)	368 (12.3)	365 (12.2)	2.2
Antiinfectives for systemic use (%)	102 (3.4)	94 (3.2)	2.6
Antineoplastic and immunomodulating agents (%)	49 (1.6)	36 (1.2)	1.6
Antiinflammatory and antirheumatic products, topic products for joint and muscular pain, muscle relaxants and antigout preparations (%)	300 (10.0)	355 (11.8)	1.5
Drugs for treatment of bone diseases (%)	110 (3.7)	113 (3.8)	1.5
Anesthetics (%)	1 (0.0)	4 (0.1)	1.6
Analgetics (%)	316 (10.5)	312 (10.3)	1.4
Antiepileptic drugs (%)	134 (4.5)	146 (4.8)	1.4
Anti-Parkinson drugs (%)	48 (1.6)	50 (1.7)	1.6
Psycholeptics and psychoanaleptics (%)	451 (14.9)	457 (15.1)	1.3
Drugs for obstructive airway diseases (%)	702 (23.6)	733 (24.7)	2.7
Cough and cold preparations (%)	71 (2.4)	43 (1.4)	1.5
Antihistamines for systemic use (%)	199 (6.6)	202 (6.7)	1.5
Ophthalmologicals (%)	267 (9.1)	299 (10.1)	3.1
Other (%)	308 (10.4)	279 (9.5)	3.5

Table S4: Interim analysis of the primary endpoint COVID-19

Intervention	#subjects	FU-time*	#events	SDHR
Placebo	3054	481.8	50	[ref]
BCG	3058	485.2	57	1.13 (0.77 – 1.65)

* total person years

Table S5: Subgroup analysis of COVID-19 by BCG vaccination history

Subgroup	Intervention	#subjects	FU-time*	#events	SDHR
Prior BCG	Placebo	413	199.4	17	[ref]
	BCG	495	241.2	16	0.75 (0.36 - 1.54)
No prior BCG	Placebo	2358	1144.7	85	[ref]
	BCG	2267	1096.6	98	1.21 (0.90 - 1.62)
Unknown BCG	Placebo	283	135.7	13	[ref]
history	BCG	296	143.0	15	0.88 (0.39 - 1.99)

* total person years

Table S6: Subgroup analysis of clinically relevant RTI by BCG vaccination history

Subgroup	Intervention	#subjects	FU-time*	#events	SDHR
Prior BCG	Placebo	413	200.6	12	[ref]
	BCG	495	244.1	6	0.39 (0.14 - 1.08)
No prior BCG	Placebo	2358	1152.2	57	[ref]
	BCG	2267	1107.6	53	0.97 (0.66 - 1.41)
Unknown BCG	Placebo	283	138.9	3	[ref]
history	BCG	296	145.8	7	2.20 (0.52 - 9.21)

Table S7: Mental, physical and social functioning

A. EQ-5D-3L questionnaire:

Endpoint	Study group	Questionnaire completed*	Change in score, mean (SD)	Difference of change (95% CI)
Change in EQ-5D-3L Quality of Life	Placebo	2954 (96.7%)	0.01 (0.12)	[ref]
	BCG	2977 (97.4%)	0.00 (0.13)	-0.002 (-0.008; 0.005)
Change in EQ-VAS score	Placebo	2952 (96.7%)	-0.00 (0.11)	[ref]
	BCG	2977 (97.4%)	-0.00 (0.11)	-0.002 (-0.008; 0.004)

B. Falls and functional decline:

Endpoint	Study group	Data available, N (%)	Frequency, N (%)	Relative Risk (95% CI)
Falls over the 6-month study period	Placebo	2962 (97.0%)	304 (10.3%)	[ref]
	BCG	2979 (97.4%)	331 (11.1%)	1.08 (0.93-1.25)
Functional decline according to Katz ADL score**	Placebo	2972 (97.3%)	182 (6.1%)	[ref]
	BCG	2990 (97.8%)	195 (6.5%)	1.06 (0.88; 1.29)
Functional decline according to Lawton & Brody iADL score**	Placebo	2972 (97.3%)	189 (6.4%)	[ref]
	BCG	2990 (97.8%)	188 (6.3%)	0.99 (0.81; 1.20)

Abbreviations: SD: standard deviation; CI: confidence interval; VAS: visual analog scale; ADL: activities of daily living; iADL: instrumental activities of daily living.

* In both study groups 97% completed both the baseline and end-of-study (EOS) questionnaire.

** Defined as either death during follow-up or at least a one-point increase (Katz score) or decrease (Lawton score) on the ADL score.

Higher Katz score implies higher level of dependence. At baseline 84% of the study population had a Katz score of 0 (best possible score), this was scored by 86% of participants at the 6-month follow-up period. Overall, 86% of participants had the same score at baseline compared to month 6.

Lower Lawton score implies higher level of dependence. At baseline 91% of the study population had a Lawton score of 5 or 8 (best possible score for males and females, respectively) and 91% of participants at the 6-month follow-up period. Overall, 89% of participants had the same score at baseline compared to month 6.

Table S8: SAEs by study group and system organ class

	Placebo (n=3,054)		BCG (n=3,058)	
System Organ Class	**Total number of events**	**Having at least 1 event**	**Total number of events**	**Having at least 1 event**
Blood and lymphatic system disorders	3	3 (0.10%)	4	4 (0.13%)
Cardiac disorders	59	55 (1.80%)	87	80 (2.62%)
Congenital, familial and genetic disorders	1	1 (0.03%)	1	1 (0.03%)
Ear and labyrinth disorders	1	1 (0.03%)	2	2 (0.07%)
Gastrointestinal disorders	11	11 (0.36%)	14	14 (0.46%)
General disorders and administration site conditions	12	12 (0.39%)	11	11 (0.36%)
Hepatobiliary disorders	4	4 (0.13%)	1	1 (0.03%)
Infections and infestations	42	39 (1.28%)	52	50 (1.64%)
Injury, poisoning and procedural complications	19	19 (0.62%)	24	24 (0.78%)
Investigations	1	1 (0.03%)	5	5 (0.16%)
Metabolism and nutrition disorders	1	1 (0.03%)	1	1 (0.03%)
Musculoskeletal and connective tissue disorders	7	7 (0.23%)	5	5 (0.16%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	12	12 (0.39%)	12	12 (0.39%)
Nervous system disorders	23	23 (0.75%)	19	19 (0.62%)
Product issues	0	0 (0.00%)	2	2 (0.07%)
Psychiatric disorders	1	1 (0.03%)	1	1 (0.03%)
Renal and urinary disorders	4	4 (0.13%)	7	6 (0.20%)
Reproductive system and breast disorders	1	1 (0.03%)	1	1 (0.03%)
Respiratory, thoracic and mediastinal disorders	15	14 (0.46%)	26	26 (0.85%)

Surgical and medical procedures	20	20 (0.65%)	15	15 (0.49%)
Vascular disorders	12	11 (0.36%)	10	10 (0.33%)

Table S9: AEs by study group and system organ class

	Placebo (n=3,054)		BCG (n=3,058)	
System Organ Class	**Total number of events**	**Having at least 1 event**	**System Organ Class**	**Total number of events**
Blood and lymphatic system disorders	7	7 (0.23%)	6	6 (0.20%)
Cardiac disorders	61	59 (1.93%)	59	59 (1.93%)
Congenital, familial and genetic disorders	3	3 (0.10%)	1	1 (0.03%)
Ear and labyrinth disorders	23	23 (0.75%)	23	23 (0.75%)
Endocrine disorders	3	3 (0.10%)	0	0 (0.00%)
Eye disorders	46	46 (1.51%)	43	43 (1.41%)
Gastrointestinal disorders	112	110 (3.60%)	104	99 (3.24%)
General disorders and administration site conditions	244	239 (7.83%)	1537	1487 (48.63%)
Hepatobiliary disorders	7	7 (0.23%)	5	5 (0.16%)
Immune system disorders	12	12 (0.39%)	9	9 (0.29%)
Infections and infestations	348	315 (10.31%)	342	302 (9.88%)
Injury, poisoning and procedural complications	118	110 (3.60%)	111	107 (3.50%)
Investigations	57	57 (1.87%)	43	41 (1.34%)
Metabolism and nutrition disorders	12	11 (0.36%)	32	30 (0.98%)
Musculoskeletal and connective tissue disorders	214	199 (6.52%)	182	175 (5.72%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	35	34 (1.11%)	39	38 (1.24%)
Nervous system disorders	78	77 (2.52%)	69	66 (2.16%)
Product issues	1	1 (0.03%)	1	1 (0.03%)
Psychiatric disorders	15	15 (0.49%)	12	12 (0.39%)
Renal and urinary disorders	30	30 (0.98%)	26	26 (0.85%)

	Placebo (n=3,054)		BCG (n=3,058)	
System Organ Class	**Total number of events**	**Having at least 1 event**	**System Organ Class**	**Total number of events**
Reproductive system and breast disorders	14	14 (0.46%)	11	11 (0.36%)
Respiratory, thoracic and mediastinal disorders	139	128 (4.19%)	147	136 (4.45%)
Skin and subcutaneous tissue disorders	78	76 (2.49%)	78	75 (2.45%)
Social circumstances	0	0 (0.00%)	1	1 (0.03%)
Surgical and medical procedures	47	47 (1.54%)	44	42 (1.37%)
Vascular disorders	45	43 (1.41%)	39	38 (1.24%)

Figure S1: Time from study start until first COVID-19 vaccination by study group

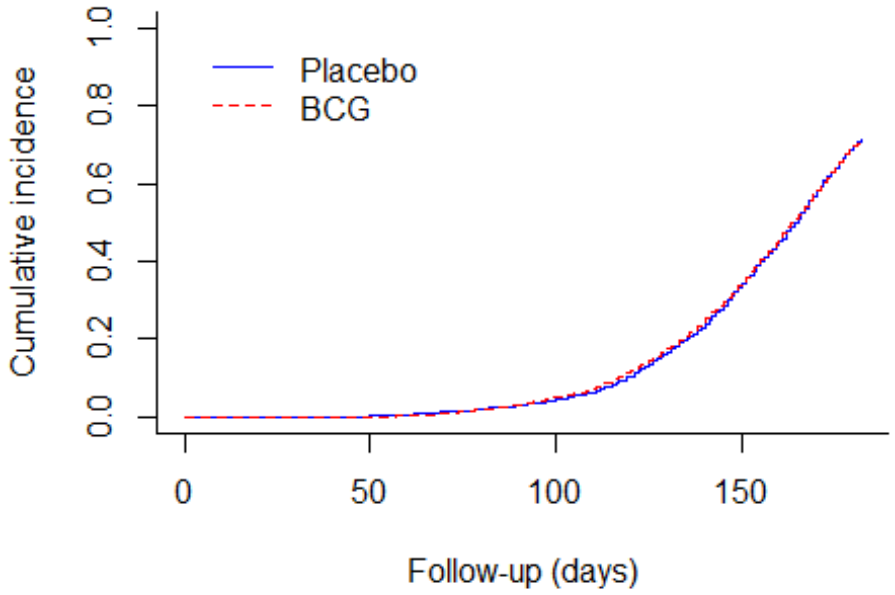
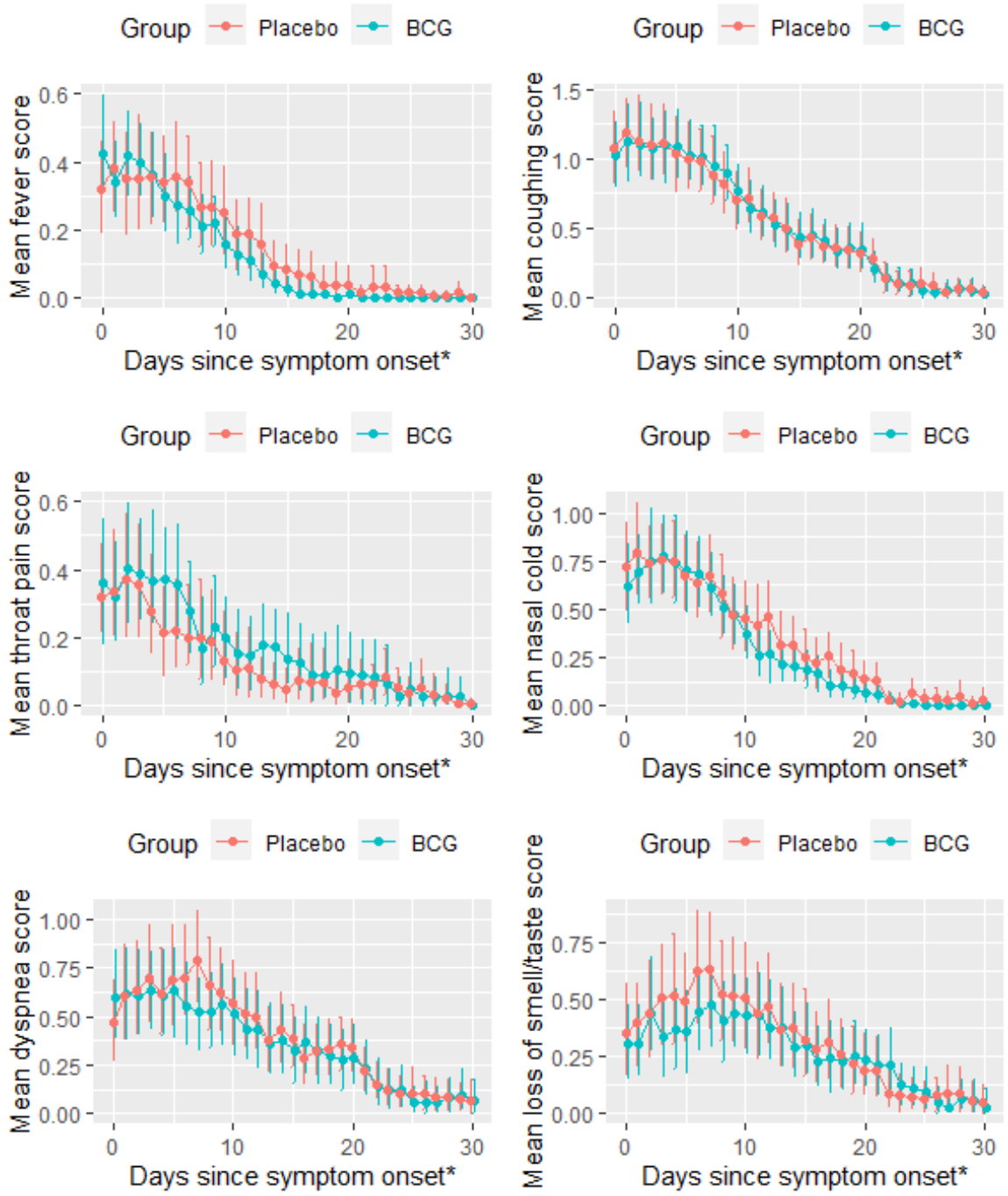


Figure S2: Severity and duration of symptoms in patients with SARS-CoV-2 infection

Day 0 was considered day of positive test in asymptomatic patients and in patients with a positive COVID-19 test prior to symptom onset, or the day of symptom onset otherwise. Symptom score could range from 0 (symptom not present), to 5 (very severe). Fever score could range from 0 (no increased temp) to 4 (fever >40 deg C; a score of 1 being temp between 37.1 and 37.9). Bars represent 95% bootstrap confidence intervals.



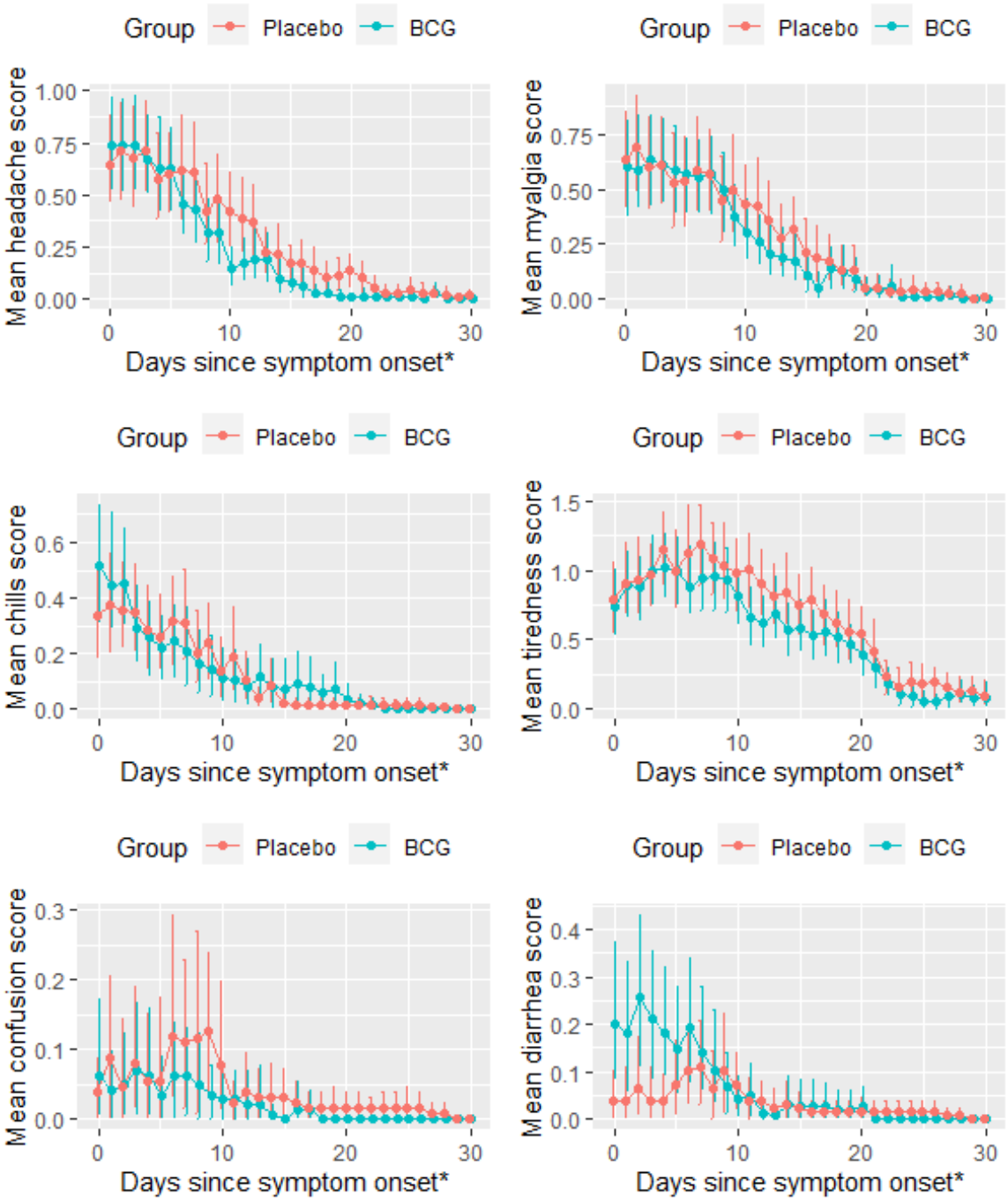

Group
Placebo
BCG
Mean headache score
1.00
0.75
0.50
0.25
0.00
0
10
20
30
Days since symptom onset*
Mean myalgia score
0.75
0.50
0.25
0.00
Mean chills score
0.6
0.4
0.2
0.0
Mean tiredness score
1.5
1.0
0.5
0.0
Mean confusion score
0.3
0.2
0.1
0.0
Mean diarrhea score
0.4
0.3
0.2
0.1
0.0

Figure S3: Incidence, severity and duration of self-reported injection-site reactions

A: Incidence and severity of injections-site reactions reported 1 to 4 weeks after vaccination; by BCG history and randomization group

B: Duration of injection site reactions reported in the final questionnaire 6 months after vaccination; by BCG history and randomization group

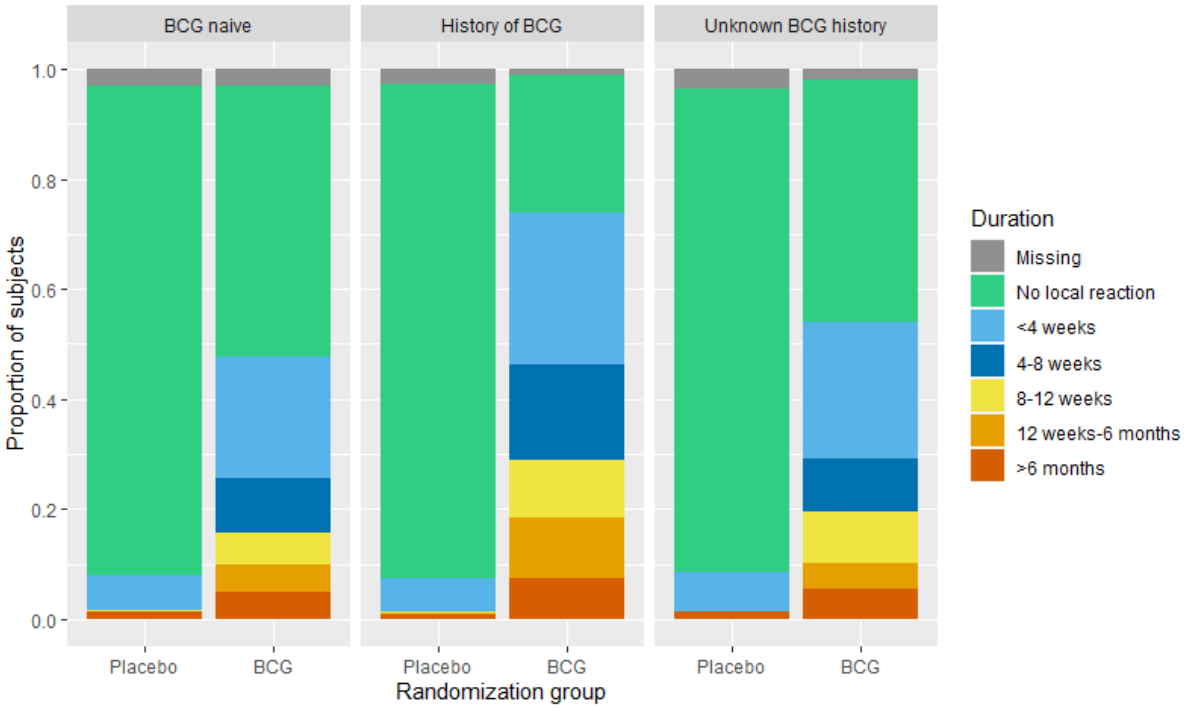
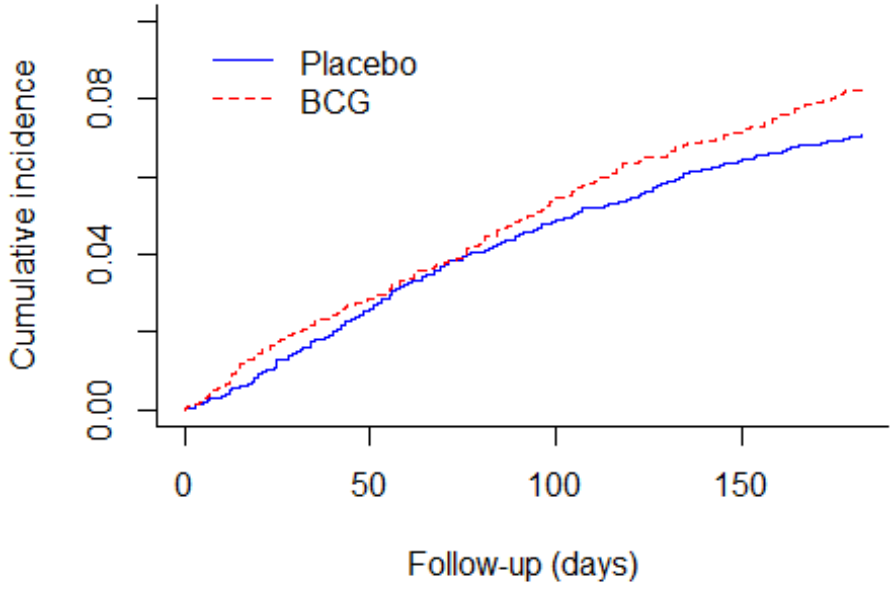
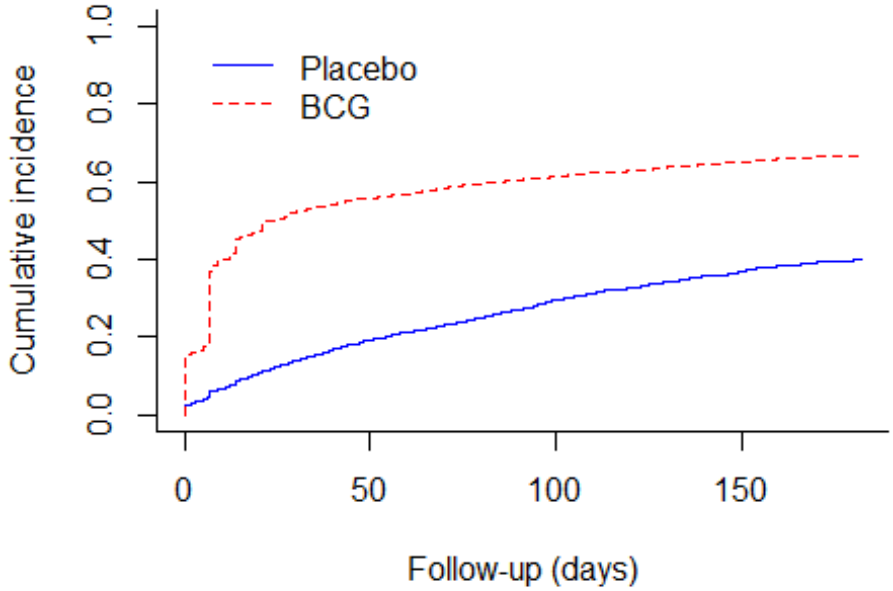


Figure S4: cumulative incidence functions of safety endpoints

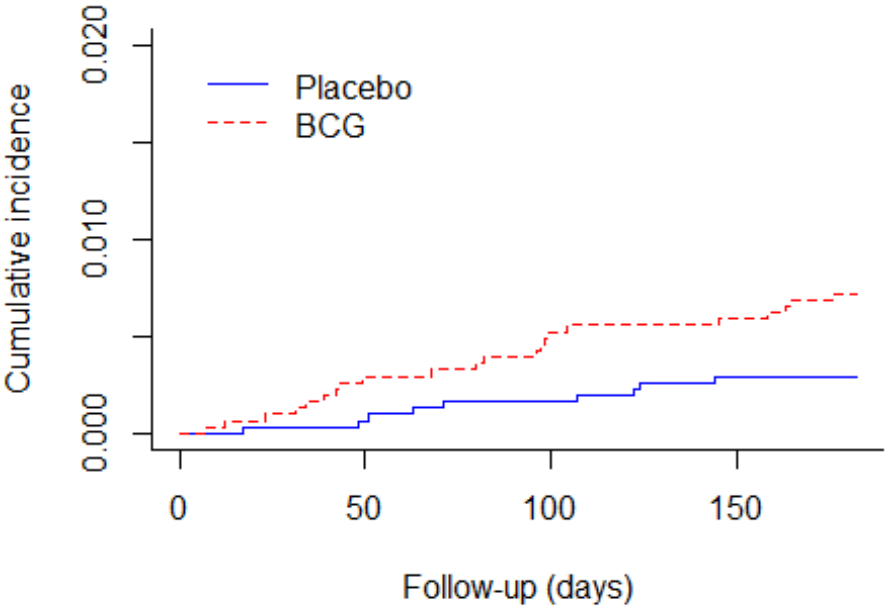
A. Having any serious adverse event



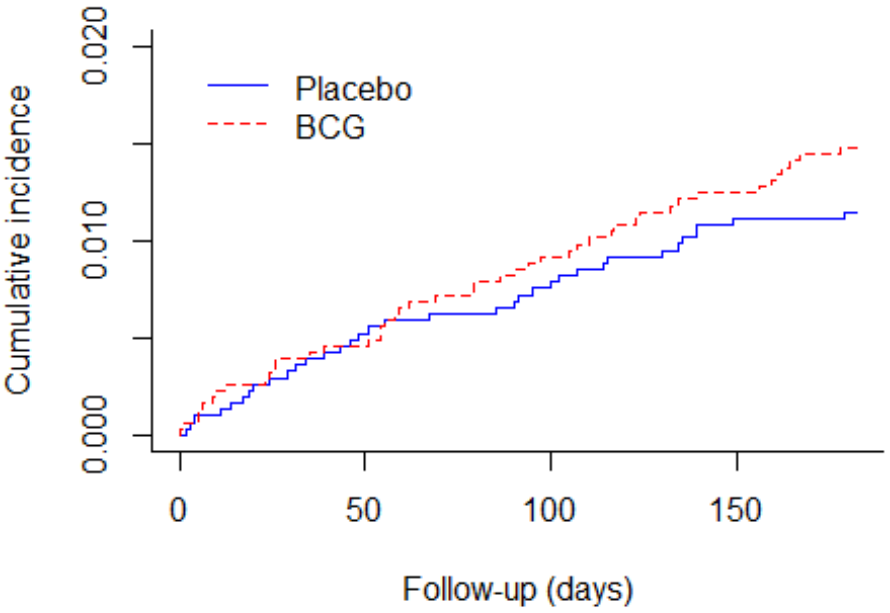
B. Having any non-serious adverse event



C. Having any coronary artery disorder serious adverse event



D. Having any cardiac arrhythmia serious adverse event



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