Supplementary material

This was provided as supplementary material to the publication by Pittet *et al.*:

Bacillus Calmette-Guérin vaccination for protection against recurrent herpes labialis: a nested randomised controlled trial

Content

Supplement to Methods

BCG batch numbers

The BCG batch numbers were the following:

	ITT population		Participants with frequent recurrent cold sores	
	Control	**BCG**	**Control**	**BCG**
BCG batch				
Received BCG	10/3411 (0.3%)	3401/3417 (99.5%)	2/46 (4%)	38/38 (100%)
Batch 118006D (Exp 08/2020)	2/2 (100%)	712/3400 (20.9%)	-	12/38 (32%)
Batch 118017F (Exp 11/2020)	-	222/3400 (6.5%)	-	6/38 (16%)
Batch 118017H (Exp 11/2020)	-	725/3400 (21.3%)	-	10/38 (26%)
Batch 200731-014 (Exp 11/2021)	-	257/3400 (7.6%)	-	4/38 (11%)
Batch 119039B (Exp 11/2021)	-	91/3400 (2.7%)	-	1/38 (3%)
Batch 119053A (Exp 08/2021)	-	673/3400 (19.8%)	-	2/38 (5%)
Batch 200904-017 (Exp 10/2020)	-	36/3400 (1.1%)	-	0/38 (0%)
Batch 118019D (Exp 01/2021)	-	684/3400 (20.1%)	-	3/38 (8%)
Batch information missing	8/10 (80%)	1/3401 (0.03%)	2/2 (100%)	0/38 (0%)

Supplement to Results

Characteristics at baseline and during the trial in the intention-to-treat population

	ITT population	
	Control	**BCG**
Baseline characteristics		
Participants	3411	3417
Sex, female	2593/3411 (76·0%)	2511/3417 (73·5%)
Age, years	42·0 (12·0)	42·0 (12·1)
Presence of comorbidities	625/3411 (18·3%)	611/3417 (17·9%)
Geographical location		
Australia	1628/3411 (47·7%)	1634/3417 (47·8%)
Europe	500/3411 (14·7%)	498/3417 (14·6%)
South America	1283/3411 (37·6%)	1285/3417 (37·6%)
Personal history of BCG, tuberculosis		
BCG in the past	2246/3410 (66·0%)	2264/3417 (66·3%)
Lived in tuberculosis endemic country	234/3410 (6·9%)	220/3417 (6·4%)
Previous known latent tuberculosis infection	24/3410 (0·7%)	29/3417 (0·9%)
Previous positive tuberculin skin test (>5 mm)	224/3410 (6·6%)	205/3417 (6·0%)
Personal history of cold sores		
Ever had a cold sore	950/3185 (29·8%)	944/3262 (28·9%)
Age at first episode of cold sore		
<1 year old	18/859 (2%)	20/832 (2%)
1-5 years old	75/859 (9%)	67/832 (8%)
6-12 years old	170/859 (20%)	173/832 (21%)
13-18 years old	237/859 (28%)	237/832 (28%)
19-35 years old	291/859 (34%)	262/832 (31%)
36-50 years old	58/859 (7%)	62/832 (7%)
>50 years old	10/859 (1%)	11/832 (1%)
Recurrence frequency in past year		
None	393/824 (47·7%)	368/809 (45·4%)
Once	234/824 (28·4%)	252/809 (31·2%)
2 to 3 times	151/824 (18·3%)	151/809 (18·7%)
4 to 6 times	36/824 (4·4%)	33/809 (4·1%)
7 to 12 times	10/824 (1·2%)	4/809 (0·5%)
More than 13 times	0/824 (0%)	1/809 (0·1%)
Impact of cold sores on quality of life		
Does not impact quality of life	538/950 (56·6%)	535/944 (56·7%)
Painful	199/950 (21·0%)	206/944 (21·8%)
Aesthetically displeasing	191/950 (20·1%)	199/944 (21·1%)
Impact social life	118/950 (12·4%)	101/944 (10·7%)
Eating/drinking painful	91/950 (9·6%)	84/944 (8·9%)
Associated with bad mood	84/950 (8·8%)	70/944 (7·4%)
Impact work	70/950 (7·4%)	72/944 (7·6%)
Other impact	7/950 (0·7%)	6/944 (0·6%)
On-study data		
Participants with 12 months of survey data[a]	2809/3411 (82·4%)	2937/3417 (86·0%)
Completed survey with 3-month recall length[b]	11066/11491 (96·3%)	11864/12193 (97·3%)
On-study use of oral therapy for cold sores	150/1922 (7·8%)	154/1965 (7·8%)
To treat active cold sores	101/150 (67·3%)	104/154 (67·5%)
To prevent cold sores[c]	6/150 (4·0%)	2/154 (1·3%)
Both (treat and prevent)[c]	43/150 (28·7%)	48/154 (31·2%)

[a] This is surveys completed and occurrence of HSV reported but is not indicative of complete data for all outcomes (e.g. individual items on survey could be missed)

[b] Denominator is the total number of surveys completed with HSV occurrence question answered

[c] Prevention therapy defined as a daily oral treatment lasting more than 1 month.

Sensitivity and supplementary analyses for the primary outcome: time to first cold sore recurrence in adults with ≥ 4 cold sore recurrences per year

Supplementary Table 1 - Limited to data ascertained through 3-month recall

	Control		BCG		P-value
Participants in intention to treat population	46		38		
Participants with cold sore occurrence by 12 months	36		30		
Participants censored	10	(21·7%)	8	(21·1%)	
Complete follow-up	3	(6·5%)	6	(15·8%)	
Missing data	7	(15·2%)	2	(5·3%)	
Person-years	12		13		
Rate per 100 person-years (95%CI)	304·60	(219·72, 422·28)	227·22	(158·87, 324·97)	
Unadjusted RMST (95%CI)	3·59	(2·67, 4·82)	4·53	(3·39, 6·04)	
Unadjusted RMST difference (BCG-Control) (95%CI)			0·94	(-0·74, 2·62)	
Adjusted RMST (95%CI)	3·14	(2·42, 4·08)	4·74	(3·72, 6·04)	
Adjusted RMST difference (BCG-Control) (95%CI)*			1·60	(0·16, 3·04)	0·034
Adjusted hazard ratio (95%CI)			0·54	(0·31, 0·95)	

RMST: restricted mean survival time, reported in months. 95%CI: 95% confidence intervals. Adjusted models included randomisation strata (age group, presence of comorbidity, geographical location, study stage) [strata with few events were collapsed to aid computation]. * Primary estimate.

Supplementary Table 2 - As-treated population

	As treated Control		As treated BCG		P-value
Participants as-treated population	44		40		
Participants with cold sore occurrence by 12 months	36		34		
Participants censored	8	(18·2%)	6	(15·0%)	
Complete follow-up	3	(6·8%)	6	(15·0%)	
Missing data	5	(11·4%)	0	(0·0%)	
Person-Years	11		14		
Rate per 100 person-years (95%CI)	329·16	(237·43, 456·32)	239·35	(171·02, 334·97)	
Unadjusted RMST (95%CI)	3·28	(2·42, 4·43)	4·37	(3·32, 5·75)	
Unadjusted RMST difference (as treated BCG-Control) (95%CI)			1·09	(-0·46, 2·64)	
Adjusted RMST (95%CI)	2·80	(2·20, 3·57)	4·71	(3·79, 5·85)	
Adjusted RMST difference (as treated BCG-Control) (95%CI)*			1·91	(0·69, 3·12)	0·003
Adjusted hazard ratio (95%CI)			0·45	(0·26, 0·76)	

RMST: restricted mean survival time, reported in months. 95%CI: 95% confidence intervals. Adjusted models included randomisation strata (age group, presence of comorbidity, geographical location, study stage) [strata with few events were collapsed to aid computation].* Primary estimate.

Supplementary Table 3 - In hypothetical scenario without access to suppressive therapy

	Control		BCG		P-value
Participants in intention to treat population	46		38		
Participants with cold sore occurrence by 12 months	34		27		
Participants censored	12	(26·1%)	11	(28·9%)	
Complete follow-up	2	(4·3%)	6	(15·8%)	
Missing data	5	(10·9%)	0	(0·0%)	
Suppressive therapy	5	(10·9%)	5	(13·2%)	
Person-years	10		12		
Rate per 100 person-years (95%CI)	327·53	(234·03, 458·39)	220·60	(151·28, 321·67)	
Unadjusted RMST (95%CI)	3·43	(2·51, 4·69)	4·60	(3·40, 6·23)	
Unadjusted RMST difference (BCG-Control) (95%CI)			1·17	(-0·58, 2·92)	
Adjusted RMST (95%CI)	2·84	(2·16, 3·73)	4·77	(3·69, 6·18)	
Adjusted RMST difference (BCG-Control) (95%CI)*			1·93	(0·47, 3·40)	0·012
Adjusted hazard ratio (95%CI)			0·47	(0·26, 0·85)	

RMST: restricted mean survival time, reported in months. 95%CI: 95% confidence intervals. Adjusted models included randomisation strata (age group, presence of comorbidity, geographical location, study stage) [strata with few events were collapsed to aid computation]. * Primary estimate.

BRACE Herpes Statistical Analysis Plan v3.0

1. Research Objective

To determine in a subgroup of adults with recurrent cold sores whether BCG vaccination compared with placebo reduces herpes simplex recurrences (such as cold sores).

2. Descriptive Statistics

All participants who were invited to participate in the BRACE trial will be accounted for as part of the CONSORT flow diagram.

The following baseline participant characteristics will be summarised by treatment arm, and by treatment arm and site, and by treatment arm and sex:

- Have you had a cold sore ever: N(%) – yes, no, missing
- How old were you when you first had a cold sore – N (%) – Never had a cold sore, <1 year, 1-5 years, 6-12 years, 13-18 years, 19-35 years, 36-50 years, >50 years, missing
- History of cold sore occurrence – N(%) – Never, Once, Twice, 3-5 times, 6-10 times, 11-20 times, more than 20 times, missing
- Frequency of cold sore occurrence in last year – N(%) – Never had a cold sore, had a cold sore but none in last year, once, 2-3 times, 4-6 times, 7-12 times, more than 13 times, missing
- Oral treatment for cold sores – N (%) – never had a cold sore, yes, no, missing

The following baseline participant characteristics will be summarised by treatment arm in participants with:

a) ≥ 4 cold sore recurrences in the last year at baseline
b) ≥ 2 cold sore recurrences in the last year at baseline
c) ≥ 1 cold sore recurrence in the last year at baseline
d) Ever had a cold sore

- How old were you when you first had a cold sore – N (%) –<1 year, 1-5 years, 6-12 years, 13-18 years, 19-35 years, 36-50 years, >50 years, missing
- Impact of cold sores on quality of life – N(%) – Do not impact quality of life, painful, aesthetically displeasing, difficulty/pain eating and/or drinking, bad mood, impacts social life, impacts work, other, declined/refused/don't know
- Oral treatment for cold sores – N(%) – Never treated, Yes- to treat an active cold sore, Yes- to prevent further cold sores (typically >1 month), Yes- to both treat and prevent cold sores, Yes- but not sure why, missing
- If to prevent cold sores, which preventative treatment was used - N(%) - Aciclovir, Valaciclovir, Famciclovir, Lysine, other, missing
- If to prevent cold sores, what is the longest period of treatment- N(%) - <1 month, 1-3 months, 4-6 months, 7-12 months, >12 months, missing
- If to prevent cold sores, was the preventive treatment was useful – N (%) – yes – the episodes were shorter, yes-the episodes were less frequent, yes- the episodes were less severe, yes- the episodes had less impact on quality of life, yes-other, yes- missing why

We will also describe the use of on-study preventative therapies by treatment arm. The following will be described:

- The use of treatment for cold sores on-study – N(%) – yes, no, missing
- Reason for cold sore treatment on study- N(%) - to treat active cold sores, to prevent further cold sores, both to treat and prevent cold sores, missing
- If to prevent cold sores, which preventative treatment was used on study: N(%) - Aciclovir, Valaciclovir, Famciclovir, Lysine, other, missing
- If used preventative treatment, average duration of use on study: median (IQR) - Aciclovir, Valaciclovir, Famciclovir, Lysine, other

We will also describe the frequency of survey completion and recall periods used in the study (for further details see *3.2 Data*).

3. General Analysis Considerations

3.1 Analytical Populations

Intention-To-Treat Population
The intention-to-treat (ITT) population will be used primarily, with all participants analysed according to the study group to which they were randomly allocated, regardless of the intervention they received. The only participants excluded from this population will be participants who were randomised in error.

A sensitivity analysis will be done in an as-treated (AT) population, with all participants analysed according to the treatment arm they received.

3.2 Data

To derive outcomes, we will use data from the self-reported questionnaires completed at 3, 6, 9, and 12-months. Participants were asked about whether they had had a cold sore episode, frequency of episodes, when the first episode began, change in cold sore recurrence including frequency, duration, severity, and impact on quality of life, treatment for cold sores since their last completed questionnaire. Depending on questionnaire completion this could result in a recall period of 3, 6, 9 or 12 months.

The frequency of survey completion at 3, 6, 9 and 12 months will be summarised by treatment arm. The frequency of recall periods will also be described by treatment arm. We will report the number and proportion of recall periods which were 3, 6, 9 and 12 months in length by treatment arm.

3.3 Multiplicity

No formal adjustments for multiplicity of testing will be applied, but outcomes will be ordered by degree of importance (i.e., primary versus secondary) and hypothesis test results will be interpreted in light of the multiple comparisons made.

3.4 Statistical Software

All analyses will be performed using Stata Release 16.0 or later.

4. Outcomes, Estimands and Analysis

4.1 Time to First Cold Sore Recurrence (Primary Outcome)

***Population**:* Adults with ≥ 4 cold sore recurrences per year
***Intervention*:** BCG vs no BCG
[combined stage 1 (BCG w/ influenza vaccine vs influenza vaccine only) and 2 (BCG vs placebo)]
***Outcome*:** Time to first cold sore recurrence by 12-months
***Intercurrent Events*:**

- Suppressive therapy (Treatment Policy)
- Subsequent vaccination (Treatment Policy)
- Illness episode including COVID (Treatment Policy)

Summary Measure: Difference in restricted mean survival times at 12-months

Primary Analysis:
The population will be defined in the trial as those who report 4 or more cold sore occurrences in the last year in the baseline questionnaire. The time to cold sore recurrence will be calculated and presented in the two intervention groups. The time origin is the date of randomisation. The episode start date of the first cold sore episode after randomisation date will be taken as the time of event. The analysis will be censored at 12 months or latest survey completion date without missing outcome data whichever occurs earlier.

The estimate of interest will be the difference in restricted mean survival times at 12 months and 95% confidence interval (1). A flexible parametric survival model (Royston-Parmar model) on the log cumulative hazard scale adjusted for stratification factors used during randomisation (age group, presence of comorbidity, geographical location -Europe/Australia/South America, stage) will be fitted to the data. We will then estimate the difference in restricted mean survival times of the standardised survival functions at 12-months using methods as described by Lambert, P.C. (https://pclambert.net/software/standsurv/standardized_survival_rmst/). This will be done in Stata using the *stpm2* and *standsurv* commands. Standard errors will be obtained using the delta-method. If a low frequency of events results in an inability to adjust for all stratum, we will aim to first collapse stratum (Europe with Australia for example) and then drop strata if issues still remain (in order of frequency of events within strata). For participants who were randomised in the incorrect stratum, the correct stratum will be used as covariate in the model. We will visually assess the proportional hazard assumption using a plot of log-negative-log of the Kaplan–Meier estimator by treatment arm and, assuming the proportional hazards assumption is found to be reasonable, will also presented hazard ratios and their corresponding 95% confidence intervals. A Kaplan–Meier plot will be used to visually present the data.

Missing Data:
Missing data could occur for participants who prematurely discontinue follow-up prior to the occurrence of the event or have non-response on survey questions related to cold sore occurrence. We will address missing data by censoring the follow-up times of such participants at their times of premature discontinuation/last survey with complete outcome data. Such censoring is noninformative and can be considered similarly to the missing at random (MAR) assumption e.g. the possibly unknown true time to the event for a participant is the same regardless of whether or not it is actually observed (or whether censoring occurs or not prior to it).

Sensitivity Analyses:
1: We will repeat the primary analysis in an AT population

2: We will repeat the primary analysis only including data which was ascertained in a three month recall period.

Supplementary Analyses:

a) In adults with ≥ 2 cold sore recurrences per year- defined in the trial as those who report two or more cold sore occurrences in the last year in the baseline questionnaire
b) In adults with ≥ 1 cold sore recurrence per year - defined in the trial as those who report one or more cold sore occurrences in the last year in the baseline questionnaire
c) In adults with ≥ 1 cold sore ever - defined in the trial as those who report one or more cold sore occurrences ever in the baseline questionnaire
d) In adults reporting no previous cold sores - defined in the trial as those who report no prior cold sore occurrences ever in the baseline questionnaire
e) In a hypothetical scenario in which suppressive therapy would not be available: We will exclude participant follow-up time and data after the start of the recall period where suppressive therapy is reporting as being taken (e.g., at 3-months if reported as having taken suppressive therapy between 3-6 months on the 6-month questionnaire). We will treat the missing data as we would other missing data (*see Missing Data*)
f) In a hypothetical scenario in which subsequent vaccination would not be available: We will exclude participant follow-up time and data after first dose of any vaccination following randomisation. We will treat the missing data as we would other missing data (*see Missing Data*)
g) In a hypothetical scenario in which intercurrent infections would not occur: We will exclude participant follow-up time and data after episode of febrile or respiratory illness following randomisation. We will treat the missing data as we would other missing data (*see Missing Data*)

Subgroup Analyses

a) Per number of recurrences in the past year at baseline (for the supplementary analysis of adults with ≥ 1 cold sore ever)
    - None
    - Once
    - 2-3 times
    - 4 or more times
b) Sex
    - Male
    - Female
c) Prior BCG vaccination at baseline
    - Received BCG vaccine
    - Did not receive BCG vaccine
d) Age at randomisation
    - <40 years
    - 40 to 59 years
    - >= 60 years
e) Region
    - Australia
    - Europe
    - South America
f) Number of cold sore episodes ever at baseline
    - One to two

- 3 to 5
- 6 to 20
- More than 20

g) Age at first cold sore episode
   - 0 to 5 years
   - 6 to 12 years
   - 13 to 18 years
   - 19 to 35 years
   - >35 years

h) Receipt of influenza vaccination at randomisation (e.g. Stage I or II)
   - Stage I (influenza vaccine given)
   - Stage II (no influenza vaccine given)

4.2 Proportion of Participants with Cold Sore Recurrence

***Population**:* Adults with ≥ 4 cold sore recurrences per year

***Intervention*:** BCG vs no BCG
[combined stage 1 (BCG w/ influenza vaccination vs influenza vaccination only) and 2 (BCG vs placebo)]
***Outcome*:** Proportion of participants with cold sore recurrence by 12 months

***Intercurrent Events*:**
- Suppressive therapy (Treatment Policy)
- Subsequent vaccination (Treatment Policy)
- Illness episode including COVID (Treatment Policy)

Summary Measure: Risk difference

Primary Analysis:
The population will be defined in the trial as those who report 4 or more cold sore occurrences in the last year in the baseline questionnaire.

Participants will be considered to:
a) Have had a cold sore recurrence if they report a cold sore recurrence at any of the 3-, 6-, 9- or 12-month questionnaires
b) Not had a cold sore recurrence if they report not having a cold sore at 3-, 6-, 9- and/or 12-month questionnaires which covers a 12- month period from randomisation
c) Missing the outcome, if they have a period of missing data for which cold sore recurrence cannot be ascertained

The number and proportion of participants with a cold sore recurrence by 12 months will be calculated and presented in the two intervention groups. The difference in proportion will be tested using a logistic regression model including the randomised treatment arm and stratification factors used during randomisation (age group, presence of comorbidity, geographical location - Europe/Australia/South America, stage). Model-fitted, marginal risk and risk difference estimates and 95% confidence interval will be obtained using the *margins* command in STATA.

Missing Data:
Missing data could occur for participants who prematurely discontinue follow-up prior to the occurrence of the event or have non-response on survey question related to cold sore occurrence

which is not covered by a later questionnaire (see 3.2 Data for further details). Multiple imputation (MI) will be used to handle missing data if >10% of participants are missing the outcome. MI will be conducted using chained equations, also known as fully conditional specification. Recurrence of cold sores by 3-months, 6-months, 9-months, and baseline characteristics will be included as auxiliary variables in the imputation model. Imputation will be carried out separately by arm, to ensure that any treatment effects are maintained, using 50 imputed datasets.

Sensitivity Analyses:
As was done for 4.1.

Supplementary Analyses:
As was done for 4.1.

Subgroup Analyses:
As was done for 4.1.

4.3 Number of Cold Sores Recurrences

Population*:* Adults with ≥ 4 cold sore recurrences per year

Intervention**:** BCG vs no BCG
[combined stage 1 (BCG w/ flu vaccine vs flu vaccine only) and 2 (BCG vs placebo)]

Outcome**:** Number of cold sores over 12 months

Intercurrent Events**:**
- Suppressive therapy (Treatment Policy)
- Subsequent vaccination (Treatment Policy)
- Illness episode including COVID (Treatment Policy)

Summary Measure: Incidence rate ratio

Primary Analysis:
The population will be defined in the trial as those who report 4 or more cold sore occurrences in the last year in the baseline questionnaire.

The mean, standard deviation, median and interquartile range for the number of cold sores over 12 months will be presented by treatment arm. The difference between BCG and placebo groups will be summarised as the incidence rate ratio and its 95%CI estimated using a Poisson regression model, adjusting for stratification factors used during randomisation (age group, presence of comorbidity, geographical location -Europe/Australia/South America, stage). If there is evidence of overdispersion on examination of standardized deviance residual plots, then a negative binomial regression model will be used to estimate the incidence rate ratio and its 95%CI.

Missing Data:
As was done for 4.2

Sensitivity Analyses:
As was done for 4.1.

Supplementary Analyses:

As was done for 4.1. Due to a hypothesized inflation of zero outcomes in the supplementary analysis - population of adults reporting no prior cold sore occurrence - we will estimate the incidence rate ratio and 95%CIs in this population suing a zero-inflated Poisson model or negative binomial model.

Subgroup Analyses:
As was done for 4.1.

4.4 Severity of Cold Sore Recurrences (duration, pain, floridness)

Population*:* Adults with ≥ 4 cold sore recurrences per year

Intervention**:** BCG vs no BCG
[combined stage 1 (BCG w/ flu vaccine vs flu vaccine only) and 2 (BCG vs placebo)]

Outcome**:**
A1) Proportion of participants with a cold sore recurrence who report an increase in duration of episodes at 3, 6, 9, 12 months
A2) Proportion of participants with a cold sore recurrence who report a decrease in duration of episodes at 3, 6, 9, 12 months
A3) Proportion of participants with a cold sore recurrence who report an increase in frequency of episodes at 3, 6, 9, 12 months
A4) Proportion of participants with a cold sore recurrence who report a decrease in frequency of episodes at 3, 6, 9, 12 months
A5) Proportion of participants with a cold sore recurrence who report an increase in severity of episodes at 3, 6, 9, 12 months
A6) Proportion of participants with a cold sore recurrence who report a decrease in severity of episodes at 3, 6, 9, 12 months
B1) Proportion of participants that have a decrease in frequency of episodes determined by number of episodes reported over 12-months on-study vs the number of episodes reported in the last 12 months at baseline

Intercurrent Events**:**
- Suppressive therapy (Treatment Policy)
- Subsequent vaccination (Treatment Policy)
- Illness episode including COVID (Treatment Policy)

Summary Measure: Risk difference at 12-months

Primary Analysis:
The population will be defined in the trial as those who report 4 or more cold sore occurrences in the last year in the baseline questionnaire.

A1-A6: The number and proportion of participants with each outcome will be presented by treatment arm and survey time. The difference in proportion at 3, 6, 9 and 12 months will be tested using separate logistic regression models which will include the randomised treatment arm and stratification factors used during randomisation (age group, presence of comorbidity, geographical location -Europe/Australia/South America, stage). Model-fitted, marginal risk and risk difference estimates and 95% confidence interval will be obtained using the *margins* command in STATA.
The primary time-point of interest is risk difference at 12-months, however, we hypothesis that a short-lasting treatment effect could also be possible so the risk difference at 3-months is a key secondary time-point for these outcomes.

B1: Frequency in last year at baseline is collected as a categorical variable (none, once, 2-3 times, 4-6 times, 7-12 times etc.). Frequency over 12-months of study will be similarly categorised. A reduction in frequency will be considered to have gone from one category to the next (e.g., from 4-6 times to 2-3 times).The number and proportion of participants with a reduction in frequency of cold sore recurrence by 12 months will be calculated and presented in the two intervention groups. The difference in proportion will be tested using a logistic regression model including the randomised treatment arm and stratification factors used during randomisation (age group, presence of comorbidity, geographical location -Europe/Australia/South America). Model-fitted, marginal risk and risk difference estimates and 95% confidence interval will be obtained using the *margins* command in STATA.

Missing Data:
As was done for 4.2

Sensitivity Analyses:
As was done for 4.1.

Supplementary Analyses:

a) In adults with ≥ 2 cold sore recurrences per year- defined in the trial as those who report two or more cold sore occurrences in the last year in the baseline questionnaire
b) In adults with ≥ 1 cold sore recurrence per year - defined in the trial as those who report one or more cold sore occurrences in the last year in the baseline questionnaire
   In adults with ≥ 1 cold sore ever - defined in the trial as those who report one or more cold sore occurrences ever in the baseline questionnaire

Subgroup Analyses:
None

4.5 Quality of Life

Population*:* Adults with ≥ 4 cold sore recurrences per year

Intervention**:** BCG vs no BCG
[combined stage 1 (BCG w/ flu vaccine vs flu vaccine only) and 2 (BCG vs placebo)]

Outcome**:**
A1) Proportion of participants that report an improvement in quality of life at 3, 6, 9, 12 months
A2) Proportion of participants that report a reduction in quality of life at 3, 6, 9, 12 months

Intercurrent Events**:**

- Suppressive therapy (Treatment Policy)
- Subsequent vaccination (Treatment Policy)
- Illness episode including COVID (Treatment Policy)

Summary Measure: Risk difference at 12-months and 95% CI

Primary Analysis:
As was done in 4.4, A1-A6.

Missing Data:
As was done for 4.2

Sensitivity Analyses:

As was done for 4.1.

Supplementary Analyses:
As was done in 4.4

Subgroup Analyses:
None

1. Royston P, Parmar MKB. Restricted mean survival time: an alternative to the hazard ratio for the design and analysis of randomized trials with a time-to-event outcome. BMC Medical Research Methodology. 2013;13(1):152.

Baseline questionnaire

Cold Sores

Have you ever had a cold sore (small painful blisters on the lips or around the mouth)? These are also known as a fever blister or herpetic infection	◯ Yes ◯ No ◯ Don't know ◯ Declined
How old were you when they had their first cold sore? (Please answer to the best of your memory)	◯ Less than 1-year old ◯ Between 1 to 5 years-old ◯ Between 6 to 12 years-old ◯ Between 13 to 18 years-old ◯ Between 19 to 35 years-old ◯ Between 36 to 50 years-old ◯ After 50 years-old ◯ Don't know ◯ Declined/refused
Have you had a cold sore on more than one occasion?	◯ No, only once ◯ Yes, more than once ◯ Don't know ◯ Declined/refused
How many times in total have you had a cold sore? (Please answer to the best of your memory)	◯ Twice ◯ 3 to 5 times ◯ 6 to 10 times ◯ 11 to 20 times ◯ More than 20 times ◯ Don't know ◯ Declined/refused
In the last year, how many times have you had a cold sore?	◯ None ◯ Once ◯ 2 to 3 times ◯ 4 to 6 times ◯ 7 to 12 times ◯ More than 13 times ◯ Don't know ◯ Declined/refused

In what way do the cold sores impact your quality of life?	☐ Having cold sores do not impact your quality of life ☐ My quality of life is reduced because cold sores are painful ☐ My quality of life is reduced because cold sores are aesthetically displeasing ☐ My quality of life is reduced because cold sores makes eating and/or drinking difficult or painful ☐ My quality of life is reduced because having cold sores put me in bad mood ☐ Having cold sores has a negative impact on my social life ☐ Having cold sores has a negative impact on my work ☐ Other, please specify ☐ Don't know ☐ Declined/refused ((Tick all that apply))
If other please specify:	_____
Have you ever had an oral treatment for cold sores?	◯ Yes ◯ No ◯ Don't know ◯ Declined
If yes, when?	◯ To treat an active cold sore ◯ To prevent further cold sores (treatment typically lasting more than 1 month) ◯ Both to treat and to prevent cold sores ◯ Don't know ◯ Declined/refused
Which oral preventive treatment have you received?	☐ Aciclovir (also called Zovirax, Acyclo-V, Lovir) ☐ Valaciclovir (also called Valtrex, Valacor, Zelitrex, Shilova) ☐ Famciclovir (also called Famir, Favic, Famlo, Ezovir) ☐ Propolis (also called Propovir) ☐ Other please specify ☐ Don't know ☐ Declined/refused (Tick all that apply)
If other, please specify:	_____
What is the longest single period that you have received an oral preventive treatment?	◯ Less than one month ◯ Between 1 to 3 months ◯ Between 4 to 6 months ◯ Between 7 to 12 months ◯ More than 12 months ◯ Don't know ◯ Declined/refused
Do you feel that the preventive treatment was useful?	◯ Yes ◯ No ◯ Don't know ◯ Declined

In what way was it useful?	☐ The episodes of cold sores were shorter ☐ The episodes of cold sores were less frequent ☐ The episodes of cold sores were less severe ☐ The episodes of cold sores had less impact on my quality of life ☐ Other ☐ Don't know ☐ Declined/refused (Tick all that apply)
If other please specify:	_____

3 months follow-up questionnaire

Have you had a cold sore episode since you enrolled in the BRACE trial on [ra_rand_datetime]?These are small painful blisters on the lips or around the mouth, also known as fever blisters or herpetic infection.	◯ Yes ◯ No
How many cold sore episodes did you have in the last 3 months?	_____ (Please answer to the best of your memory.)
When did the first episode start? Please only consider the last 3 months	_____ (Please approximate the date to the best of your memory.)
Have you noticed any change in your cold sores recurrence in the last 3 months, in terms of:- Frequency (how often you get cold sores)- Duration (how long a cold sore episode lasts)- Severity (how painful, disabling, extensive the lesions are)- Impact on quality of life (social, aesthetic, work, etc.)	◯ Yes ◯ No
To what extent has it changed?	
Frequency(how often you get cold sores)	◯ The episodes were less frequent ◯ The episodes were more frequent ◯ The episodes occur at the same frequency
Duration(how long a cold sore episode lasts)	◯ The episodes were shorter ◯ The episodes were longer ◯ The episodes had the same duration
Severity(how painful, disabling, extensive the lesions are)	◯ The episodes were less severe ◯ The episodes were more severe ◯ The episodes had the same severity
Impact on quality of life(social, aesthetic, work, etc.)	◯ The episodes had less impact on my quality of life ◯ The episodes had more impact on my quality of life ◯ The impact on my quality of life did not change
You previously said that you have taken prophylactic (preventive) treatment [ph_hsv_prevent], to prevent cold sore recurrences.Were you taking [ph_hsv_prevent] on the day of randomisation ([ra_date])?	◯ Yes ◯ No
Are you still taking [ph_hsv_prevent] today?	◯ Yes ◯ No
You previously said that you have taken prophylactic (preventive) treatment [ph_hsv_treat_oth], to prevent cold sore recurrences.Were you taking [ph_hsv_treat_oth] on the day of randomisation [ra_date]?	◯ Yes ◯ No
Are you still taking [ph_hsv_prevent_oth] today?	◯ Yes ◯ No
Have you received any treatment for cold sores in the last 3 months?	◯ Yes ◯ No

If yes, why?	◯ To treat an active cold sore ◯ To prevent further cold sores (treatment typically lasting more than 1 month) ◯ Both to treat and to prevent cold sores
Which preventive treatment have you received in the last 3 months?(Tick all that apply).	☐ Aciclovir (also called Zovirax, Acyclo-V, Lovir) ☐ Valaciclovir (also called Valtrex, Valacor, Zelitrex, Shilova) ☐ Famciclovir (also called Famir, Favic, Famlo, Ezovir) ☐ Lysine ☐ Other, please specify ☐ Don't know (Tick all that apply)
If other, please specify:	_____
For how long were you taking Aciclovir? Please only consider the last 3 monthsPlease answer in months. If less than a month, please answer in fraction of month (1 week = 0.24 months).	_____ (In months, or fraction of months)
Are you still taking Aciclovir treatment today?	◯ Yes ◯ No
For how long were you taking Valaciclovir? Please only consider the last 3 monthsPlease answer in months. If less than a month, please answer in fraction of month (1 week = 0.24 months).	_____ (In months, or fraction of months)
Are you still taking Valaciclovir treatment today?	◯ Yes ◯ No
For how long were you taking Famciclovir? Please only consider the last 3 monthsPlease answer in months. If less than a month, please answer in fraction of month (1 week = 0.24 months).	_____ (In months, or fraction of months)
Are you still taking Famciclovir treatment today?	◯ Yes ◯ No
For how long were you taking Lysine? Please only consider the last 3 monthsPlease answer in months. If less than a month, please answer in fraction of month (1 week = 0.24 months).	_____ (In months, or fraction of months)
Are you still taking Lysine treatment today?	◯ Yes ◯ No
For how long were you taking [m3_hsv_prevent_other]? Please only consider the last 3 monthsPlease answer in months. If less than a month, please answer in fraction of month (1 week = 0.24 months).	_____ (In months, or fraction of months)
Are you still taking [m3_hsv_prevent_other] treatment today?	◯ Yes ◯ No

For how long were you taking this preventive treatment? Please only consider the last 3 monthsPlease answer in months. If less than a month, please answer in fraction of month (1 week = 0.24 months).	_____ (In months, or fraction of months)
Are you still taking this preventive treatment today?	◯ Yes ◯ No

6 months follow-up questionnaire

Have you had a cold sore episode since [m6_datestart]?These are small painful blisters on the lips or around the mouth, also known as fever blisters or herpetic infection.

◯ Yes
◯ No

How many cold sore episodes did you have between [m6_datestart] and [m6_datedue]?

_____
(Please answer to the best of your memory.)

When did the first episode start? Please only consider the period of time between [m6_datestart] and [m6_datedue].

_____
(Please approximate the date to the best of your memory.)

Have you noticed any change in your cold sores recurrence between [m6_datestart] and [m6_datedue], in terms of:- Frequency (how often you get cold sores)- Duration (how long a cold sore episode lasts)- Severity (how painful, disabling, extensive the lesions are)- Impact on quality of life (social, aesthetic, work, etc.)

◯ Yes
◯ No

Has it changed?

Frequency (how often you get cold sores)

◯ The episodes have been generally less frequent
◯ The episodes been generally more frequent
◯ The frequency has not changed

Duration (how long a cold sore episode lasts)

◯ The episodes have been generally shorter
◯ The episodes have been generally longer
◯ The duration has not changed

Severity (how painful, disabling, extensive the lesions are)

◯ The episodes have been generally less severe
◯ The episodes have been generally more severe
◯ The severity has not changed

Impact on quality of life (social, aesthetic, work, etc.)

◯ The episodes have had less impact on my quality of life
◯ The episodes have had more impact on my quality of life
◯ The impact on my quality of life did not change

You previously said that you have taken prophylactic (preventive) treatment [m3_hsv_prevent], to prevent cold sore recurrences.Are you still taking [m3_hsv_prevent] today?

◯ Yes
◯ No

You previously said that you have taken prophylactic (preventive) treatment [m3_hsv_treat_oth], to prevent cold sore recurrences.Are you still taking [m3_hsv_treat_oth] today?

◯ Yes
◯ No

Have you received any treatment for cold sores in the period between [m6_datestart] and [m6_datedue]?

◯ Yes
◯ No

If yes, why?

◯ To treat an active cold sore
◯ To prevent further cold sores (treatment typically lasting more than 1 month)
◯ Both to treat and to prevent cold sores

Which preventive treatment have you received between [m6_datestart] and [m6_datedue]?(Tick all that apply).
(Tick all that apply)

☐ Aciclovir (also called Zovirax, Acyclo-V, Lovir)
☐ Valaciclovir (also called Valtrex, Valacor, Zelitrex, Shilova)
☐ Famciclovir (also called Famvir, Favic, Famlo, Ezovir)
☐ Lysine
☐ Other, please specify
☐ Don't know

If other, please specify:

_____

For how long were you taking Aciclovir? Please only consider the period between [m6_datestart] and [m6_datedue].Please answer in weeks

_____
(In weeks)

Are you still taking Aciclovir treatment today?

◯ Yes
◯ No

For how long were you taking Valaciclovir? Please only consider the period between [m6_datestart] and [m6_datedue].Please answer in weeks

_____
(In weeks)

Are you still taking Valaciclovir treatment today?

◯ Yes
◯ No

For how long were you taking Famciclovir? Please only consider the period between [m6_datestart] and [m6_datedue].Please answer in weeks

_____
(In weeks)

Are you still taking Famciclovir treatment today?

◯ Yes
◯ No

For how long were you taking Lysine? Please only consider the period between [m6_datestart] and [m6_datedue].Please answer in weeks

_____
(In weeks)

Are you still taking Lysine treatment today?

◯ Yes
◯ No

For how long were you taking [m6_hsv_prevent_other]? Please only consider the period between [m6_datestart] and [m6_datedue].Please answer in weeks

_____
(In weeks)

Are you still taking [m6_hsv_prevent_other] treatment today?

◯ Yes
◯ No

For how long were you taking this preventive treatment? Please only consider the period between [m6_datestart] and [m6_datedue].Please answer in weeks

_____
(In weeks)

Are you still taking this preventive treatment today?

◯ Yes
◯ No

We noticed you haven't provided your Medicare number as yet. If possible, could you provide it here: _____

Thank you so much for your participation in the BRACE trial!Please do not hesitate to contact us via e-mail or phone if you have any concerns.For Victoria: brace@mcri.edu.auFor Perth Children's Hospital (WA): brace@telethonkids.org.auFor Sir Charles Gairdner (WA): Brace.scgh@health.wa.gov.auFor Fiona Stanley Hospital (WA): fsh.bracetrial@health.wa.gov.auFor South Australia: BRACE.trial@sahmri.comFor New South Wales: schn-bracestudy@health.nsw.gov.auFor Netherlands: BRACE@umcutrecht.nlFor Spain: BRACE@umcutrecht.nlFor UK: bracetrial@exeter.ac.uk

Thank you - Gracias - Dank u - Obrigado

9 months follow-up questionnaire

Section 9: Cold sore questions

Have you had a cold sore episode since [m9_datestart]?These are small painful blisters on the lips or around the mouth, also known as fever blisters or herpetic infection.

◯ Yes
◯ No

How many cold sore episodes did you have between [m9_datestart] and [m9_datedue]?

_____
(Please answer to the best of your memory.)

When did the first episode start? Please only consider the period of time between [m9_datestart] and [m9_datedue].

_____
(Please approximate the date to the best of your memory.)

Have you noticed any change in your cold sores recurrence between [m9_datestart] and [m9_datedue], in terms of:- Frequency (how often you get cold sores)- Duration (how long a cold sore episode lasts)- Severity (how painful, disabling, extensive the lesions are)- Impact on quality of life (social, aesthetic, work, etc.)

◯ Yes
◯ No

Has it changed?

Frequency (how often you get cold sores)

◯ The episodes have been generally less frequent
◯ The episodes been generally more frequent
◯ The frequency has not changed

Duration (how long a cold sore episode lasts)

◯ The episodes have been generally shorter
◯ The episodes have been generally longer
◯ The duration has not changed

Severity (how painful, disabling, extensive the lesions are)

◯ The episodes have been generally less severe
◯ The episodes have been generally more severe
◯ The severity has not changed

Impact on quality of life (social, aesthetic, work, etc.)

◯ The episodes have had less impact on my quality of life
◯ The episodes have had more impact on my quality of life
◯ The impact on my quality of life did not change

You previously said that you have taken prophylactic (preventive) treatment [m3_hsv_prevent], to prevent cold sore recurrences.Are you still taking [m3_hsv_prevent] today?

◯ Yes
◯ No

You previously said that you have taken prophylactic (preventive) treatment [m3_hsv_treat_oth], to prevent cold sore recurrences.Are you still taking [m3_hsv_treat_oth] today?

◯ Yes
◯ No

Have you received any treatment for cold sores in the period between [m9_datestart] and [m9_datedue]?

◯ Yes
◯ No

If yes, why?

◯ To treat an active cold sore
◯ To prevent further cold sores (treatment typically lasting more than 1 month)
◯ Both to treat and to prevent cold sores

Which preventive treatment have you received between [m9_datestart] and [m9_datedue]?(Tick all that apply).
(Tick all that apply)

☐ Aciclovir (also called Zovirax, Acyclo-V, Lovir)
☐ Valaciclovir (also called Valtrex, Valacor, Zelitrex, Shilova)
☐ Famciclovir (also called Famvir, Favic, Famlo, Ezovir)
☐ Lysine
☐ Other, please specify
☐ Don't know

If other, please specify:

_____

For how long were you taking Aciclovir? Please only consider the period between [m9_datestart] and [m9_datedue].Please answer in weeks

_____
(In weeks)

Are you still taking Aciclovir treatment today?

◯ Yes
◯ No

For how long were you taking Valaciclovir? Please only consider the period between [m9_datestart] and [m9_datedue].Please answer in weeks

_____
(In weeks)

Are you still taking Valaciclovir treatment today?

◯ Yes
◯ No

For how long were you taking Famciclovir? Please only consider the period between [m9_datestart] and [m9_datedue].Please answer in weeks

_____
(In weeks)

Are you still taking Famciclovir treatment today?

◯ Yes
◯ No

For how long were you taking Lysine? Please only consider the period between [m9_datestart] and [m9_datedue].Please answer in weeks

_____
(In weeks)

Are you still taking Lysine treatment today?

◯ Yes
◯ No

For how long were you taking [m9_hsv_prevent_other]? Please only consider the period between [m9_datestart] and [m9_datedue].Please answer in weeks

_____
(In weeks)

Are you still taking [m9_hsv_prevent_other] treatment today?

◯ Yes
◯ No

For how long were you taking this preventive treatment? Please only consider the period between [m9_datestart] and [m9_datedue].Please answer in weeks

_____
(In weeks)

Are you still taking this preventive treatment today?

◯ Yes
◯ No

We noticed you haven't provided your Medicare number as yet. If possible, could you provide it here: _____

12 months follow-up questionnaire

Section 9: Cold sore questions

Have you had a cold sore episode since [m12_datestart]?These are small painful blisters on the lips or around the mouth, also known as fever blisters or herpetic infection.

◯ Yes
◯ No

How many cold sore episodes did you have between [m12_datestart] and [m12_datedue]?

_____
(Please answer to the best of your memory.)

When did the first episode start? Please only consider the period of time between [m12_datestart] and [m12_datedue].

_____
(Please approximate the date to the best of your memory.)

Have you noticed any change in your cold sores recurrence between [m12_datestart] and [m12_datedue], in terms of:- Frequency (how often you get cold sores)- Duration (how long a cold sore episode lasts)- Severity (how painful, disabling, extensive the lesions are)- Impact on quality of life (social, aesthetic, work, etc.)

◯ Yes
◯ No

Has it changed?

Frequency (how often you get cold sores)

◯ The episodes have been generally less frequent
◯ The episodes been generally more frequent
◯ The frequency has not changed

Duration (how long a cold sore episode lasts)

◯ The episodes have been generally shorter
◯ The episodes have been generally longer
◯ The duration has not changed

Severity (how painful, disabling, extensive the lesions are)

◯ The episodes have been generally less severe
◯ The episodes have been generally more severe
◯ The severity has not changed

Impact on quality of life (social, aesthetic, work, etc.)

◯ The episodes have had less impact on my quality of life
◯ The episodes have had more impact on my quality of life
◯ The impact on my quality of life did not change

Have you received any treatment for cold sores in the period between [m12_datestart] and [m12_datedue]?

◯ Yes
◯ No

If yes, why?

◯ To treat an active cold sore
◯ To prevent further cold sores (treatment typically lasting more than 1 month)
◯ Both to treat and to prevent cold sores

Which preventive treatment have you received between [m12_datestart] and [m12_datedue]?(Tick all that apply). (Tick all that apply)

☐ Aciclovir (also called Zovirax, Acyclo-V, Lovir)
☐ Valaciclovir (also called Valtrex, Valacor, Zelitrex, Shilova)
☐ Famciclovir (also called Famvir, Favic, Famlo, Ezovir)
☐ Lysine
☐ Other, please specify
☐ Don't know

If other, please specify:

_____

For how long were you taking Aciclovir? Please only consider the period between [m12_datestart] and [m12_datedue].Please answer in weeks

_____
(In weeks)

Are you still taking Aciclovir treatment today?

◯ Yes
◯ No

For how long were you taking Valaciclovir? Please only consider the period between [m12_datestart] and [m12_datedue].Please answer in weeks

_____
(In weeks)

Are you still taking Valaciclovir treatment today?

◯ Yes
◯ No

For how long were you taking Famciclovir? Please only consider the period between [m12_datestart] and [m12_datedue].Please answer in weeks

_____
(In weeks)

Are you still taking Famciclovir treatment today?

◯ Yes
◯ No

For how long were you taking Lysine? Please only consider the period between [m12_datestart] and [m12_datedue].Please answer in weeks

_____
(In weeks)

Are you still taking Lysine treatment today?

◯ Yes
◯ No

For how long were you taking [m12_hsv_prevent_other]? Please only consider the period between [m12_datestart] and [m12_datedue].Please answer in weeks

_____
(In weeks)

Are you still taking [m12_hsv_prevent_other] treatment today?

◯ Yes
◯ No

For how long were you taking this preventive treatment? Please only consider the period between [m12_datestart] and [m12_datedue].Please answer in weeks

_____
(In weeks)

Are you still taking this preventive treatment today?

◯ Yes
◯ No

HREC no: 62586

BCG vaccination to Reduce the impact of COVID-19 in Australian healthcare workers following Coronavirus Exposure (BRACE) Trial

Adverse Events Following Immunisation (AEFI)
Stage 1
Report number 31

Period covered: 30 March to 16 March 2022

Sponsor: Murdoch Children's Research Institute, represented by Lead Investigator Prof Nigel Curtis
Affiliation: Murdoch Children's Research Institute, The Royal Children's Hospital Melbourne
Address: 50 Flemington Road | Parkville | 3052 | VIC | Australia

Introduction

This is the is the 31st AEFI Report, covering the period from 30 March, 2020 (date of inclusion of the first participant) to 16 March 2022, for the BRACE clinical trial on the administration of the Bacille Calmette-Guérin (BCG) to healthcare worker during the COVID-19 pandemic. The primary objectives are to determine if BCG vaccination (Intervention) compared with no BCG vaccination (Comparator) reduces the incidence of COVID-19 disease (first co-primary outcome) and of severe COVID-19 disease (second co-primary outcome) measured over the 6 months following randomisation (Time) in healthcare workers in Australia exposed to SARS-CoV-2 (Participants).

Participants in Stage 1 are randomised to receive or not BCG vaccine; participants receive their annual influenza vaccine at the same time. Blood samples are collected prior to randomisation, to determine previous SARS-CoV-2 exposure.

As of 16 March 2022, there were **2840 participants randomised** in Stage 1 of the trial, **1418** were randomised to receive the BCG vaccine.

The tables below give the details and a cumulative summary of adverse event reports received from the participants. Participants unshaded are new since report ending 29 December 2021.

A total of **209** AEFI were reported for this period and these are listed below.
To date there have been **17** SAE reported (details in Table 1 below).
To date there have been **192** AE reported (details in Table 2 below; **5** fainting episodes, **4** systemic reactions, **183** local reactions). These include **4** referrals to a Specialist Immunisation Clinic (SIC) clinic.

Table 1: Summary report of serious adverse events received for the BRACE study for the period 30 March 2020 to 16 March 2022

Participant ID number and Site	Sex	Report no.	I/S	Date vaccinated and dose number	Onset following vaccination (incl date)	Description of adverse event	SAE type	Treatment	*Relationship to vaccine Site Investigator (S) assessment MCRI Sponsor (M) assessment	*Severity of SAE	Outcome (incl date resolved)	Date of last contact with participant
1763 RCH	F	1	I	06/04/2020: BCG vaccine (1st dose) and influenza vaccine (previously annually for 12years)	8 hours (06/04/20)	06/04/20 at ~8:30-9 pm, participant developed sudden onset headache ('worst headache in life') then myalgia, vomiting, fever 38.3°C, tachycardia. Went back to RCH (06/04/20) and had COVID-19 swab (Negative). Admitted to Box hill hospital overnight via ambulance	3	In hospital symptoms settled with IV paracetamol, ondansetron, metoclopramide, IV fluids. Discharged home on 07/04/20 at 7am. Follow-up by GP on 8/4/20: normal vital signs.	Likely reaction to influenza vaccine (A/Prof Nigel Crawford and Prof Nigel Curtis)	Severe	Resolved D2 (07/04/20) SAEFVIC Report 09/04/20	09/04/20
5481 SCGH	F	2	I	14/04/2020 BCG vaccine and influenza vaccine	10 hours (14/04/20)	Developed sore throat and felt unwell late on the evening of the 14th, the next morning woke up with a sore throat, wheeze and cough, which worsened over the next hours. Used Ventolin at home, with limited effect. Had COVID-19 testing (negative) at SCGH and went home. Developed worsening cough and wheeze, and presented to ED at SCGH at 12 midday, on examination there was no sign of respiratory distress or audible wheeze on auscultation. There was mild generalised erythema around the pharynx, she was afebrile; RR 15 per minute. She was discharged within 2 hours.	7	Treatment with salbutamol nebuliser and 25mg of oral prednisolone. Self-isolation.	Likely reaction to flu vaccine in the context of past medical history of previous mild asthma (never hospitalised for asthma not on preventer. Dr M Lucas (PI)	Severe	Resolved 14/04/20 WAVSS form submitted (reference w2004-003153) on 16/04/2020	15/04/20
8069 SCGH	F	3	I	24/4/20: Influenza vaccine only	D83 (16/07/20)	5-day hospitalisation in MHU, from 16/7/20-20/7/20. COVID-19 symptoms 16/7 - 6/7 during hospital admission. Tested negative twice for COVID-19 during hospital stay, with swab and blood test.	3	Hospitalisation in MHU, no further details obtained.	(S) Unrelated (M) Unrelated	Severe	Discharged home but remains on leave from work (29/07/20).	29/07/20
1033 RCH	F	4	I	2/4/20: BCG vaccine and Influenza vaccine	D58 (30/5/20)	Overnight hospitalisation on 30/5/20 for an episode of pyelonephritis/complicated UTI. Participant reports chronic urological health Issues - long term stoma & indwelling catheter. Frequent UTI's. Treating hospital did not perform COVID-19 swab.	3	Hospitalisation requiring 24 hours of intravenous antibiotics and intravenous fluid therapy. Not treated with oxygen.	(S) Unrelated (M) Unrelated	Severe	Discharged home 31/05/20 (D59)	02/06/20
7110 PCH	F	5	I	16/4/20: Influenza vaccine only	D64 (19/6/20)	Fractured ankle requiring internal fixation In hospital 19/6/20 - 21/6/20	3	Hospitalisation; surgery for fractured ankle requiring internal fixation. Unable to work; off work for 35 days	(S) Unrelated (M) Unrelated	Severe	Discharged home 21/06/20 (D66)	21/06/20
2714 RCH	F	6	I	3/04/20: Influenza	D27 (01/05/20)	Fever, sore throat and headaches/photophobia. Tonsillitis. Hospitalisation 01/05/20-05/05/20.	3	Hospitalisation; IV fluid therapy for 3 days and regular analgesia, Multiple IV	(S) Unrelated (M) Unrelated	Severe	Discharged home 05/05/20 (D33).	06/07/20

				vaccine only		Investigated with COVID-19 swab, blood cultures, bloods, urine, CT brain, LP.		antibiotics and antivirals.			Took about 5 weeks off work afterwards for side-effects of antibiotic (stomach - not disclosed in detail).	
7108 FSH	M	7	I	16/04/20: Influenza vaccine only	D80 05/07/20	Sports injury; lower limb fractures requiring surgery- hospitalisation 05/07/20-07/07/20.	3	Hospitalisation; surgery for lower limb fractures.	(S) Unrelated (M) Unrelated	Severe	Discharged home 07/07/20	12/11/20
4436 FSH	M	8	I	10/04/2020	D1 immediatel y post blood draw	Vasovagal syncope post blood draw and hence not received vaccination. Loss of consciousness and some twitching. Immediately felt dizzy, sweaty and nausea, brief LOC. Nil other injuries. Seen at FSH ED. PMHx of Syncope	7	Sent to FSH ED. Discharge midday. Bloods NAD ECG- NAD 2x troponin NAD	(S) Definite (M) Unrelated to vaccination (Vaccine not received. Syncopal event related to venipuncture)	Severe	Resolved D1	
5886 SCGH	F	9	I	14/04/2020 Influenza vaccine only	D20 (04/05/20)	infected sebaceous cyst at lower aspect of neck- overnight hospitalisation	3	Hospitalisation: drainage of cyst & IV antibiotics	(S) Unrelated (M) Unrelated	Severe	Discharged home 5/5/20 (D21)	
7124 FSH	F	10	I	16/4/20: BCG vaccine and Influenza vaccine	D68 (23/06/20)	Inpatient hospitalisation for shoulder surgery, secondary to accident in workplace.	3	Hospitalisation: shoulder surgery	(S) Unrelated (M) Unrelated	Severe	Discharged home 25/06/20 (D70)	25/02/21
5604 SCGH	F	11	I	15/4/20: BCG vaccine (2^{nd} dose) and Influenza vaccine	D71 (25/06/20)	5-night hospitalisation for abdominal pain with history of diverticulitis. Diagnosed with diverticulitis.	3	CT to confirm diagnosis Blood tests: CRP & Blood Cultures - Treated with antibiotics & analgesia	(S) Unrelated (M) Unrelated	Severe	Discharged home 01/07/20 (D77)	6/10/21
8515 SCGH	F	12	I	23/4/20: BCG vaccine (1^{st} dose) and Influenza vaccine	D63 (25/06/20)	Hospitalisation for unmanageable back pain, & pins & needles & altered sensation in L) foot. - MRI diagnosis of L5 & S1 nerve impingement & L4, L5 & S1 disc prolapse -Past history of 'broken back' as a 9 year old.	3	Insertion of indwelling catheter Assistance with movement & mobility Analgesia and CT guided nerve block. Altered sensation in L) left for 9 months following nerve block, post hospital discharge	(S) Unrelated (M) Unrelated	Severe	Discharged home 03/07/20 (D71)	6/10/21
5236 FSH	F	13	I	13/4/20: BCG vaccine (1^{st} dose) and Influenza vaccine	D23 (06/05/20)	Acute appendicitis – admitted to hospital for 2 nights	3	Ultrasound, laparoscopic appendectomy	(S) Unlikely (M) Unrelated	Severe	Discharged home 08/05/20 (D25)	12/10/21

7109 FSH	M	14	I	16/04/2020 Influenza vaccine only	D56 (11/06/20)	Admitted to hospital for 2 nights with increasing lower abdominal pain	3	Diverticulitis confirmed via Bloods and CT imaging Rx: IV antibiotics, anti-emetics, analgesia	(S) Unlikely (M) Unrelated	Severe	Discharged 13/06/20 (D58)	12/10/21
6400 PCH	F	15	I	20/4/20: BCG vaccine (1st dose) and Influenza vaccine	D23 (13/05/20)	13/05/2020-16/05/2020 hospitalisation for mental health	3	Hospitalisation: mental health care	(S) Unrelated (M) Unrelated	Severe	Discharged 16/05/20 (D26)	29/10/21
4367 SCGH	F	16	I	14/4/20: Influenza vaccine only	D14 (28/04/20)	Whilst hospitalised for investigation for iron deficiency and possible IBS, fell & hit head, had a seizure and was subsequently found to have hyponatremia. Phx of childhood epilepsy.	3	Hospitalised for 3 nights. Electrolyte abnormality corrected. Prophylactic antibiotics administered. Investigations: EEG, lumbar puncture, MRI brain.	(S) Unrelated (M) Unrelated	Severe	Discharged 01/05/20	NA
6763 SCGH	F	17	I	16/4/20: BCG vaccine (1st dose) and Influenza vaccine	D17 (03/05/20)	Infected multiple puncture marks and cellulitis from cat bites.	3	Hospitalised for 2 nights. Surgical washout & debridement of injured right wrist & hand under GA. 48 hours of intravenous antibiotics - piperacillin and tazobactam.	(S) Unrelated (M) Unrelated	Severe	Discharged 05/05/20	NA

I/S = index / subsequent

SAE type = Criteria for seriousness
1. Resulted in death
2. Immediately life-threatening
3. Requires inpatient hospitalisation (i.e. minimum overnight admission, that is non-elective).
4. Results in prolongation of existing hospitalisation
5. Results in persistent or significant disability/incapacity
6. Is a congenital anomaly/birth defect
7. In the medical judgment of the treating physician and/or investigator, it may jeopardise the participant or require intervention to prevent one of the above outcomes

*Severity of SAE:
- Severe (Severe medically significant but not immediately life threatening)
- Life-threatening (**immediately** life-threatening (not 'hypothetically life-threatening if more severe'), urgent intervention)
- Death related to adverse event

*Definition of relationship to the intervention
- Unrelated (The AE is clearly NOT related to intervention)
- Unlikely (The AE is doubtfully related to the intervention)
- Possible (The AE may be related to the intervention)
- Probable (The AE is likely related to the intervention)
- Definite (The AE is clearly related to the intervention)

Table 2: Summary report of adverse events reported 30 March 2020 to 16 March 2022
*Note one report may have included several events

Participant ID number	Sex	Report no.	Date vaccinated and dose number	Onset following vaccination	Description of adverse event	Treatment	Reaction Review BCG/Flu	Outcome	Local reaction Grade
Fainting episodes on randomisation day									
1900 RCH	F	1	31/03/2020: BCG (1st dose) and influenza vaccine	NA	After having her blood taken (no vaccine given yet), participant became pale and fainted whilst sitting on chair. MET called.	Legs elevated, laid down. Regained consciousness within a minute. Vital signs stable, normal blood glucose. Was observed by MET team. She was able to sit within 10 minutes and felt much better, drank glass of water. Subsequently walked to have her BCG vaccine administered with Immunisation Nurse (planned lying down). Participant reported having had previous faint with blood test.	NA	Resolved D4	NA
1147 RCH	F	2	02/04/2020: BCG and influenza vaccine	Day of vaccination; Immediately post vaccines	After having her blood taken and both vaccines given, participant felt dizzy. Set down for 12 minutes, then was asked to stand up, felt dizzy again, set down again => MET call. Found to have low BP, ambulance to Royal Melbourne Hospital.	In RMH ED, had an ECG (normal), was discharged without treatment. Participant is known to have a low BP and claims being very needle phobic, has already had many similar episode in the past.	NA	Resolved D1	NA
4302 SCGH (1st AE)	F	3	14/04/2020: BCG and influenza vaccine	Immediately post vaccines	Sudden loss of consciousness after final injection with BCG. Collapsed; head strike on table leg with gash to face due to glasses. Returned to normal conscious state within one minute. Bradycardia (40-70 BPM). Hx: Previous vaso vagal episodes, especially in the context of needles.	Wound care Further cardiology follow-up organised by the emergency department. Likely vaso-vagal episode. Dr M Lucas (PI)	Vasovagal syncope related to study procedure	Resolved D1	NA
7227 PCH	F	4	16/04/2020: BCG and influenza vaccine	Immediately post blood sampling and influenza vaccination	Warned phlebotomist that she might faint during blood test, stated she felt dizzy, hand clammy, vasovagal episode, unconscious- but breathing, seizure-w/o loss of consciousness. Lasted for 3 minutes in duration- called second nurse & doctor to assist. Participant still consented to receive her vaccinations. She received her influenza vaccination and immediately felt light headed and clammy. The PI was consulted regarding whether to continue with the BCG. Subject was happy to continue and the BCG vaccine was given while participant was lying down. Reviewed by sub-investigator during both episodes. During review, she was pale and clammy. Seizure has stopped by that stage. She was conscious and answering questions appropriately. GCS 15/15. Discussed with PI.	Laid down, feet raised, cold compress & glass of water with good recovery. Pulse taken post influenza vaccination was approx. 30-40bpm. Colour improved after elevation of legs. Tea and chocolate given. Observed in family resource centre for another 20min. Colour improved. GCS 15/15. Gait normal. Participant went back to work on ward and is aware to contact us if any concern. She reported that she has a background of hypotension and has previous history of vasovagal with blood test and vaccinations.	Vasovagal Syncope Definite relation to Blood sampling and influenza injection	Resolved D1	NA
3731 PCH	F	5	17/04/2020 BCG and influenza vaccine	Immediately post influenza vaccination	Felt lightheaded, nauseous. Experienced facial flushing 5 minutes post receipt of influenza vaccine (please note BCG not administered yet)	Laid down. Recovered completely. Agreed to proceed with the BCG vaccine. Observed in the centre for 20 minutes.	Vasovagal episode following	Resolved D1	NA

Participant ID number	Sex	Report no.	Date vaccinated and dose number	Onset following vaccination	Description of adverse event	Treatment	Reaction Review BCG/Flu	Outcome	Local reaction Grade
					Examination: Strong pulse, 70BPM. Not clammy.		influenza vaccine		
Systemic adverse event									
1806 RCH	F	1	30/03/2020: BCG (1st dose) and influenza vaccine	D3 01/04/2020 (Within 48 hours)	D3: nausea, lethargy, then headache, diarrhoea and dizziness. D4 saw a BRACE trial medical doctor at recruitment site, and went home from work early due to lethargy and nausea. Dizziness and lethargy on and off until D7.	Rest and observation	Influenza	Resolved D7 SAEFVIC Report 11/04/20	NA
7177 PCH (1st AE)	F	2	16/04/2020 BCG (2nd dose) and influenza vaccine	D2	Tiredness and fever for one day, myalgia and tiredness for 4 days, resolved.	Rest and observation	Influenza	Resolved D6	NA
4445 FSH (1st AE)	F	3	16/04/2020 BCG (2nd dose) and influenza vaccine	D5	Off work due to feeling unwell with constant headaches + nausea, body aches with intermittent fatigue and a weird body twitch which felt like muscles twitching constantly	Rest and analgesia	Influenza	Resolved D6	NA
6232 SCGH (3rd AE)	F	4	15/04/2020 BCG (1st dose) and influenza vaccine	Unknown	Onset of Acne- described as cystic since BCG vaccine and also worsened post isoniazid treatment. Onset of food intolerances meat and dairy. Also has unexplained episodes of vertigo	Review at the AEFI clinic- not true intolerances. Not related to vaccination.	Unrelated	Ongoing	NA
Local adverse event									
Intervention group 1: Influenza vaccine ('standard care')									
1704 RCH	F	1	30/03/2020: Influenza vaccine only	D1	D1-2: Tender flu vaccination site causing significant discomfort at rest; somewhat interfering with daily activities. Did not need to take any medication, nor see a medical doctor. Resolved by day 3.	Observation	Influenza	Resolved D3	3 (tenderness)
2303 RCH	F	2	06/04/2020: Influenza vaccine only	D1	Significant discomfort at rest at site of influenza vaccination until D3, did not require analgesia or interfere with activities	Observation	Influenza	Resolved D3	3 (tenderness)
8164 RCH	F	3	21/04/2020: Influenza vaccine only	D1	Significant discomfort at rest at site of influenza vaccination on D1, did not require analgesia. Describes as 7/10 pain. Worse with movement. Somewhat interfered with activities. Much improved D2. Resolved D4	Observation	Influenza	Resolved D4	3 (tenderness)
7539 Epworth	F	4	17/04/2020: Influenza vaccine only	D1	Significant discomfort at rest at site of influenza vaccination on D1, did not require analgesia. Had to avoid using arm. Improving D2. Was able to sleep. No swelling or lump	Observation	Influenza	Resolved D3	3 (tenderness)
4763 PCH	M	5	12/04/2020: Influenza vaccine only	D2	Onset D2 (13/04/20), same arm as flu vaccine, axillary LN max size 1cm, mildly painful, self-resolved after 2 days (i.e. by D4, 15/04/20). No overlying redness nor discharge from gland.	Observation	Influenza	Resolved D4	LA, axillary
5485 FSH	F	6	14/04/2020: Influenza vaccine only	D2	Redness at influenza vaccine site, greater than 10cm diameter (Gr3 redness). Max 11cm diameter on 15/04/2020. Redness onset D2, duration 4 days (no redness D6)	Observation	Influenza	Resolved D6	3 (redness)

Participant ID number	Sex	Report no.	Date vaccinated and dose number	Onset following vaccination	Description of adverse event	Treatment	Reaction Review BCG/Flu	Outcome	Local reaction Grade
4540 FSH	F	7	10/04/2020 influenza vaccine only	D1	Significant discomfort at rest reported by participant at influenza vaccine site.	Observation	Influenza	Resolved D3	3 (tenderness)
4050 PCH	F	8	09/04/2020 influenza vaccine only	D1	Significant discomfort at rest report by participant at influenza vaccine site. Tender D1-D3	Observation	Influenza	Resolved D3	3 (tenderness)
7631 PCH	F	9	17/04/2020 influenza vaccine only	D1	Significant discomfort at rest report by participant at influenza vaccine site. Tender D1-D2	Observation	Influenza	Resolved D2	3 (tenderness)
3802 FSH	M	10	09/04/2020 influenza vaccine only	D1	Significant discomfort at rest report by participant at influenza vaccine site.	Paracetamol 2 days	Influenza	Resolved D2	3 (tenderness)
4710 FSH	F	11	11/04/2020 influenza vaccine only	D2	Significant discomfort at rest report by participant at influenza vaccine site. tender and painful D2. Prevented daily activity for one day.	Analgesia	Influenza	Resolved D2	3 (tenderness) 3 (pain)
4118 PCH	M	12	11/04/2020 influenza vaccine only	D1	Significant discomfort at rest report by participant at influenza vaccine site. tender D1-D2	paracetamol +ibuprofen used for 1 day	Influenza	Resolved D2	3 (tenderness)
Intervention group 2: BCG + influenza vaccine									
Abscess at BCG injection site									
1601 RCH	F	1	30/03/2020: BCG (previous BCG vaccine >20 years ago) and influenza vaccine	D3	Concerned regarding pain and swelling at BCG vaccination site. BRACE trial email 3/4/2020, advised to observe and keep us updated; likely abscess formation. Significant discomfort experienced at rest. Max 2 cm diam. On day 6 pus noted to discharge from site which resulted in reduced pain. Continued improvement noted since.	Observation	BCG	Resolved D6	Abscess 3 (tenderness)
1059 RCH	F	2	30/03/2020: BCG and influenza vaccine	D5	Initially developed what appeared to be an abscess on 5/4/20 with significant discomfort at rest. 4x2cm at largest. Developed a 'necrotic scab' with discharge. Scab fell off leaving a sloughy patch underneath. Participant used hydrocolloid dressings. Significant discomfort at rest improved on 9/4/20. No lymphadenopathy.	Observation	BCG	Resolved D11	Abscess 3 (tenderness)
~~1680 RCH~~	~~M~~	~~3~~	~~30/03/2020: BCG (1st dose)~~	~~D11~~	~~Onset D11 small injection site abscess evolving, max 1x1cm.~~	~~Observation~~	~~BCG~~	~~Resolved D13~~	Does not meet abscess definition

Participant ID number	Sex	Report no.	Date vaccinated and dose number	Onset following vaccination	Description of adverse event	Treatment	Reaction Review BCG/Flu	Outcome	Local reaction Grade
			~~and influenza vaccine~~		~~D13 consistent with a small healing abscess~~				(size)
1643 RCH	M	4	30/03/2020: BCG (2nd dose) and influenza vaccine	D12	Onset D12 tender bump at BCG injection site (max 2cm), that discharged in the shower (yellow/white pus), resolved D14. Previous BCG when child in Philippines	Observation	BCG	Resolved D14	Abscess
1426 RCH	F	5	31/03/2020: BCG (2nd dose) and influenza vaccine	D12	Onset D12 (11/4/20) tender BCG injection site (max swelling size diameter recorded 2cm), that discharged ooze. D14 appeared healing. Reviewed by Dr Crawford (SAEFVIC Director and BRACE medical doctor) in clinic on 14/4/20 (D15); consistent with healing local injection site abscess (Please see SIC review section). Discharge stopped ~10/12/20 D243 (crusted over)	Observation	BCG	Resolved D243	Abscess 3 (tenderness),
1749 RCH	F	6	02/04/2020 BCG (2nd dose) and influenza vaccine	D5	Significant discomfort at rest D5-6, improved since D7- only tenderness to touch D16 increased tenderness participant sent photo- potentially evolving injection site abscess. Max size 1.7cm diam. D20 abscess popped with discharge (serous and pus); tenderness improved, likely evolving into small ulcer	Observation	BCG	Resolved D20	Abscess 3 (tenderness),
~~1084 RCH~~	~~F~~	~~7~~	~~06/04/2020: BCG (2nd dose) and influenza vaccine~~	~~D12~~	~~Onset D12: oozing pus. (max swelling 1x1cm) D15, oozing pus again, decreased swelling and tenderness. D18 ulcer formation~~	~~Observation~~	~~BCG~~	~~Resolved D18~~	Does not meet abscess definition (size)
~~2965 RCH~~	~~M~~	~~8~~	~~06/04/2020: BCG (2nd dose) and influenza vaccine~~	~~D11~~	~~Onset D11: Minimal discharge (white) with pain and increasing tenderness, 1.8cm diameter. Participant self-initiated co-amoxicillin D11-13. Minimal non-purulent discharge lasting for less than a day. Dry site D14. D16 more discharge, participant self-re-initiated oral antibiotics (flucloxacillin), ceased D19~~	~~Participant self-initiated oral antibiotic: co-amoxicillin D11-D13 followed by flucloxacillin D16-19 (21-24/4)~~	~~BCG~~	~~Resolved D22~~	Dr subsequently reported was not abscess
7061 Epworth	M	9	16/04/2020: BCG (2nd dose) and influenza vaccine	D5	Onset D5. Very painful, red, indurated, pus expressed D7. Size 3cm diameter, raised at least 1cm. Significant discomfort at rest D19 Resolving. Little exudate, not much more pus.	Observation	BCG	Resolving D19	Abscess 3 (tenderness)
2527 RCH	F	10	02/04/2020: BCG (2nd dose) and influenza vaccine	D24	Reported D24, red swollen painful, 2x1.5cm, pus discharge. Headache also. Discharge ceased approx 20/6/20	Observation	BCG	Resolved D80	Abscess
7240 Epworth	F	11	16/04/2020: BCG (2nd dose) and influenza vaccine	D9	D9 significant discomfort at rest (throbbing pain). She knocked it yesterday and felt a stabbing pain. Initial redness 8cm and swelling 4cm. D9 appears like it may be coming to a head (maximal size ~1.5cm diameter). D12 (27/4/20) pus discharged, pain significantly decreased. By D21 site is dry, healing well.	Paracetamol 6 days	BCG	Resolved by D21	Abscess 3 (tenderness) 2 (pain)
1198 RCH	M	12	31/03/2020: BCG (1st dose)	D27	First two weeks no concerns post vaccination. D20 redness, tender, raised; participant applied topical	Observation	BCG	Resolved D35	Abscess

Participant ID number	Sex	Report no.	Date vaccinated and dose number	Onset following vaccination	Description of adverse event	Treatment	Reaction Review BCG/Flu	Outcome	Local reaction Grade
			and influenza vaccine		antiseptic. D27 noticed local abscess formation (~1.5cm diameter) with discharge. Used non-occlusive dressing and medicated paraffin gauze. Discharge stopped D35.				
2300 RCH	F	13	01/04/2020: BCG (2nd dose) and influenza vaccine	D20	Onset D20 (20/4), associated with muscle ache left shoulder/neck and left scapula, taking ibuprofen for pain. Max size ~1.5cm. No axillary or neck lymphadenopathy. She has been able to work (dental therapist) and has full range of movement of arm. Significant pus discharge on D22 until D27. Resolving; occasional ooze since (sometimes with shower). Dry since D47	Ibuprofen for pain D20	BCG	Resolved D47	Abscess 3 (tenderness)
1405 RCH	F	14	03/04/2020: BCG (1st dose) and influenza vaccine	D20	Onset D20 redness, swelling, throbbing pain at injection site, abscess 2x2cm formed, discharged on D22 (25/4) when touched it; yellow pus. Discharge ceased 4/5/20	Observation	BCG	Resolved D31	Abscess 3 (tenderness)
2955 RCH	F	15	06/04/2020: BCG (2nd dose) and influenza vaccine	D22	Onset D22 (27/4/20) muscle pain left shoulder (felt like 'pulled shoulder', significant discomfort at rest. Had full range of movement), swelling at site ~2cm diameter maximum. D24 (29/4/29) pus self-drained, decreased muscle ache, now sharp pain localised to site. No axillary lymphadenopathy. Also has sore throat (likely unrelated to BCG. Children with URTIS, tested for COVID-19 at GP). Site oozing on and off until D50 (25/5/20)	Observation	BCG	Resolved D50	Abscess 3 (tenderness)
1921 RCH 2nd AE	F	16	31/03/2020: BCG (2nd dose) and influenza vaccine	D30	Previous AE for significant tenderness at rest D1-D5. New AE Onset D30, evolving injection site abscess with increasing pain at site, redness, swelling, 2x2cm, left upper arm tenderness. D31 (30/4/20) a lot of pus discharge in shower. Due to localised pain and amount of pus from injection site, she has taken two days off work. Stopped discharge ~01/06/20 (D63)	Observation	BCG	Resolved D63 SAEFVIC report 3/5/20 (V2005-017624)	Abscess
5498 Epworth	F	17	21/04/2020: BCG (2nd dose) and influenza vaccine	D2 (tenderness) D9 (abscess)	Sore BCG site D2 and very sore for about 4 days. Decreased by D9 although still sore. Can't sleep on her L side. There has been a tiny amount of discharge but she can still see pus in there. It hasn't stopped her performing her usual daily activities. Maximum redness diameter 3 cm, swelling 2cm. 29/4 Evolving injection site abscess; self-discharged in shower; tenderness significantly decreased post. Minimal discharge 1/5, improving.	Paracetamol D2-D5	BCG	Resolving	Abscess 2 (pain) 3 (tenderness)
5567 PCH	F	18	14/04/2020: BCG (2nd dose) and influenza vaccine	D7	Redness D1-6 (max 1.5 cm), swelling D2-6 (max 6 cm), pain D1+D7-8, tenderness D1-5+D7-8 with abscess (max 2cm) formation, discharged in shower	Offered review by the team – seen once. Returning 1/5	BCG	Resolved	Abscess 2 (swelling) 3 (tenderness)
3762 FSH	F	19	11/04/2020 BCG (3rd dose, last 34y ago) and	D15	D1-3 Tenderness, redness, and swelling. D4 to D11: Swelling and redness D12: Return of tenderness	Observation	BCG	Resolved	Abscess

Participant ID number	Sex	Report no.	Date vaccinated and dose number	Onset following vaccination	Description of adverse event	Treatment	Reaction Review BCG/Flu	Outcome	Local reaction Grade
			influenza vaccine		D15: Abscess formed, pus self-discharge for 36 hours. Still swollen and inflamed				
5726 SCGH	F	20	15/04/2020 BCG (1st dose) and influenza vaccine	D12	Papule but increased size and redness and swelling within 24 hours. Reported redness 2-3cm but swelling about 5cm. Significant pain and then discharge 27/04/2020. Felt faint/vasovagal episode - no loss of consciousness. Sweaty and pale. No Fevers. Heart rate increased. Vasovagal likely due to the pain associated with it and tendency to this. Also noted LA in the neck last 24 hours. One lymph node (left cervical) - likely 1-2 cm rather. Email sent to let Dr Wadia know of the swab results.	She called health direct who then instructed to seek medical review within 2 hours. Presented to SCGH ED- diagnosed with likely secondary infection - on cephalexin and topical bactroban. Paracetamol for pain. Review in Clinic on 4/05/2020	BCG	Resolved	Abscess 4 (pain) Vasovagal episode secondary to pain Lymphadenopathy, left cervical
5348 SCGH	F	21	15/04/2020 BCG (2nd dose) and influenza vaccine	D3	D3 Large 7cm redness reported (17/04/2020) D4 Swelling 4 cm reported (18/04/2020) D3-D7 Pain, redness, tenderness and swelling D8-ongoing: Tenderness, redness and swelling Grade 2 redness BUT note on reviewing pictures- small abscess	Observation	BCG	Resolved	Abscess
1260 RCH (2nd AE)	F	22	03/04/2020: BCG (1st dose) and influenza vaccine	D26	Initial swelling and erythema at injection site (self-resolved, no discharge. D1-D8) and Gr3 tenderness D1-D3 (1st AE). Subsequent stable papule 1cm, until D26. This AE: injection site abscess (onset D26) that discharged pus D29. D26 (28/4/20) she noticed fluctuance and 'head' forming at injection site, max diameter 2cm, self-discharge large amount of pus (>teaspoon) on D29, followed by haemoserous ooze, with subsequent improvement. No lymphadenopathy. No further d/c since D42	Observation	BCG	Resolved D42	Abscess
2087 RCH	M	23	31/03/2020: BCG (2nd dose) and influenza vaccine	D28	Onset D28 (27/4/20) increased redness, tenderness and swelling at BCG injection site, becoming softer to touch. Photo 1/5/20 consistent with evolving injection site abscess. Max 2.5cm diameter. Stopped discharging on 17/06/20 (D78)	Observation	BCG	Resolved D78	Abscess
2629 RCH	F	24	02/04/2020: BCG (2nd dose) and influenza vaccine	D21	Onset D21 (22/4/20) increased redness, swelling, tenderness at BCG injection site, max 1.5cm diameter. D25 and D28 pus self-discharged, with improvement in swelling and tenderness. No pus discharge in July.	Observation	BCG	Resolved D90	Abscess
1734 RCH	F	25	30/03/2020: BCG (2nd dose) and influenza vaccine	D27	Onset ~D27 (25/4) with increasing fluctuance at BCG injection site, max diameter 3cm, and self-discharged ~D31 (1/5/20), in warm shower. It seemed to build up again, then discharge pus again ~D34. It has not affecting ADLs, however can be sore if sleeping on L side. No axillary lymphadenopathy.	Observation	BCG	Resolved by D54	Abscess 3 (tenderness),
6615 FSH	M	26	15/4/2020: BCG (3rd dose)	D6 (LA) D8 (Abscess)	Onset on 22/4. Abscess - Ongoing tenderness, pain, swelling and	Observation	BCG (Right side)	Resolved D8 - Lymphadenopathy	Abscess Lymphadenopathy

Participant ID number	Sex	Report no.	Date vaccinated and dose number	Onset following vaccination	Description of adverse event	Treatment	Reaction Review BCG/Flu	Outcome	Local reaction Grade
			and influenza vaccine		redness. At the same time, increasing pain "looked like a carbuncle". Discharged in the shower 5 days ago. D16 - 0.7cm ulcer, redness 3cm and swelling 2 cm. Getting better, drying out. Lymphadenopathy D6- Right side of the neck- NB participant had vaccine on their right side as already had influenza vaccine on the left prior to randomisation. Resolved in 2 days			D16 - Abscess	– Right Cervical
7177 (2nd AE) PCH	F	27	16/04/2020 BCG (2nd dose) and influenza vaccine	D5	Redness and sore – initially felt like a rope underneath (straight). Induration for one week, then pointed and swollen. Green discharge. Very painful. Throbbing. Represented to clinic but not able to see (will see tomorrow)- ongoing issue at the site with induration and discharge (recollection)- concerned regarding abscess	Observation Clinical review 07/05/2020	BCG	Resolved (D100)	Abscess 3 (tenderness)
2185 RCH	F	28	2/04/2020 BCG (2nd dose) and influenza vaccine	D33	D25 ooze bleed from injection site, erythema 2.5x2cm. D33 ooze++ following shower. Saw dermatologist (for separate condition) who expressed pus from BCG injection site, and applied topical antibiotic cream with dressing. D36 improvement; smaller lumps beneath injection site. Discharge stopped D61	D33 Dermatologist expressed pus from BCG injection site, and applied topical antibiotic cream	BCG	Resolved D61	Abscess
1170 RCH	F	29	1/04/2020 BCG (2nd dose) and influenza vaccine	D41	Initially, D5-D18 very tender to touch, improved then tender again D32 (2/5). D41 (11/5): Red, swollen, 25mm diameter, raised 5mm, fluctuant. Discharged pus +++from D59 (29/5/20), d/c only with showers, then stopped discharging 28/6/20(D89). 19/7 Can palpate ulcer underneath injection site; healing site.	Observation	BCG	Resolved D89	Abscess
6243 PCH	F	30	15/04/2020 BCG (2nd dose) and Influenza Vaccine	D23	Initially red and swollen. Over one to two days, increasing tenderness, swelling and redness. Significant discomfort reported at rest (no medications). Reviewed in clinic (11/05/2020)- 2X2cm abscess Self discharged	Observation	BCG	Resolved D28	Abscess 3 (tenderness)
8226 PCH	M	31	21/04/2020 BCG (2nd dose) and Influenza Vaccine	D16	Initially 4cm redness, this reduced to about 1.5cm. Last week Wednesday and Thursday increased swelling. Friday evening (D17) - discharged- 4-5ml of pus. Not a papule- an abscess, induration around it. Over Saturday ongoing discharge. Yesterday haemoserous discharge. Now, dried, scab over it. Not tender anymore. Was tender initially when it swelled up on wed-friday. No LN swelling, no other symptoms.	Observation	BCG	Resolved D21	Abscess
6906 SCGH	F	32	17/04/2020 BCG (2nd dose) and Influenza Vaccine	D19	Over the past 1w, developed an ~2x2cm fluctuant swelling at the vaccine site that has become progressively more swollen, painful, erythematous and warm to touch. Using warm compresses to the site with	Observation initially Felt unwell and so commenced a course of Cefalexin (1g bd 10days) and eventually FNA on 7/6/20 (pt herself) and drained	BCG	Resolved D49	Abscess

Participant ID number	Sex	Report no.	Date vaccinated and dose number	Onset following vaccination	Description of adverse event	Treatment	Reaction Review BCG/Flu	Outcome	Local reaction Grade
					very little effect.	about 5-8ml of thick, purulent yellow pus from the abscess/site.			
5774 SCGH	F	33	17/04/2020 BCG (3rd dose) and influenza vaccine	D18	In week 3, had worsening swelling and tenderness. Then in this past week, 2 episodes of discharging about 5mls of pus consistent with abscess formation. It is still a fluctuant mass (D26). Ongoing ooze D 32. Nil lymphadenopathy	Observation IGRA- Negative	BCG	Resolved D80	Abscess 3 (tenderness)
1475 RCH	F	34	1/04/2020 BCG (1st dose) and influenza vaccine	D23	~D23, increased swelling (max 2cm) redness 14/5 drained pus in shower. Discharge stopped 27/5	Observation	BCG	Resolved D57	Abscess
2973 RCH	F	35	6/04/2020 BCG (1st dose) and influenza vaccine	D30	~D30 site became very tender, red, swollen (5cm diameter), raised. ~D36 2cm redness/purple centre, w surrounding bruising yellow/green, fluctuant in centre, as though there's fluid, firmer at edges. No lymphadenopathy. D57 site top came off in shower, D58 discharged +++ (~5-8ml fluid). Site swelling, redness, pain improved post.	Observation	BCG	Resolved D58	Abscess
7498 SCGH	F	36	20/04/2020 BCG (1st dose) and influenza vaccine	D21	D21 increasing redness and swelling. She is a doctor- Incision and drainage- 5ml of pus- definitely 1cm track- 15/05/2020. Used a needle to drain. Oozing on and off. Iodine dressing. Sterile abscess likely. No lymphadenopathy Did have neck pain but unclear when and why.	Advised to leave it to air out- no creams/ointments FNA. self-prescribed cephalexin for 5 days. Improved last few days.	BCG	Resolved D56 27/07/2020	Abscess
7372 PCH	F	37	16/04/2020 BCG (2nd dose) and Influenza vaccine	D21	Increasing in size after settling down the first 2 weeks. Increased tenderness (unable to sleep on that arm) and seems to have a firm 2cm disc beneath it, with some redness and warmth to the area. No LN reported. On clinical review D29, BCG site - red, warmth with induration, approx. 2-2.5cm in diameter. Appears to be abscess. No palpable lymph nodes	Observation	BCG	Resolved D36	Abscess
6232 SCGH (1st AE)	F	38	15/04/2020 BCG (1st dose) and influenza vaccine	D33	Increasing pain since D33. Increasing redness and swelling. Raised 1cm. Self-discharged D42 Clinical Review post discharge- abscess- 4x3cm in size-induration.	Observation (see 2nd AE) Commenced on Isoniazid D62	BCG	Resolved D146	Abscess
4302 SCGH (2nd AE)	F	39	14/04/2020 BCG (1st dose) and influenza vaccine	D27	2 weeks of swellings, redness and tenderness. Self-discharge one week after. On and off ooze, with ongoing redness and swelling. Clinical review - abscess	Observation Review in Clinic- confirmed abscess	BCG	Resolved	Abscess
5854 SCGH	F	40	16/04/2020 BCG (2nd dose) and influenza vaccine	D26	Onset of increasing swelling week 3-4 and worsening over the last 3 weeks. Increasing pain and not able to lie on that side. Has not discharged at all. 4.5cm by 4.5 cm abscess on examination. Duration 149 days approx.	Review by specialist : recommended to start isoniazid for 3 months. (wanted a second opinion- organised) Commenced isoniazid D68 (22/6/20). Completed.	BCG	Resolved by D175	Abscess 3 (pain)

Participant ID number	Sex	Report no.	Date vaccinated and dose number	Onset following vaccination	Description of adverse event	Treatment	Reaction Review BCG/Flu	Outcome	Local reaction Grade
1483 RCH	M	41	31/03/2020 BCG (2nd and 3rd dose) and influenza vaccine	D7	Two BCG vaccines given on 31/3/20. First was "too deep", second attempt given correctly. Onset of swelling at first BCG injection site, largest 1.5cm diameter, persisted soft swelling since, skin coloured, non-tender, no discharge, no associated lymphadenopathy. Intradermal BCG site followed expected reaction. Swelling at deeper site subsequently self-discharged for 2 days sometime between 27/06/2020 and 17/08/2020; dry and flat since.	Observation	BCG	Resolved ~D108	Abscess
2045 RCH	F	42	31/03/2020 BCG (1st dose) and influenza vaccine	D45	Vaccine site was ok in first month. Abscess onset ~D45, max 3x2cm diameter at injection site, tender, self-discharge 'a lot' of pus (>5ml), ongoing discharge then serous fluid until ~D117. Dry since then and continued to heal. No lymphadenopathy.	Observation	BCG	Resolved D117	Abscess
1124 RCH	M	43	30/03/2020 BCG (2nd dose) and influenza vaccine	D14 (approx)	Abscess developed ~D14. It did not come to a throbbing head and burst but was more indurated. It oozed pus every night in bed for about 4 weeks. It self resolved. Maximum diameter redness 3cm, swelling 2cm.	Observation	BCG	Resolved approx D42	Abscess
7656 SCGH	M	44	17/04/2020 BCG (3rd dose) and influenza vaccine	D21	Onset of redness, swelling and tenderness day 21 post vaccination. Self-prescribed flucloxacillin as prone to skin infections and redness increasing. Max 2cm diam. Described as 'more of an abscess'. Self-discharged and dried. Tenderness and redness improved. Resolved after 21 days.	Oral flucloxacillin	BCG	Resolved D42	Abscess
Lymphadenopathy									
1364 RCH	F	1	31/03/2020: BCG (1st dose) and influenza vaccines	D3	Swollen left submandibular lymph node D3-D4, max 1.5cm, mildly tender to touch, no overlying redness, no fluctuance. Nil lymphadenopathy elsewhere. Felt 'rundown'/tired at same time. Self-resolved by D5	Observation	BCG vs unrelated?	Resolved D5	Lymphadenopathy, left sub-mandibular
1315 RCH	F	2	31/03/2020: BCG (1st dose) and influenza vaccines	D3	Axillary lymph node 2-3cm (not painful, no overlying redness, no discharge). Also left cervical swollen lymph 2x3cm (mildly tender, had sore throat at same time). Onset ~ 2 days post vaccination (2/4/20), duration 2 days, now completely resolved. No concerns with BCG vaccination site reported.	Observation	BCG	Resolved D5	Lymphadenopathy, left axilla and left cervical
1367 RCH	F	3	03/04/2020: BCG (1st dose) and influenza vaccines	D2	Swollen lymph node left supraclavicular D2-3, for 2-3 days, max 8mm, tender, self-resolved Left neck lesion D2, max 1cm, improving to 6mm D14 (16/4/20). D34 only 2mm, no discomfort. Completely resolved as per email 12/09/2020. Possibly blind pimple. Past Hx: L parotid gland tumour resection 2005 (pleomorphic adenoma benign)	Observation	BCG	1.Lymphadenopathy left supraclavicular resolved D3 2.Neck lesion (unclear aetiology) resolved	1.Lymphadenopathy, left supra-clavicular 2. Unusual neck lesion
1956	F	4	31/03/2020:	D4	Lymphadenopathy – swollen gland left axilla. Onset	Observation	BCG	Resolved D7	Lymphadenopathy,

Participant ID number	Sex	Report no.	Date vaccinated and dose number	Onset following vaccination	Description of adverse event	Treatment	Reaction Review BCG/Flu	Outcome	Local reaction Grade
RCH			BCG (2nd dose) and influenza vaccine	03/04/2020	~day 4 and duration ~3 days. Maximum diam 2 cm. Lymph node was not painful but was a bit tender with movement. Now fully resolved.				left axilla
3976 FSH	F	5	09/04/2020: BCG (1st dose) and influenza vaccine	D6	D1 tenderness, D2 redness, D3-5 redness and swelling max 2cm. No interference with daily activities, no medication, mild discomfort to touch Axillary LN, 1.5 cm , no pus. LN onset 14/04/20, duration 12 days.	Email sent, unable to contact via phone.	BCG	Resolved by D18	Lymphadenopathy, axilla
5429 SCGH 1st AE	F	6	14/04/2020: BCG (1st dose) and influenza vaccines	D1	Tenderness, redness, swelling Pain under the armpit, 1 cm gland Pain resolved D2	Observation	BCG	Resolved D2	Lymphadenopathy, axilla
6132 PCH	F	7	17/04/2020: BCG (3rd dose, last dose >5 years ago) and influenza vaccine	D1 (tenderness) D3 (lymphadenopathy)	D1 Pain D2-5 Pain, tenderness, swelling (max 2 cm) and redness (max 3cm), paracetamol used for 2 days LN axillary, 0.5cm (D3), painful, settled within 2d	3 days of paracetamol	BCG	Resolved Tenderness -D4 Lymphadenopathy-D5	Lymphadenopathy, axillary 3 (tenderness) 2 (pain)
5842 SCGH	F	8	15/04/2020: BCG (2nd dose) and influenza vaccine	D8	Lymphadenopathy, supraclavicular, 3cm when largest reported. No tenderness. 30/04/2020	Observation	BCG	Resolved D12	Lymphadenopathy, supra-clavicular
6082 SCGH	F	9	20/04/2020: BCG (2nd dose) and influenza vaccine	D3	Lymph node swelling reported D3 Tenderness, pain and swelling of the site. 5cm redness and 2cm swelling	Observation	BCG	Resolved D9	Lymphadenopathy, axillary
6003 SCGH	F	10	20/04/2020: BCG (2nd dose, previous 1-5 years ago) and influenza vaccine	D2	No local reaction but reported lymph node swelling of 3cm.	Observation	BCG	Resolved – D4	Lymphadenopathy, cervical
1540 RCH	F	11	31/03/2020: BCG (2nd dose) and influenza vaccine	D10	Noted 1 cm lump R axilla D10 after discomfort sleeping on R side overnight. No pus, redness. No other lymphadenopathy. Otherwise well. D23 reduced to 0.5 cm and tenderness reducing	Observation	Influenza	Resolving D23	Lymphadenopathy, right axilla
6377 FSH	F	12	15/04/2020 BCG (2nd dose, previous dose in childhood) and influenza vaccine	D6	Lymphadenopathy reported on 20/04/2020 in left side of the neck (1 cm) and left posterior auricular area (1.5 cm), painful. Settled and then come back but now also right submandibular Previous neck injury- tenderness LTBI- treated 2012->6 months of isoniazid History of likely fibromyalgia	Paracetamol for 5 days Advised GP review as now gland on the other side. Consider SARS-CoV2 if meets criteria (as per current health department criteria)	BCG	Resolved D15	Lymphadenopathy, left cervical and posterior auricular 3 (pain)
6390 FSH	F	13	16/04/2020 BCG (2nd dose) and influenza vaccine	D9	2cm axillary LN (24/04/2020), resolved in 10 days. Large local reaction: D1 tenderness, D2 -D5- all 4, D6 onwards tenderness and redness. D11- only tenderness 10 cm of swelling (Entry on 24th April 2020), 6cm redness	Observation	BCG	Resolved D19	Lymphadenopathy, axillary

Participant ID number	Sex	Report no.	Date vaccinated and dose number	Onset following vaccination	Description of adverse event	Treatment	Reaction Review BCG/Flu	Outcome	Local reaction Grade
					Same large local reaction for Influenza vaccine site				
8173 SCGH	F	14	22/04/2020 BCG (2nd dose) and influenza vaccine	D6	Lymphadenopathy since D6 (27/04/2020), in the neck (1cm) and under the armpit (2cm), Headache for 2-3 days on the left side.	Observation	BCG	Resolved D10	Lymphadenopathy, axillary and cervical
5862 FSH	F	15	14/04/2020 BCG (2nd dose) and influenza vaccine	D3	Lymphadenopathy 1cm in the neck, noticed on D3 and resolved on D5	Observation	BCG	Resolved D5	Lymphadenopathy, cervical
8529 SCGH	F	16	23/04/2020 BCG (2nd dose) and influenza vaccine	D3	D1 ongoing Pain, redness (max 4cm), swelling (max 3.5cm) and tenderness, blister formation, popped on D5 LN max 2cm reported on D3 (25/04/2020) axillary, peanut size, still present, and supraclavicular. Examined on 4th May 2020 – axillary lymph node 0.5cm in size. Supraclavicular resolved.	Paracetamol and diclofenac for 4 days	BCG	Resolving D11	Lymphadenopathy, axillary and supra-clavicular 2 (pain)
3215 RCH	M	17	07/04/2020 BCG (1st dose) and influenza vaccine	D24	Lethargy and headaches since D20, had sore throat D20; COVID-19 test negative. B/G history of migraines. Also discomfort in left armpit, which he palpated ~2cm diam lymph nodes on D24 (1/5/20); feels like marbles joined. Not painful, feels some discomfort though, no discharge from lymph node, not red. BCG site unremarkable. 5/5 He reports lymph nodes left axilla much smaller, no pain, no discomfort. Review offered, however he is happy that it is self-resolving.	Observation	BCG	Resolving D28	Lymphadenopathy, left axilla
4467 FSH	F	18	10/04/2020 BCG(2nd dose) and influenza vaccine	D19	Swelling of the left armpit, with increase in the swelling and pain very quickly. Works in COVID clinic so got advice to go to ED for review. FSH ED review 29/04/20. IV access and needed buprenorphine (opiate) for initial examination. Told had enlarged lymph nodes (size 3 cm). None in the neck or supraclavicular. Tiredness.	ED review. ED staff consulted with ID physician at FSH- not for Antibiotics but monitor. Analgesia for 4 days	BCG	Resolved lymph gland swelling 29/04/2020?	Lymphadenopathy-Left axilla 4 tenderness (not BCG site but lymph node)
8173 FSH	F	19	09/04/2020 BCG (2nd dose) and Influenza vaccine	D7	Onset of 0.5cm LN and pain in the armpit, for one day. Site still red with minor swelling. It is still slightly raised, peeling. Not concerned about the site.	Observation	BCG	Resolved D8	Lymphadenopathy-Axillary
6776 SCGH	F	20	22/04/2020 BCG (1st dose) and influenza vaccine	D5	Swelling and redness throughout. Return of tenderness D11 and D12. Popped D15. Ongoing discharge. Lymphadenopathy reported (awaiting email)	Observation	BCG	Resolved D7	Lymphadenopathy – left axilla and cervical
4574 FSH	F	21	11/04/2020 BCG (2nd dose) and influenza vaccine	D2	Rigors on the first night, needed to go home from work (night shift). Colleagues at work noticed that she had swelling of the right side of the neck and right axilla (NOTE vaccine administered right side). Temperature reported to be 37.5-38, 3cm cervical LN and 2cm Axillary LN. Uncomfortable. 17042020- Only redness now on the BCG site LN 0.5cm in the axilla, no Pain	Paracetamol and codeine for two days	BCG	Resolved D12	Lymphadenopathy – Right Axilla and Cervical -Gr3 tender & pain

Participant ID number	Sex	Report no.	Date vaccinated and dose number	Onset following vaccination	Description of adverse event	Treatment	Reaction Review BCG/Flu	Outcome	Local reaction Grade
4090 FSH	F	22	09/04/2020 BCG (2nd dose) and influenza vaccine	D1	Onset of lymph node day 1-2, resolved.	Observation	BCG	Resolved D2	Lymphadenopathy –Left Neck
8419 SCGH	F	23	22/04/2020 BCG (2nd Dose) and influenza vaccine	D7	Woke up 0400 on 28 April with discomfort in the armpit. Pea size lump felt and gone by that afternoon. Discomfort resolved the next day, no other glands felt. BCG in Scotland. LTBI with positive TST and quantiferon, Normal CXR	Observation	BCG	Resolved D8	Lymphadenopathy-Axillary
7540 MMC	F	24	17/04/2020 BCG (2nd Dose) and influenza vaccine	D2	Lymphadenopathy developed on D2 in both axillary and cervical chains D2-D10, mild tenderness, maximum diameter approx 3cm in axilla. Participant did not seek medical attention. Resolved D10 post BCG vaccination. PHx BCG vaccine at approx 13years of age. Significant discomfort at rest . Experienced tenderness D2-30.	Observation Ibuprofen 2 days.	BCG	Resolved D10	Lymphadenopathy Left axilla and Left anterior cervical chain 3 (tenderness)
6766 SCGH	F	25	22/04/2020 BCG (1st dose) and influenza vaccine	D5	Swollen glands under left armpit (BCG also administered in the left arm) and on the left side of neck. They appeared about 5 days after the vaccination. 2cm axilla and 1cm neck. The swollen glands resolved within 18 hours but there was general tenderness in left shoulder and neck for 2 days after.	Observation	BCG	Resolved D6	Lymphadenopathy Left Axilla and Left Cervical
7844 PCH	F	26	23/04/2020 BCG (1st dose) and influenza vaccine	D24	3cm LN in the armpit. D35 About 1cm now Worse on the left rather than right. Usually gets bilateral axillary LN swelling when menstruating. This time worse on the left. No Worsening or inflammation of the BCG site. Associated symptoms of pain bilaterally but improving.	Observation	? Probable BCG	Resolved D40	Lymphadenopathy – Bilateral left worse than right
8150 PCH	M	27	21/04/2020 BCG (2nd dose) and Influenza vaccine	D10	LN has resolved - lasted for approx 5 days. It was a painless swelling with mild tenderness on palpation. Also, collection at the BCG vaccination site which had spontaneously popped and drained a couple of weeks ago with a healing ulcer at the site currently.	Observation	BCG	Resolved D16	Lymphadenopathy – Left cervical
6232 SGCH (2nd AE)	F	28	15/04/2020 BCG (1st dose) and Influenza vaccine	D56	Onset of armpit pain, followed by lump. Seen in clinic on 11/06/2020 (D57) - subcentimeter tender lymph node. Referral to specialist organised as also abscess (not worse than previous)- see 1st AE in the abscess section. D58 increased in size- reported to be olive shaped but 4by2.5cm and onset of another swollen gland. Fatigued.	Medically attended visit (saw GP) Specialist review organised and seen on D62 – Isoniazid commenced for abscess (see Above) CXR abnormal CT chest NAD COVID negative	BCG	Resolved D66 20/6/2020	Lymphadenopathy Axillary
6146 PCH	F	29	17/04/2020 BCG (2nd dose) and Influenza	D6	Tender to touch from when it appeared (22/4) for about 2 weeks, pain probably correlated with pain at injection site as it settled the gland settled.	Observation	BCG	Resolved D20 06/05/2020	Lymphadenopathy-Left neck

Participant ID number	Sex	Report no.	Date vaccinated and dose number	Onset following vaccination	Description of adverse event	Treatment	Reaction Review BCG/Flu	Outcome	Local reaction Grade
			Vaccine		BCG site okay				
6501 FSH	F	30	15/04/2020 BCG (2nd dose) and Influenza Vaccine	D11	One day of tender LN in the neck. Resolved spontaneously	Nil	BCG	Resolved D12	Lymphadenopathy-Left Neck
6670 FSH	F	31	09/04/2020 BCG (1st dose) and Influenza Vaccine	D8	One week post vaccine. Onset of pain and axillary LN increased in size- 3cm at its largest. Then decreased. Painful and present for about 2 weeks after. Now a very small size gland.	Observation	BCG	Resolved D22	Lymphadenopathy-Axillary
1398 RCH	F	32	02/04/2020 BCG (1st dose) and Influenza Vaccine	D14	Since D14, occipital lymph node noted, max 2cm diameter, left of midline. Not painful,not red, not discharging, no fluctuance. Reviewed by her GP, who reported no concerns. She has regular follow-ups with her GP due to fibromyalgia and chronic fatigue. BCG injection site photo appears consistent with expected reaction in 3-month survey photo.	Observation	?BCG	Ongoing SAEFVIC report 9/7/20 (lymphadenopathy >2 weeks) V2007-018099	Lymphadenopathy-left occipital
1625 RCH	F	33	30/03/2020 BCG (2nd dose) and influenza vaccine	D42	Approximately 6 weeks after vaccination, 1 lymph node size of grape (approx 2cm x 1cm) left side neck under jaw. Vaguely tender. No redness, pain or discharge. Lasted 48 hours maximum. States her husband also felt another possible lymph node back of neck around same time but she was unaware of this one and it also resolved within a day or 2.	Observation	?BCG	Resolved D44	Lymphadenopathy - Left submandibular
1094 RCH	F	34	07/04/2020 BCG (1st dose) and Influenza vaccine	D15	1 lymph node noticed left axilla. Unsure of date of onset – best guess D15. Size 2cm x 1cm. Lasted about 1 week. No discharge or redness. Mildly tender. Self-resolved	Observation	?BCG	Resolved D22	Lymphadenopathy – Left axilla
2620 RCH	F	35	03/04/2020 BCG (1st dose) and Influenza vaccine	D14	1 lymph node left axilla. Unsure of date of onset – best guess D14. Lasted only 2 days. No discharge or redness. Mildly tender. Self-resolved. Size of node 1cm x1cm. Redness over node 2cmx2cm	Observation	?BCG	Resolved D16	Lymphadenopathy – Left axilla
8326 Epworth	M	36	22/04/2020 BCG (2nd dose) and Influenza vaccine	D30	LA left cervical 1cm max diameter, onset 1-2 months post vaccine, slight tenderness to touch, not painful, self-resolved within 2 weeks.	Observation	?BCG	Resolved D44	Lymphadenopathy – Left cervical
2379 RCH	F	37	03/04/2020 BCG (1st dose) and influenza vaccine	D7	A left submandibular 1cm max diameter, onset ~D7 post vaccine, tender, associated with sore throat, self-resolved within 5 days.	Observation	Unlikely BCG	Resolved D12	Lymphadenopathy - Left submandibular
1161 RCH	F	38	03/04/2020 BCG (2nd dose) and Influenza vaccine	D21	Noticed small LN left axilla (5mm x 5mm) about day 21. Lasted 2 days and self resolved. Note she had mantoux test in New Zealand when she started nursing degree. It was negative so she had BCG vaccination (in 1999). There was absolutely no local response at all to BCG	Observation	BCG	Resolved D23	Lymphadenopathy – Left axilla

Participant ID number	Sex	Report no.	Date vaccinated and dose number	Onset following vaccination	Description of adverse event	Treatment	Reaction Review BCG/Flu	Outcome	Local reaction Grade
					vaccination. Her repeat mantoux just after the vaccination was inconclusive				
8509 SCGH	F	39	27/04/2020 BCG (2nd dose) and Influenza vaccine	D5	Noticed a 2cm axillary lymph node. Only 2cm on 27/04/2020. Resolved in two days.	Observation	BCG	Resolved D7	Lymphadenopathy – Left axilla
6132 PCH	F	40	17/04/2020 BCG (3rd dose) and Influenza vaccine	D4	Participant reported 0.5cm axillary LN on 20/04/2020 associated with pain. Resolved within 2 days.	Observation	BCG	Resolved D6	Lymphadenopathy – Left axilla
4083 FSH	F	41	14/04/2020 BCG (1st dose) and Influenza vaccine	D3	Neck lymphadenopathy (self-reported) 1cm on 16/04/20, resolved in 1 day.	Observation	BCG	Resolved D4	Lymphadenopathy – Left cervical
3902 FSH	F	42	9/04/2020 BCG (1st dose) and Influenza vaccine	~D16	Bilat neck lymphadenopathy (self-reported), max1cm, at time of intercurrent URTI, reported in Vaccine diary on D16	Observation	Unrelated	Resolved	Lymphadenopathy – bilat cervical
7607 Epworth	F	43	17/04/2020 BCG (1st dose) and Influenza vaccine	D7	Bilat neck lymphadenopathy (self-reported), max1-2cm, at time of having a sore throat, self-resolved	Observation	Unrelated	Resolved D10	Lymphadenopathy – bilat cervical
6176 Epworth	F	44	15/04/2020 BCG (2nd dose) and Influenza vaccine	D30	Bilat neck lymphadenopathy (self-reported), max2cm, not tender, several weeks after vaccination, self-resolved about a month later	Observation	Unrelated	Resolved D40	Lymphadenopathy – bilat cervical
2379 RCH	F	45	15/04/2020 BCG (2nd dose) and Influenza vaccine	D7	left submandibular, onset ~D7, lasted 5 days, max size 1cm, tender, associated with sore throat, self-resolved	Observation	Unrelated	Resolved D12	Lymphadenopathy – left cervical
1527 RCH	M	46	30/03/2020 BCG (2nd dose) and Influenza vaccine	D5	Left cervical lymphadenopathy ~D5 (03/04/2020), lasting max 4 days, max size 2cm, assoc with sore throat.	Observation	Unlikely	Resolved D9	Lymphadenopathy – left cervical
1564 RCH	F	47	14/04/2020 BCG (1st dose) and Influenza vaccine	~D45	Left cervical and axillary lymphadenopathy, max size 3cm, self-reported, onset sometime between month 1-2 post vaccination, persisted for few weeks. Participant had 'lymphatic drainage massage', and swollen glands	Observation and lymphatic drainage massage	Possible	Resolved ~D60	Lymphadenopathy – left cervical, left axillary

Participant ID number	Sex	Report no.	Date vaccinated and dose number	Onset following vaccination	Description of adverse event	Treatment	Reaction Review BCG/Flu	Outcome	Local reaction Grade
					reduced back to normal. No overlying redness. Tender left armpit on movement and when pushed.				
3892 FSH	F	48	09/04/2020 BCG (2nd dose) and Influenza vaccine	~D7	Left axillary lymphadenopathy, max size 0.5cm,, self-reported, no overlying redness, not painful. Self-resolved after ~1 week.	Observation	Possible	Resolved ~D14	Lymphadenopathy left axillary
3976 FSH	F	49	09/04/2020 BCG (1st dose) and Influenza vaccine	~D6	Left axillary lymphadenopathy, max size 1.5cm, self-reported, no overlying redness, not painful. Self-resolved within ~1 week.	Observation	Possible	Resolved ~D18	Lymphadenopathy left axillary
5391 FSH	F	50	14/04/2020 BCG (1st dose) and Influenza vaccine	~D6	Left neck lymphadenopathy max size 1cm, self-reported, painful, associated with tonsillitis, self-resolved after ~1week.	Observation	Unlikely	Resolved ~D17	Lymphadenopathy – Left cervical
5806 FSH	F	51	14/04/2020 BCG (2nd dose) and Influenza vaccine	~D8	Neck lymphadenopathy max size 2cm, self-reported, unsure regarding site, no overlying redness, not painful. Self-resolved within ~1 week	Observation	Unlikely	Resolved ~D15	Lymphadenopathy - neck
3808 FSH	F	52	09/04/2020 BCG (1st dose) and Influenza vaccine	~D?	Neck lymphadenopathy max size 0.5cm, self-reported, no overlying redness, not painful. Onset sometime between D14 and 3months. Self-resolved in less than 2 weeks.	Observation	Unlikely	Resolved	Lymphadenopathy - neck
3836 FSH	F	53	09/04/2020 BCG (1st dose) and Influenza vaccine	~D6	Left axillary lymphadenopathy max size 1cm, self-reported, no overlying redness, not painful. Self-resolved in a few days.	Observation	Probable	Resolved ~D9	Lymphadenopathy left axillary
3983 FSH	F	54	10/04/2020 BCG (1st dose) and Influenza vaccine	~D3	Left neck lymphadenopathy max size 2cm, self-reported, no overlying redness, not painful. Self-resolved in a few days.	Observation	Possible	Resolved D5	Lymphadenopathy – left cervical
5450 FSH	F	55	14/04/2020 BCG (2nd dose) and Influenza vaccine	D2	Left neck lymphadenopathy max size 1cm, self-reported, no overlying redness, not painful. Self-resolved in a few days.	Observation	Possible	Resolved ~D3	Lymphadenopathy – left cervical
7372 PCH	F	56	16/04/2020 BCG (2nd dose) and Influenza vaccine	D7	Left axillary LN enlargement max 0.5cm, onset D7, tender, assoicated with injection site abscess developement. No overlying redness. Self-resolved after 1 week (i.e. by D14). Associated with injection site abscess development.	Observation	Definite	Resolved D14	Lymphadenopathy-left axilla
3924	F	57	09/04/2020	D4	Onset a few days after vaccination (~D4 13/04/20), left	Observation	Probable	Resolved D34	Lymphadenopathy-

Participant ID number	Sex	Report no.	Date vaccinated and dose number	Onset following vaccination	Description of adverse event	Treatment	Reaction Review BCG/Flu	Outcome	Local reaction Grade
PCH			BCG (1st dose) and Influenza vaccine		axillary LN max size 1cm, some pain, self-resolved after approx. 1 month (i.e. by D34 (17/05/20). Possible slight redness? No discharge from gland.				left axilla
5398 SCGH	F	58	14/04/2020 BCG (1st dose) and Influenza vaccine	D6	Onset D6, left cervical LN max size 0.5cm, pain, but no overlying redness. Self-resolved within a week (i.e. by D13)	Observation	Possible	Resolved D13	Lymphadenopathy-left cervical
5780 SCGH	F	59	14/04/2020 BCG (2nd dose) and Influenza vaccine	D20	Onset by D20 left cervical LN max size 1.5cm, associated with cold sore (usually has enlarged left gland with left sided cold sores associated with some discomfort), self-resolving within 1-2 days (i.e by D22),	Observation	Unrelated	Resolved D22	Lymphadenopathy-left cervical
6003 SCGH	F	60	21/04/2020 BCG (2nd dose) and Influenza vaccine	D2	Onset D2, left cervical LN max size 3cm, mild pain, self-resolved after approx 3 days (i.e. resolved by D5). No associated cold-like symptoms.	Observation	Possible	Resolved D5	Lymphadenopathy-left axilla
6365 SCGH	M	61	28/04/2020 BCG (2nd dose) and Influenza vaccine	D2	Onset within D2 (29/04/20), left axillary LN max size 0.5cm, non-tender, self-resolved within a week (ie by D9 (06/05/20). No overlying redness nor discharge from gland.	Observation	Probable	Resolved D9	Lymphadenopathy-left axilla
6581 SCGH	F	62	21/04/2020 BCG (1st dose) and Influenza vaccine	D7	Onset within 1-2 weeks (D7 ~28/04/2020), left axillary LN max size 2cm, tender to touch, self-resolved after at least 2weeks (i.e. D21 12/05/2020). No overlying redness nor discharge from gland. Possible also smaller gland max 1cm in right axilla, self-resolved after a week.	Observation	Probable	Resolved D21	Lymphadenopathy-left axilla
Other									
1921 RCH	F	1	31/03/2020: BCG (2nd dose) and influenza vaccine	Day of vaccination; following vaccinations	First three days: Tender BCG vaccination site causing significant discomfort at rest, somewhat interfered with daily activities, using paracetamol until day 3, then improved and only mild tenderness on day 5 (4/4/20)	Paracetamol 3 days	BCG	Resolved by D5 4/4/2020	3 (tenderness) 2 (pain)
2268 RCH	F	2	01/04/2020: BCG (2nd dose) and influenza vaccines	D3 03/04/20	Significant discomfort (at BCG site) at rest requiring analgesia (paracetamol) and restricting movement and daily activities on day 3. Improved since then. Vaccine site subsequently only tender to touch (10/04/20) and not causing restriction of movement or activities.	1 dose paracetamol on D3	BCG	Resolved by D10	3 (tenderness)
1199 RCH	M	3	01/04/2020: BCG (2nd dose) and influenza vaccines	D5	Left axillary pain/significant tenderness onset D5 until D8, could not palpate discrete axillary lymph gland swelling, no overlying redness in axillary region, no discharge, self-resolved. Also, vaccination site redness and swelling has improved (reduced in redness and swelling) compared to photo (D6) taken; had mild clear ooze, no pus discharge. Previous BCG in 1992. Lived in	Observation	BCG	Resolved D8	Left axilla pain / significantly tender (Gr3)

Participant ID number	Sex	Report no.	Date vaccinated and dose number	Onset following vaccination	Description of adverse event	Treatment	Reaction Review BCG/Flu	Outcome	Local reaction Grade
					Philippines for 3 years when a child.				
1260 RCH	F	4	3/04/2020: BCG (1st dose) and influenza vaccine	D3	Significant discomfort at rest D1-3, with swelling and erythema at BCG injection site. Swelling self-resolved D8	Observation	BCG	Resolved D3	3 (tenderness)
~~3836 FSH~~	~~F~~	~~5~~	~~09/04/2020: BCG and influenza vaccine~~	~~D2~~	~~BCG vaccine site tenderness D2, D3-4 tenderness, pain and swelling No significant change to daily activities Mild discomfort Swollen gland reported But in Dairy BCG site 16/04/2020 reported to be increased in size (to be followed up)~~	~~Observation~~	~~BCG~~	~~Resolved tenderness~~	~~2 (redness and swelling) 3 (tenderness)\~~ Tenderness not Gr3
3997 FSH	F	6	09/04/2020: BCG (2nd dose) and influenza vaccines	D1	Pain (D1-3), tenderness (D1-4), redness (D1-5, max 1.5 cm) and swelling (D1-5) Significant discomfort at rest reported No medications	Observation	BCG	Resolved D4	3 (tenderness)
4478 FSH	F	7	10/04/2020: BCG (2nd dose) and influenza vaccines	D3	D1 redness, no entry d2, d3 reported redness max 5 cm, swelling max 2 cm, pain, tenderness, with significant discomfort at rest, but no interference with activity, no medication, no LN	Observation	BCG	Resolved D3	3 (tenderness)
~~5164 FSH~~	~~M~~	~~8~~	~~13/04/2020: BCG (2nd dose) and influenza vaccines~~	~~D2~~	~~Tenderness and redness D2 to 4 Redness is getting bigger and looks like blister if forming~~	~~Observation~~	~~BCG~~	~~Resolved~~	No AE
5793 SCGH	F	9	16/04/2020 BCG (2nd dose) and influenza vaccine	D6	Pain and tenderness Significant discomfort D6 Use of paracetamol for 6 days Max 2 cm redness and205 4cm swelling	Paracetamol for 6 days	BCG	Resolved D12	3 (tenderness) 2 (pain)
1398 RCH	F	10	02/04/2020: BCG (1st dose) and influenza vaccines	D2-3	Significant discomfort at rest, onset D2, duration 2-3 days, mainly at night when she couldn't lie on her left side because of the discomfort at the vaccination site. Able to continue usual daily activities. Required ibuprofen and paracetamol for ~ 3 days. Associated local swelling (max 5 cm), much improved. Hx: Fibromyalgia for which she also takes ibuprofen and paracetamol but felt that this discomfort was different to her fibromyalgia pain.	Analgesia at the time of discomfort – ibuprofen and paracetamol for 2-3 days	BCG	Resolved	3 (tenderness) 2 (pain)
2080 RCH	F	11	31/03/2020: BCG (1st dose) and influenza vaccines	D1	Obvious bruising at site of influenza vaccine, on day of vaccination (following vaccine), maximum diam ~2.5cm, almost all resolved by D16. Non painful. Fully resolved by D18. No previous history or bruising with flu vaccines	Observation	Influenza	Resolved D18 SAEFVIC report 18/4/20	Significant local reaction- bruising
2028 RCH	M	12	31/03/2020: BCG (1st dose) and influenza vaccines	D2	Redness (20cm) and swelling (25cm) at BCG vaccination site, maximal D2-D3, as well as significant discomfort at rest night of D2. This has since markedly improved and he has no current concerns with his BCG reaction site.	Paracetamol 3 days	BCG	Resolved D4	3 (tenderness, swelling, redness) 2 (pain)

Participant ID number	Sex	Report no.	Date vaccinated and dose number	Onset following vaccination	Description of adverse event	Treatment	Reaction Review BCG/Flu	Outcome	Local reaction Grade
1883 RCH	F	13	01/04/2020: BCG (2nd dose) and influenza vaccines	D10	Significant discomfort at rest D10 for 2 days, then resolve. She has no current concerns about her BCG site	Observation	BCG	Resolved D12	3 (tenderness)
5586 SCGH	F	14	14/04/2020: BCG vaccine (2nd dose, previous dose 40 years ago) and influenza vaccines Previous LTBI – no treatment	D1	D1 reported to have pain, redness, and tenderness. D3 swelling onset (max 3 cm) with above. Largest redness 6 cm D3 and 4. Settled Tenderness significant resolved D5 5 days of paracetamol Painful to start with but now only minimal tenderness with touching it. Still oozing a bit. Redness improving – 1cm No LN swelling or pain	Use of non-occlusive dressing. She was using gauze but aggravated it so has been using a non-stick dressing. Care advised. Paracetamol for 5 days	BCG	Resolved	3 (tenderness) 2 (redness) 2 (pain)
7626 PCH	F	15	17/04/2020: BCG (1st dose) and influenza vaccine	D2	D2 Redness and swelling D3- all D4 – Tenderness, Redness, swelling Significant tenderness, ibuprofen for 2 days	Ibuprofen for 2 days	BCG	Resolved D6	3 (tenderness) 2 (pain)
5544 FSH	F	16	14/04/2020: BCG (1st dose) and influenza vaccine	D1	Influenza vaccine site- Bruising which was described as significant. Not had this before. No other concerns raised	Observation	Influenza vaccine	Resolved D9	Significant local reaction- bruising
4994 SCGH	F	17	16/04/2020: BCG (2nd dose) and influenza vaccine	D3	D2 – ongoing redness, tenderness and swelling. Paracetamol for 1 day (D3) for tenderness	Paracetamol for 1 day	BCG	Resolved D4	3 (tenderness)
6423 SCGH	F	18	15/04/2020: BCG (2nd dose) and influenza vaccine	D3	D3-4 Tenderness, pain, redness (max 6cm), swelling (max 4 cm). Use of paracetamol D3-4 for significant discomfort at rest.	Paracetamol for 2 days	BCG	Resolved D5	3 (tenderness) 2 (pain)
5929 SCGH	F	19	15/04/2020: BCG (2nd dose) and influenza vaccine	D4	Onset of pustule 4 days post injection at the BCG site. D5 Pustule in the ear which is similar looking to the BGC site. Throbbing and painful. Never had this before. No underlying skin disorder. Medically attended visit – kenacomb (topical)	Squeezed it out, kenacomb for 3 days on ear pustule	Neither, unrelated	Resolved D10	Ear Pustule
7630 MMC	F	20	17/04/2020: BCG (2nd dose) and influenza vaccine	D2	Significant discomfort at rest noted in vaccine diary. Began D2 and lasted about 3 days. D7 much improved. She mainly noticed it when driving and when in bed at night. She would lie on her R side but the weight of the blanket on the L BCG site was uncomfortable. The pain didn't stop her sleeping unless she rolled onto her L side in which case she would wake up and roll back to the R side. No analgesia taken. There was also redness (6 cm) and swelling at BCG site - now resolving.	Observation	BCG	Resolving D5	3 (tenderness) 2 (redness)
7150	F	21	16/04/2020 BCG (2nd dose) and influenza	D10	Discomfort BCG site started D2 or D3. Very uncomfortable at rest. No analgesia required. Able to perform daily activities. Unable to lie on her L side.	Observation	BCG	Resolved D14	3 (tenderness)

Participant ID number	Sex	Report no.	Date vaccinated and dose number	Onset following vaccination	Description of adverse event	Treatment	Reaction Review BCG/Flu	Outcome	Local reaction Grade
			vaccine		About D10, knocked vaccination site and a small amount of pus came out and it felt much better. No pain (D14) but is itchy.				
7903 Epworth	F	22	20/04/2020 BCG (2nd dose) and influenza vaccine 1994: TST+ (20-25mm), CXR normal	D8	D8 -D9 quite tender BCG vaccination site; paracetamol and ibuprofen taken. The discomfort has not stopped her performing her daily activities. Pustule drained pus overnight which was present on her pyjamas morning of D10 (29/4). Ongoing discharge (gauze pad changed 3x morning of D10). Pustule resolved D11	Paracetamol and ibuprofen for 2 days (D8-D9) D10 commenced antibiotic Augmentin by GP for different indication (sinusitis flare; she usually has flare 6-weekly). Had azithromycin for 4 days prior.	BCG	Resolved D9	3 (tenderness)
7066 FSH	F	23	16/04/2020 BCG (2nd dose) and influenza vaccine	D9	Pain and redness from D3 to D5. Day 6 onset of tenderness. Use of paracetamol for grade 3 tenderness	Paracetamol 5 days (end date 24/04/2020)	BCG	Resolved D14	3 (tenderness) 2 (pain)
~~8538 SCGH~~	~~F~~	~~24~~	~~24/04/2020 BCG (1st dose) Influenza vaccine~~	~~D4~~	~~Grade 3 tenderness reported, no medication~~	~~Observation~~	~~BCG~~	~~Resolved~~	~~3 (tenderness)~~
5683 PCH	F	25	16/04/2020 BCG (2nd dose) and influenza vaccine	D12	D1-6 redness, swelling and tenderness D7-11 Tenderness D12 Grade 3 tenderness "swelling erupted, discharged a large amount of pus"	Observation	BCG	Resolved	3 (tenderness)
6128 PCH	F	26	22/04/2020 BCG (2nd dose) and influenza vaccine	D1	D1 -2 Tenderness Grade 3 on Day 2	Observation	Influenza	Resolved D2	3 (tenderness)
8477 PCH	F	27	23/04/2020 BCG (2nd dose) and influenza vaccine	D1	Significant discomfort at rest reported for influenza vaccine site D1 and D2.	Observation	Influenza	Resolved D2	3 (tenderness)
8228 Epworth	M	28	21/04/2020 BCG (1st dose) and influenza vaccine	D4	Significant discomfort at rest, pain D4 to D8, at BCG vaccination site.	Paracetamol and ibuprofen 7 days	BCG	Resolved D8	3 (tenderness)
7882 PCH	F	29	21/04/2020 BCG (2nd dose) and Influenza Vaccine	D7	27th April increase in pain. Paracetamol for pain on 29/04/2020. Had oozed out some pus on 30/4 and 1/5/2020. Now cleaned and drying up.	Paracetamol for 1 day	BCG	Resolved D11	3 (tenderness)
5683 PCH	F	30	16/04/2020 BCG (2nd dose) and Influenza vaccine	D11	Grade 3 tenderness on D11, much improved post discharge on D13 Hx: BCG at 11 years of age. Immigrated here from UK Positive TST, CXR NAD (20 years ago)	Observation	BCG	Resolved D13	3 (tenderness)
4445 (2nd AE) FSH	F	31	16/04/2020 BCG (2nd dose) and influenza vaccine	D5	The BCG site has been tender at rest since day 5 and has settled weekend being 2nd & 3rd May which is day 16 & 17.	Daily Panadol 1g QDS & Ibuprofen 400mg TDS since day 5 (20th April)	BCG	Resolved D17	3 (tenderness)

Participant ID number	Sex	Report no.	Date vaccinated and dose number	Onset following vaccination	Description of adverse event	Treatment	Reaction Review BCG/Flu	Outcome	Local reaction Grade
4494 FSH	F	32	16/04/2020 BCG (1st dose) and influenza vaccine	D1	Significant discomfort at rest reported.	Use of paracetamol for one day	Influenza vaccine	Resolved D1	3 (tenderness)
7983 SCGH	F	33	21/04/2020 BCG (2nd dose) and Influenza Vaccine	D19	Redness only for the last 3 weeks. Since Sunday 10/05/2020 left sided neck pain, headache (left sided), pain around the jaw line. BCG site itchy but no increase in redness, tenderness. Puffiness – around ear and corner of the jaw. No temperature -37.3. Headaches usually but this time different. Usually right side of neck (but this time not). Not painful with movement, pain with yawning. Headache getting better Denied lymph node swelling or armpit swelling.	Ibuprofen for pain. Advised for her to see GP for examination and rule out an alternative cause for this including making sure no lymphadenopathy/dental or ear Seen by GP ? Salivary gland issue or TMJ issue	?BCG related	Resolved D22	Headache ?TMJ injury
1924 RCH	F	34	31/03/2020 BCG (2nd dose) and Influenza Vaccine	D51	20/5 (D51) Sore 'inside the left shoulder' with restricted left shoulder internal rotation. No lymphadenopathy, no fevers. Took day off work due to the restricted movement and pain in L shoulder. Advised to see GP. By D57 no pain, movement almost normal. Injection site history: D7 swelling at BCG injection site; increased until D50 was 1.5cm diameter 'lump' at BCG site, with 0.5cm height, soft and tender to touch. Some surrounding yellow bruising. Informal Ultrasound of BCG site (she is a radiographer): '1ml debris, mainly fluid'. D51 Smaller in size, firmer, never discharged.	GP assessment	unclear	Resolving D57 SAEFVC report 22/5/20 V2005-017803	3 (pain) left shoulder and restricted movement
1096 RCH	F	35	08/04/2020 BCG (2nd dose) and influenza vaccine	D55	1/6 (D55) gradual onset 'bony aching pain at rest left humerus', no restricted range of movement. 'Bony pain' had completely resolved next day (D56). However, also had tender left axilla extending to left shoulder/neck/breast at rest. Nil obvious history of trauma. BCG site photo appears okay. GP visit D58; no lymphadenopathy. Axillary tenderness much improved.	Paracetamol and codeine on D55	unclear	Resolved Gr3 pain D56 Resolving tenderness D58	3 (pain) left upper arm 3 (tenderness) axilla
3978 FSH	F	36	09/04/2020 BCG (3rd dose) and Influenza vaccine	D80	27/6 (D80) Initial BCG site reaction as expected. No large or accelerated reaction. Over the last week, increasing pain left BCG site region and shoulder extending to the neck. Restricting some movements "catches". However, still able to continue work. BCG site reported to have no increased redness or swelling and continuing to heal. Review clinically (8/7/2020)- BCG site looks healed, no fluctuant swelling. Minimally tender. Deltoid tender when palpated. Significant tenderness with palpation of the acromion area. Trapezius also tender with palpation. Range of movement full but painful. No obvious rotator cuff injury- abduction is normal. Nil LN. Denies any triggering events D/W Dr Manning (Site PI) - Agrees for imaging – left	Imaging ordered- Xray NAD. USS: 1.High grade partial tear in the superior insertional fibres of the subscapularis tendon on a background of mild-moderate tendinopathy. The tear is between 5 and 10mm in diameter and involves slightly more than 50% tendon thickness. 2.Small articular surface partial tear in the anterior insertional fibres of the supraspinatus on a background of mild tendinopathy. The tear is under 5mm in diameter and involves 25% or less of the tendon thickness. 3.Mild subacromial bursal thickening in	Unrelated to vaccine	Until D100	Mild subacromial bursitis

Participant ID number	Sex	Report no.	Date vaccinated and dose number	Onset following vaccination	Description of adverse event	Treatment	Reaction Review BCG/Flu	Outcome	Local reaction Grade
					shoulder Ultrasound and X-ray. Pain duration 20 days	keeping with mild bursitis. Slight bursal bunching on abduction may indicate impingement. 4.Mild tenderness and capsular thickening at the AC joint. 5.No abscess / collection. Follow up with GP/sports physician			
1090 RCH	F	37	01/04/2020 BCG (1st dose) and influenza vaccine	~D30	Significant discomfort at rest documented in 3-month diary. States developed an 'abscess' that began drainage on May 3 2020. Need further details from participant to confirm- not provided.	2 courses of flucloxacillin. Unclear if analgesia taken	BCG	Resolved	3 (tenderness) Possibly abscess- not confirmed.
1637 RCH	M	38	31/03/2020 BCG (3rd dose) and influenza vaccine	D35	Inflammation, firm swelling at vaccine site since D35 (4/5/20), ~min 3cm diameter (50cent size) in redness and swelling. Tender to touch. Initially overlying redness, then redness only in perimeter. Never discharged, no associated lymphadenopathy. Firm swelling present for ~3months, then self-resolved. Vaccinator training; no vaccine bleb photo available.	Observation	BCG	Resolved D125	Local reaction: firm swelling ~3cm diameter at BCG site persistent for 3 months
2372 RCH	F	39	06/04/2020 BCG (1st dose) and influenza vaccine	~D90	Vaccine site was swollen and red from week 1(max swelling documented within first 3 months was 4cm). In July (~D90) a lot of pus came out one day when she pressed it, however it still seemed swollen underneath. It subsequently felt like a "hard bump". It did not affect her daily activities, but sometimes mildly tender to touch. She was always systemically well, no regional lymphadenopathy. Her GP removed lesion in his rooms (29/07/20) with local anaesthetic- sent for histopathology- 'necrotising granulomatous inflammation' of the dermis'. She subsequently (26/10/20) has a 2cm healing scar at the site.	One week course of amoxicillin with GP in July (~D90); the site remained unchanged. 29/07/20 (D114): GP excised vaccine site lesion with local anaesthetic- sent for histopathology- 'necrotising granulomatous inflammation' of the dermis'	BCG	Resolved D114	Local reaction, firm persistent swelling at BCG site ?granuloma (firmness ~D90)
2024 RCH	F	40	31/03/2020 BCG (2nd+ dose) and influenza vaccine	D10	Pain D10-D14 at vaccine site, prevented daily activities. Discomfort with movement. No pain meds used. No pain beyond D14.	Observation. No meds.	BCG	Resolved D14	3 (pain)
1618 RCH	F	41	31/03/2020 BCG (2nd+ dose) and influenza vaccine	~D60	Disseminated granuloma annulare. Onset of red bite-like lesion on buttock approx May June 2020. Not anywhere near vaccine site. Over the next few months, progressively more lesions spreading throughout body (mainly abdomen, legs), became red larger, pale centre, flat lesions. Not painful. A bit itchy. Skin biopsy ~March 2021, dx confirmed by dermatologist.	Hydroxycholoroquine from 1 April 2021	?BCG	Ongoing	
7849 SCGH	F	42	29/04/2020 BCG (1st dose)	D1	Significant discomfort at rest D1-7 at influenza vaccine site	Observation	Influenza	Resolved D7	3 (tenderness)

Participant ID number	Sex	Report no.	Date vaccinated and dose number	Onset following vaccination	Description of adverse event	Treatment	Reaction Review BCG/Flu	Outcome	Local reaction Grade
			and influenza vaccine						
8732 SCGH	M	43	28/04/2020 BCG (2nd+ dose) and influenza vaccine	D1	Pain on D1. Prevented daily activities	Observation	Influenza	Resolved D1	3 (pain)
7430 PCH	F	44	29/04/2020 BCG (1st dose) and influenza vaccine	D1	Pain on D1 and D2 at influenza vaccine site Prevented daily activities	Observation	Influenza	Resolved D2	3 (pain)
3912 FSH	F	45	09/04/2020 BCG (1st dose) and influenza vaccine	D1	Significant discomfort at rest reported by participant at influenza site.	Observation	Influenza	Resolved D3	3 (tenderness)
4163 FSH	F	46	14/04/2020 BCG (1st dose) and influenza vaccine	D1	Significant discomfort at rest report by participant at influenza vaccine site. tender D1-D2	Observation	Influenza	Resolved D2	3 (tenderness)
3721 PCH	F	47	09/04/2020 BCG (1st dose) and influenza vaccine	D20	Significant discomfort, ~day 20 to about 4 weeks. This was at rest and caused being aware of how she slept.	Observation, PRN paracetamol	BCG	Resolved D28	3 (tenderness)
6298 PCH	F	48	17/04/2020 BCG (2ndose) and influenza vaccine	D4	Significant discomfort at rest D4 to D30	Paracetamol for 7 days	BCG	Resolved D30	3 (tenderness)
6552 PCH	F	49	22/04/2020 BCG (1st dose) and influenza vaccine	D1	Significant discomfort at rest for D1, preventing swimming/running as felt throbbing at site	Paracetamol for 1 day	BCG	Resolved D2	3 (tenderness)
7225 PCH	F	50	16/04/2020 BCG (2ndose) and influenza vaccine	D1	Significant discomfort at rest, used paracetamol and ibuprofen for 4 days	Paracetamol and ibuprofen 4 days	BCG	Resolved D4	3 (tenderness)
7633 PCH	F	51	23/04/2020 BCG (2ndose) and influenza	D16	Significant discomfort at rest D16-D20, painful when oozed pus.	Observation	BCG	Resolved D20	3 (tenderness)

Participant ID number	Sex	Report no.	Date vaccinated and dose number	Onset following vaccination	Description of adverse event	Treatment	Reaction Review BCG/Flu	Outcome	Local reaction Grade
			vaccine						
7946 PCH	F	52	20/04/2020 BCG (2ndose) and influenza vaccine	D1	Significant discomfort at rest for 1 week, preventing riding to work	Panadeine for 1 day	BCG	Resolved D7	3 (tenderness) 3 (pain)
8290 PCH	F	53	21/04/2020 BCG (1st dose) and influenza vaccine	D7	Significant discomfort at rest (tenderness; throbbing and hot mainly at night) for 1 week used paracetamol, then tenderness until D30	Paracetamol for 1 week	BCG	Resolved D14	3 (tenderness)
8369 PCH	F	54	22/04/2020 BCG (1st dose) and influenza vaccine	D8	Significant discomfort at rest D8-14	Observation	BCG	Resolved D14	3 (tenderness)
4046 FSH	M	55	09/04/2020 BCG (2nd dose) and influenza vaccine	D1	Significant discomfort at rest D1-3, preventing daily activities	Observation	BCG	Resolved D3	3 (tenderness)
7366 FSH	F	56	16/04/2020 BCG (1st dose) and influenza vaccine	D4	Significant discomfort at rest onset D4 for 2 weeks	Paracetamol for 4 days	BCG	Resolved D18	3 (tenderness)
7543 SCGH	F	57	20/04/2020 BCG (2nd dose) and influenza vaccine	D8	Significant discomfort at rest and pain with associated inability to perform daily tasks	Paracetamol 7 days	BCG	Resolved D15	3 (tenderness, pain)
8600 SCGH	F	58	24/04/2020 BCG (2nd dose) and influenza vaccine	D1	Significant discomfort at rest on and off for 30 days, with use of paracetamol or paracetamol/ibuprofen. The pain at rest was like knife stabs. The vaccination site remained tender to touch for approx 80-90 days post injection with slow progressive improvements over time- the stabbing pain reduced to tender on touch to no pain (over the 3 months).	Paracetamol+/-ibuprofen 30 days	BCG	Resolved D30	3 (tenderness)

Participant ID number	Sex	Report no.	Date vaccinated and dose number	Onset following vaccination	Description of adverse event	Treatment	Reaction Review BCG/Flu	Outcome	Local reaction Grade
5894 SCGH	F	59	17/04/2020 BCG (1st dose) and influenza vaccine	D3	Pain at BCG vaccine site D3-D4. Used Dolased (codeine-containing) for one day	Dolased (codeine-containing) for 1 day	BCG	Resolved D4	3 (pain)
2610 RCH	F	60	03/04/2020 BCG (1st dose) and influenza vaccine	D2	Significant discomfort at rest D2-D5 that did not interfere with daily activities.	Observation	BCG	Resolved D5	3 (tenderness)
4445 FSH	F	61	16/04/2020 BCG (2nd dose) and influenza vaccine	D5	Significant discomfort at rest D5-D12. Tenderness settled by D16-D17	Paracetamol and ibuprofen for 7 days	BCG	Resolved D12	3 (tenderness)
5912 PCH	F	62	16/04/2020 BCG (2nd dose) and influenza vaccine	D1	Significant discomfort at rest. Tenderness experienced D1-D14	Observation	BCG	Resolved D14	3 (tenderness)
6030 PCH	F	63	03/04/2020 BCG (1st dose) and influenza vaccine	D3	Significant discomfort at rest. Tenderness experienced D--D14	Paracetamol and ibuprofen for 2 days	BCG	Resolved D14	3 (tenderness)
6120 PCH	F	64	16/04/2020 BCG (2nd dose) and influenza vaccine	D1	Significant discomfort at rest. Tenderness experienced D1—D60	Observation	BCG	Resolved D60	3 (tenderness)
6201 SCGH	M	65	16/04/2020 BCG (2nd dose) and influenza vaccine	D4	Significant discomfort at rest. Tenderness experienced D4-12	Observation	BCG	Resolved D12	3 (tenderness)

8542 PCH	F	66	23/04/2020 BCG (1st dose) and influenza vaccine	D4	Pain preventing daily activity D1&D2	Observation	BCG	Resolved D2	3 (pain)

Table 3: Summary report participants reviewed in Specialist Immunisation Clinic/Specialist Clinic; 30 March 2020 to 16 March 2022

Participant ID number	Sex	Report no.	Date vaccinated and dose number	Onset following vaccination	Description of adverse event	Treatment	Reaction Review BCG/Flu	Outcome	Local reaction Grade
1426 RCH	F	1	31/03/2020 BCG (2nd dose) and influenza vaccine	D12	Onset D12 (11/4/20) tender BCG injection site (max swelling size diameter recorded 2cm), that discharged ooze. D14 appeared healing. Reviewed by Dr Crawford (SAEFVIC Director and BRACE medical doctor) in clinic on 14/4/20 (D15); consistent with healing local injection site abscess.	Observation	BCG	Resolved D243	Abscess
5429 SCGH (2nd AE)	F	2	14/04/2020 BCG (1st dose) and Influenza vaccine	D2	Reported lymphadenopathy/pain post vaccination within first 48 hours but resolved when called on 16/04/2020. BCG site still active – expected BCG reaction. Review organised after speaking with PI (Dr Lucas) and Dr Justin Waring (Medical Director of the WA TB service). Concerning symptoms: Genuine night sweats- on and off since the vaccination -Not every night but when it happens, then she needs to change her night dress/sheets. Lethargy (a few have reported this as a symptom), Cough- dry since one week ago. Currently taken a day off from work as feels unwell. Also concerning on history was that she thought that might have had TB when returned from travel to Burma in 2014. Felt unwell at the time– night sweats, 10kg weight loss, persistent cough – no investigation for potential TB infection at the time and resolved. However, she feels the same now and cough similar.	Review by TB specialist – CXR-normal. Bloods- QIFN not known CT chest to rule out ?miliary lesion – not doing it anymore as symptoms resolved. SAR-CoV2 PCR Negative	BCG Cough-causality pending	Cough and night sweats (Resolved D40) CT scan – declined	Lymphadenopathy – Axillary Likely accelerated BCG reaction Cough- persistent
1147 RCH (2nd AE)	F	3	2/04/2020 BCG (1st dose) and Influenza vaccine	D50	Burning pain at injection site at rest, and participant unsure about lymph gland L axilla; she asked for in-person review. Reviewed by Dr N Crawford 2/6: BCG site appears ok; no fluctuance, some focal tenderness, minimal erythema. No axillary lymphadenopathy, no neurological symptoms/signs. Impact is discomfort; cannot sleep on that side. Not affecting work/ADLs. Strong family hx breast cancer, has regular screening and previous procedures. Understandable participant anxiety regarding getting an infection on L side. Reassurance provided for vaccine site. Routine f/u with GP as planned (part of screening routine). Ongoing contact with BRACE.	Observation	BCG	3 (tenderness) resolved D60	3 (tenderness)
1921 RCH	F	4	31/03/2020 BCG (2nd dose) and influenza vaccine	D30	Previous AEs for significant tenderness at rest D1-D5, and injection site abscess onset D30, pus discharge D31. Missed day off work due to localised pain and pus D31. Subsequent healing of injection site. On D66, participant requested clinical review due to concern regarding ongoing "redness and pain when bumped lightly into anything". Reviewed by Dr Crawford and SAEFVIC fellow; site appears ok. No new AE.	Observation	BCG	Resolved D63	Healing injection site

Abbreviations

AEFI	Adverse event following immunisation	LN	Lymph node
BCG	Bacille Calmette-Guérin	LTBI	Latent tuberculosis infection
BD	Twice daily	MET	Medical Emergency Team
BPM	Beats per minute	MHU	Mental Health Unit
BPM	Beats per minute	MMC	Monash Medical Centre, Victoria
CXR	Chest X-ray	NA	Not applicable
D	Day	NAD	No abnormalities detected
Diam	diameter	NSAID	Non steroid anti-inflammatory drugs
ECG	Electrocardiograph	RCH	Royal Children's Hospital Melbourne
ED	Emergency Department	RR	Respiratory rate
FSH	Fiona Stanley Hospital, WA	SAE	Serious adverse event
Gr	Grade	SAEFVIC	Surveillance of Adverse Events Following Vaccination In the Community
GSC	Glasgow Coma Scale	SCH	Sir Charles Gairdner Hospital, WA
GP	General practitioner	SIS	Special immunisation clinic
Hx	Medical history	WA	Western Australia
ISR	Injection site reaction	WAVSS	Western Australian Vaccine Safety Surveillance system
IV	Intravenous	w/o	Without
QIFN	Quantiferon Gold Test		

Overview of all local reactions

Local reaction to vaccination are monitored using standardised diary completed by the participant up to 14 days after vaccination(s). The diary is sent to participants to complete just after randomisation, with reminders sent at day 5, 10, and 15 after vaccination(s).
Participants also complete a questionnaire at 3 months after vaccination(s) asking similar questions. These data are used to complete participants' previous answers with events that occurred beyond the 14-day period, and for those who did not complete the 14-day standardised diary.

A toxicity grading scale is used to categorise the reports (Food and Drug Administration 2007):

Local reaction	Grade 0 None	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Potentially life threatening
Pain	None	Does not interfere with activity	Repeated use of nonnarcotic pain reliever > 24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	Emergency room visit or hospitalization
Redness	None	2.5 - 5 cm	5.1 - 10 cm	>10 cm	Necrosis or exfoliative dermatitis
Tenderness	None	Mild discomfort to touch	Discomfort with movement	Significant discomfort at rest	Emergency room visit or hospitalization
Swelling / induration	None	2.5 - 5 cm and does not interfere with activity	5.1 - 10 cm or interferes with activity	>10 cm or prevents daily activity	Necrosis
Itch	None	Itching localised to injection site that is relieved spontaneously or in <48 hours of treatment	Itching beyond the injection site that is not generalised OR Itching localised to injection site requiring ≥48 hours of treatment	Generalised itching causing inability to perform usual social & functional activities	Not applicable

Adapted from Food and Drug Administration. (2007). "Guidance for Industry: toxicity grading scale for healthy adult and adolescent volunteers enrolled in preventive vaccine clinical"
Retrieved 08.04.2020, from
https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Vaccines/ucm091977.pdf.

Participants reporting any concern, or an event greater than moderate are contacted by phone.
As of 16 March 2022, 2714 participants have logged-in to report local reaction (97.5% in the BCG group, 93.3% in the no-BCG group). The proportion of participants reporting a local reaction event greater than moderate are 6.3% in the BCG group (88/1387) and 1.8% in the no-BCG group (24/1327).

The following tables summarise the local reaction to BCG and influenza vaccines in the first 3 months after vaccination(s).

BCG vaccination site	Total	No previous BCG	Previous BCG
N	1387	673	714
Pain	567 (40.9%)	262 (39.0%)	305 (42.7%)
None	820 (59.1%)	411 (61.1%)	409 (57.3%)
Grade 1	399 (28.8%)	194 (28.8%)	205 (28.7%)
Grade 2	155 (11.2%)	65 (9.7%)	90 (12.6%)
Grade 3	11 (0.8%)	2 (0.3%)	9 (1.3%)
Grade 4	2 (0.1%)	1 (0.2%)	1 (0.1%)
Duration [day]	3 (2-9)	3 (2-7)	4 (2-10)
Apparition day	2 (1-4)	2 (1-3)	2 (1-5)
Redness	1223 (88.2%)	572 (85.0%)	651 (91.2%)
None	164 (11.8%)	101 (15.0%)	63 (8.8%)
Grade 1	1171 (84.4%)	560 (83.2%)	611 (85.6%)
Grade 2	48 (3.5%)	11 (1.6%)	37 (5.2%)
Grade 3	4 (0.3%)	1 (0.2%)	3 (0.0%)
Grade 4	0 (0.0%)	0 (0.0%)	0 (0.4%)
Duration [day]	14 (11-30)	13 (9-28)	14 (12-30)
Apparition day	2 (1-3)	2 (1-3)	2 (1-3)
Maximal diameter [cm]	1.5 (1.0, 2.5)	1.3 (1.0, 2.0)	2.0 (1.0, 3.0)
Tenderness	1071 (77.2%)	497 (73.8%)	574 (80.4%)
None	316 (22.8%)	176 (26.2%)	140 (19.6%)
Grade 1	739 (53.3%)	362 (53.8%)	377 (52.8%)
Grade 2	272 (19.6%)	120 (17.8%)	152 (21.3%)
Grade 3	58 (4.2%)	14 (2.1%)	44 (6.2%)
Grade 4	2 (0.1%)	1 (0.2%)	1 (0.1%)
Duration [day]	3 (2-8)	6 (3-14)	9 (4-14)
Apparition day	2 (1-3)	1 (1-2.5)	2 (1-3)
Swelling	950 (68.5%)	405 (60.2%)	545 (76.3%)
None	437 (31.5%)	268 (39.8%)	169 (23.7%)
Grade 1	783 (56.5%)	341 (50.7%)	442 (61.9%)
Grade 2	157 (11.3%)	61 (9.1%)	96 (13.5%)
Grade 3	10 (0.7%)	3 (0.5%)	7 (1.0%)
Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)
Duration [day]	10 (4-14)	8 (3-14)	11 (6-14)
Apparition day	2 (2-4)	2 (1-4)	2 (2-4)
Maximal diameter [cm]	1.0 (1.0, 2.0)	1.0 (1.0, 2.0)	1.5 (1.0, 2.0)
Itch	673 (55.1%)	294 (50.1%)	379 (59.7%)
None	549 (44.9%)	293 (49.9%)	256 (40.3%)
Grade 1	635 (52.0%)	272 (46.3%)	363 (57.2%)
Grade 2	38 (3.1%)	22 (3.8%)	16 (2.5%)
Grade 3	0 (0.0%)	0 (0.0%)	0 (0.0%)
Duration [day]	10 (5-20)	7 (5-14)	10 (5-21)
Apparition day	4 (2-7)	4 (2-7)	4 (2-7)
Lymph node	48 (3.5%)	18 (2.7%)	30 (4.2%)

Data are presented as n (%) or median (interquartile range)

Influenza vaccination site	Total	BCG + Influenza vaccines	Influenza vaccine only
N	2714	1387	1327
Pain	792 (29.6%)	407 (30.0%)	385 (29.1%)
None	1887 (70.4%)	948 (70.0%)	939 (70.9%)
Grade 1	678 (25.3%)	350 (25.8%)	328 (24.8%)
Grade 2	109 (4.1%)	52 (3.8%)	57 (4.3%)
Grade 3	3 (0.1%)	3 (0.2%)	0 (0.0%)
Grade 4	2 (0.1%)	2 (0.1%)	0 (0.0%)
Duration [day]	2.0 (1.0, 2.0)	2.0 (1.0, 2.0)	1.0 (1.0, 2.0)
Apparition day	1.0 (1.0, 1.0)	1.0 (1.0, 1.0)	1.0 (1.0, 1.0)
Redness	180 (6.7%)	101 (7.5%)	79 (6.0%)
None	2499 (93.3%)	1254 (92.5%)	1245 (94.0%)
Grade 1	164 (6.1%)	95 (7.0%)	69 (5.2%)
Grade 2	15 (0.6%)	6 (0.4%)	9 (0.7%)
Grade 3	1 (<1%)	0 (0.0%)	1 (0.1%)
Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)
Duration [day]	2.0 (1.0, 3.0)	2.0 (1.0, 3.0)	2.0 (1.0, 3.0)
Apparition day	1.0 (1.0, 2.0)	1.0 (1.0, 2.0)	1.0 (1.0, 2.0)
Maximal diameter [cm]	1.0 (0.5, 3.0)	1.0 (0.5, 2.0)	2.0 (1.0, 5.0)
Tenderness	1634 (61.0%)	815 (60.1%)	819 (61.9%)
None	1045 (39.0%)	540 (39.9%)	505 (38.1%)
Grade 1	988 (36.9%)	552 (40.7%)	436 (32.9%)
Grade 2	627 (23.4%)	255 (18.8%)	372 (28.1%)
Grade 3	16 (0.6%)	6 (0.4%)	10 (0.8%)
Grade 4	3 (0.1%)	2 (0.1%)	1 (0.1%)
Duration [day]	2.0 (1.0, 3.0)	2.0 (1.0, 3.0)	2.0 (2.0, 3.0)
Apparition day	1.0 (1.0, 1.0)	1.0 (1.0, 1.0)	1.0 (1.0, 1.0)
Swelling	204 (7.6%)	84 (6.2%)	120 (9.1%)
None	2475 (92.4%)	1271 (93.8%)	1204 (90.9%)
Grade 1	159 (5.9%)	62 (4.6%)	97 (7.3%)
Grade 2	45 (1.7%)	22 (1.6%)	23 (1.7%)
Grade 3	0 (0.0%)	0 (0.0%)	0 (0.0%)
Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)
Duration [day]	2.0 (1.0, 3.0)	2.0 (1.5, 3.0)	2.0 (1.0, 2.5)
Apparition day	1.0 (1.0, 2.0)	1.0 (1.0, 2.0)	1.0 (1.0, 2.0)
Maximal diameter [cm]	2.0 (1.0, 3.5)	1.5 (1.0, 3.0)	2.0 (1.0, 4.0)

HREC no: 62586

BCG vaccination to Reduce the impact of COVID-19 in healthcare workers following Coronavirus Exposure (BRACE) Trial

Adverse Events Following Immunisation (AEFI)
BRACE Stage 2
Report number 24

Period covered: 14 May 2020 to 16 March 2022

Sponsor: Murdoch Children's Research Institute, represented by Lead Investigator Prof Nigel Curtis
Affiliation: Murdoch Children's Research Institute, The Royal Children's Hospital Melbourne
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Introduction

This is the is the 24th AEFI Report, covering the period from 14 May, 2020 (date of inclusion of the first participant) to 16 March 2022, for Stage 2 of the BRACE clinical trial on the administration of the Bacille Camette-Guérin (BCG) to healthcare worker during the COVID-19 pandemic. The primary objectives are to determine if BCG vaccination (Intervention) compared with no BCG vaccination (Comparator) reduces the incidence of COVID-19 disease (first co-primary outcome) and of severe COVID-19 disease (second co-primary outcome) measured over the 6 months following randomisation (Time) in healthcare workers exposed to SARS-CoV-2 (Participants).

In Stage 2, participants are randomised to receive BCG vaccine or placebo in a blinded setting. Blood samples are collected prior to randomisation, to determine previous SARS-CoV-2 exposure.

As of 16 March 2022, there were **3988** participants randomised in Stage 2 of the trial (**6828** BRACE total; Stage 1 and Stage 2).

The tables below give the details and a cumulative summary of adverse event reports received from Stage 2 participants. Participants unshaded, are new since report ending 1 September 2021.

A total of **224** AEFI were reported for this period and these are listed below.
To date there have been **31** SAE reported; 24 events that required hospitalisation (details in Table 1 below).
To date there have been **191** AE reported (details in Table 2 below; 2 fainting episodes, 4 systemic reactions, 185 local reactions). These include 3 referrals to a Specialist Immunisation Clinic (SIC)/ Specialist Clinic.

Table 1: Summary report of serious adverse events received for the BRACE study for the period 14 May 2020 to 16 March 2022

Participant ID number and Site	Sex	Report no.	I/S	Date of vaccination and PHx of BCG	Onset following vaccination (incl date)	Description of adverse event	SAE type	Treatment	*Relationship to vaccine Site Investigator (S) assessment MCRI Sponsor (M) assessment	°Severity of AE	Outcome (incl date resolved)	Date of last contact with participant
10118 CHW	F	1	I	7/07/2020 PHx: 1 BCG, >5y ago	D29 (04/08/20)	3-day hospitalisation (4/8/20-6/8/20) for cellulitis secondary to a cat scratch on her right hand. No associated lymphadenopathy or fever at any stage. ISR healing well. Seen by plastics team on Monday 10/08/20 for hand.	3	Hospitalisation: treated with IV then oral antibiotics	(S) Unrelated (M) Unrelated	Severe	Discharged home 6/8/20. subsequently completed oral antibiotics by 12/8/20; no ongoing concerns.	12/8/20
12549 Antonius NL	F	2	I	24/09/2020	D5 (28/09/20)	Discovered lump in right breast, for which referral to breast specialist. Pathology results from biopsy showed presence of breast cancer.	7	Chemotherapy in first instance.	(S) Unrelated (M) Unrelated	Severe	Unblinding and withdrawal from study on 5/10/20 (day 13)	5/10/2020
15304 Exeter UK	F	3	I	24/11/2020 PHx: 1 BCG, >5y ago	D21 (14/12/20)	Developed injection site **abscess** with pus discharge (approx. 80ml) and systemic symptoms. Hospitalisation started 14/12/20-15/12/20 Discharged home on IV antibiotics Represented to hospital on 19/12/20. Plastics team review. Referred to immunology for assessment. Ongoing medical f/u and investigations.	3	Hospitalisation: treated with IV flucloxacillin and gentamicin, IV fluids	(S) Probable (M) Probable	Severe	SUSAR Unblinding on 20/12/20 at request of treating physician. Resolved D37 (30/12/20)	20/12/2020
14609 MS Brazil	F	4	I	7/11/2020 PHx: 1 BCG, >5y ago	D23 (1/12/20)	COVID-19, hospitalised since 06/12 08/12 - ICU and mechanical ventilation	2	Hospitalisation: ICU	(S) Unrelated (M) Unrelated	Life-threatening	Death 25/12/2020	26/12/20 - her son
14275 MS Brazil	M	5	I	30/10/2020 PHx: 1 BCG, >5y ago	D23 (22/11/20)	Participant presented acute vomiting, diarrhea and dehydration. He was hospitalized for 1 day.	3	Hospitalisation for hydration	(S) Unrelated (M) Unrelated	Severe	Discharged home 23/11/2020	15/12/2020
15960 MS Brazil	M	6	I	26/11/2020 PHx: 1 BCG, >5y ago	D19 (16/12/20)	COVID-19, hospitalised in non-invasive ventilation	2	Hospitalisation	(S) Unrelated (M) Unrelated	Life-threatening	Discharged home 23/12/2020	23/12/2020
15886 MS Brazil	F	7	I	25/11/2020 PHX: No BCG	D 27 (22/12/20)	COVID-19, hospitalised in non-invasive ventilation	2	Hospitalisation	(S) Unrelated (M) Unrelated	Life-threatening	Discharged home 25/11/2020	24/12/2020
14994 MS Brazil	M	8	I	14/11/2020 PHx: 1 BCG,	D 42 26/12/20	COVID-19, hospitalized since 26/12 02/01 - ICU and mechanical ventilation	2	Hospitalisation: ICU	(S) Unrelated (M) Unrelated	Life-threatening	Discharged home	01/04/2021

				>5y ago							01/04/2021	
13696 HUGTiP ESP	F	9	I	22/10/2020 PHx: no BCG	D90 20/01/21	COVID-19 pneumonia, hospitalized from 20/01/21 until 25/01/21	3	Hospitalisation	(S) Unrelated (M) Unrelated	Severe	Discharged home 25/01/2021	25/01/2021
12243 St Antonius NL	M	10	I	15/09/2020 PHx: no BCG	D67 21/11/20	Acute appendicitis, hospitalised from 21/11/20 until 22/11/20	3	Hospitalisation	(S) Unrelated (M) Unrelated	Severe	Discharged home 22/11/20	18/01/2021
16882 MS Brazil	M	11	I	10/12/2020 PHx: 1 BCG, >5y ago	D 46 (24/01/20)	24/01 COVID-19, hospitalized 29/01- ICU and mechanical ventilation	2	Hospitalisation	(S) Unrelated (M) Unrelated	Life-threatening	Discharged home 11/02/2021	17/02/2021
12893 Amphia Breda NL	F	12	I	08/10/2020 PHx: no BCG	D67 (11/12/20)	Cardiac symptoms, related to underlying chronic disease, hospitalised from 11/12/20 until 14/12/20	3	Hospitalisation	(S) Unrelated (M) Unrelated	Severe	Discharged home 14/12/20	01/02/2021
15196 Rio Brazil	F	13	I	16/11/2020 PHx: 1 BCG, >5y ago	D87 (13/02/21)	6-day hospitalisation (13/02/2021-19/02/2021) for ankle fracture secondary to being run over.	3	Hospitalisation: ankle surgery (right tibia)	(S) Unrelated (M) Unrelated	Severe	Discharged home 19/02/2021	19/02/2021
17290 MS Brazil	F	14	I	19/12/2020 PHx: 1 BCG, >5y ago	(01/03/21)	Covid-19, hospitalized shortness of breath and decompensated diabetes (ketoacidosis)	2	Hospitalisation: ICU	(S) Unrelated (M) Unrelated	Life-threatening	Discharged home 10/03/2021	10/03/2021
13966 MS Brazil	F	15	I	07/11/2021 PHx: 1 BCG, >5y ago	(27/02/21)	Hospitalised for breathlessness. Suspected Covid, but after examinations confirmed pulmonary thrombosis	2	Hospitalisation	(S) Unrelated (M) Unrelated	Life-threatening	Discharged home 03/03/2021	03/03/2021
17311 Rio Brazil	F	16	I	18/12/2020 PHx: 1 BCG, >5y ago	D72 (27/08/21)	6-day hospitalisation (27/FEB/2021-05/MAR/2021) for femur fracture secondary to fall skate	3	Hospitalisation: hip surgery (left femur)	(S) Unrelated (M) Unrelated	Severe	Discharged home 05/03/2021	16/03/2021
11775 Westmead	M	17	I	04/09/2020 PHx: 1 BCG, >5y ago	D53 (27/10/20)	Overnight admission to ICU following planned surgery for removal of wires from previously fractured patellar & Trans urethral resection of prostate	4	Hospitalisation, ICU; blood tests, cardiac ECHO, right leg doppler, CXR.	(S) Unrelated (M) Unrelated	Life-threatening	Discharged home 21/11/21	23/03/2021
11775 Westmead	M	18	S	04/09/2020 PHx: 1 BCG, >5y ago	D79 (22/11/20)	4 nights of observation in hospital for haematuria, fever post TURP	3	Hospitalisation; urinary tract ultrasound, CXR, MSU, blood cultures.	(S) Unrelated (M) Unrelated	Severe	Discharged home 26/11/21	23/03/2021
19313 Rio Brazil	M	19	I	13/02/2021 PHx: 1 BCG, >5y ago	D39 (23/03/21)	3-day hospitalisation (23/MAR/2021-26/MAR/2021) for myocardial infarction	3	Hospitalisation: subcutaneous and oral medications ,	(S) Unrelated (M) Unrelated	Severe	Discharged home 26/03/21	30/03/2021
18008 MS Brazil	M	20	I	07/01/2021 PHx: 1 BCG, >5y ago	29/03/2021	Hospitalized due Dengue with complications	2	Hospitalisation	(S) Unrelated (M) Unrelated	Life-threatening	Discharged home 01/04/2021	12/04/2021

18484 MS Brazil	F	21	I	19/01/2021 PHx: 1 BCG, >5y ago	19/04/2021	Hospitalized with cough, shortness of breath. 2 covid tests - negative	2	Hospitalisation	(S) Unrelated (M) Unrelated	Severe	Discharged home 22/04/2021	28/04/2021
17384 MS Brazil	M	22	I	20/12/2020 PHx: 2 BCG, >5y ago	15/03/2021	Covid-19, hospitalized shortness of breath	2	Hospitalisation	(S) Unrelated (M) Unrelated	Life-threatening	Discharged home 30/03/2021	16/03/2021
14680 MS Brazil	M	23	I	06/11/2020 PHx: 1 BCG, >5y ago	30/01/2021	Hospitalized for appendicitis, with emergency surgery	3	Hospitalisation	(S) Unrelated (M) Unrelated	Severe	Discharged home 01/02/2021	02/06/2021
19279 Brazil Amazonas	F	24	I	12/02/2021 PHx: 1 BCG, >5y ago	D37 (20/03/2021)	3-day hospitalisation (20/03/2021-23/03/2021) for epigastric pain	3	Hospitalisation: symptomatic treatment	(S) Unrelated (M) Unrelated	Severe	Discharged home 23/03/2021	08/07/2021
9425 Monash	F	25	I	02/06/2020 PHx: No BCG	19 (21/06/21)	Hospitalisation for 5 nights. Abdominal pain- Gallstone blocking bile duct.	3	Hospitalisation: Surgery to remove gallstones	(S) Unrelated (M) Unrelated	Severe	26/6/20 discharged home	22/07/2021
12679 NL	F	26	I	01/10/2020	28 28/12/2020	Prolonged hospitalisation due to complication following Endoscopic submucosal dissection for removal of a rectal carcinoma (T1 stage).	3	Surgery successful regarding removal of carcinoma, pt does not require chemo- or radiotherapy.	(S) Unrelated (M) Unrelated	Severe	Recovered or resolved without sequelae, 30/12/2020	04/10/2021
9675 CHW NSW	F	27	I	18/09/20 PHx: No BCG	D77 (03/09/2020)	Overnight stay in Emergency Department (ED) with ? Crohn's disease following months of investigations by GP	3	Faecal calprotectin test. Subsequent colonoscopy 22/09/20 diagnosed Inflammatory Bowel Disease (Crohn's disease)	(S) Unlikely (M) Unlikely	Severe	Discharged home 04/09/20	28/10/2021
18398 MS Brazil	F	28	I	09/01/2021 PHx: 1 BCG, >5y ago	D87 06/04/2021	Hospitalization for kidney infection	2	Hospitalisation	(S) Unrelated (M) Unrelated	Severe	Discharged home 09/04/2021	27/10/2021
18103 MS Brazil	F	29	I	09/01/2021 PHx: 1 BCG, >5y ago	D63 12/03/2021	Hospitalization for psychiatric illness - depression	2	Hospitalisation	(S) Unrelated (M) Unrelated	Life-threatening	Discharged home 26/03/2021	27/10/2021
14093 MS Brazil	F	30	I	26/10/2020 PHx: 1 BCG, >5y ago	D3 29/10/2020	Hospitalization for vascular catheterization; portocath removal, which was inserted in 2017 during mx of breast cancer. Participant fell in pool and damaged portocath	2	Hospitalisation	(S) Unrelated (M) Unrelated	Severe	Discharged home 30/10/2020	08/12/2021
19102 Rio Brazil	F	31	I	04/02/2021 PHx: 1 BCG, >5y ago	D15 18/02/2021	Hospitalisation. Participant had a domestic knife incident causing a blunt cut injury to left hand-> left index finger paresthesia. Admitted for exploratory surgery for neurological	3	Hospitalisation	(S) Unrelated (M) Unrelated	Severe	Discharged home 19/02/2021	29/09/2021

						damage. In the same surgery, the carpal tunnel was released.						

I/S = index / subsequent

SAE type = Criteria for seriousness

1. Resulted in death
2. Immediately life-threatening
3. Requires inpatient hospitalisation (i.e. minimum overnight admission, that is non-elective).
4. Results in prolongation of existing hospitalisation
5. Results in persistent or significant disability/incapacity
6. Is a congenital anomaly/birth defect
7. In the medical judgment of the treating physician and/or investigator, it may jeopardise the participant or require intervention to prevent one of the above outcomes

°Severity of SAE:

- Severe (Severe medically significant but not immediately life threatening)
- Life-threatening (**immediately** life-threatening (not 'hypothetically life-threatening if more severe'), urgent intervention)
- Death related to adverse event

Table 2: Summary report of adverse events reported 14 May 2020 to 16 March 2022
***Note one report may have included several events**

Participant ID number	Sex	Report no.	Date of vaccination and PHx of BCG	Onset following vaccination	Description of adverse event	Treatment	Relationship to vaccine *	Outcome	Local reaction Grade
Fainting episodes on randomisation day									
10717 UMCU NL	M	1	06/08/2020 PHx: no BCG; 2016 fainting after vaccination	D1	Developed dizziness and clammy skin, had relatively low pulse (+/- 60 bpm), and became pale 5-10 min after the injection. After laying down for +/- 15-20 min and consuming some food and beverage, symptoms resolved. Discharged after 15 min of observation without recurrence of symptoms.	Observation	Unrelated	Resolved D1	NA
11235 RCH	F	2	No vaccine given	NA	Onset 20/8/20, whilst having blood taken (no vaccine given), participant felt dizzy, clammy, hyperventilating. Total duration of episode <20 minutes. Episode occurred in RCH pathology; MET Call. Recovered 20/8/20 same day following period of rest, and she went back to work. Blood test performed by MET Call team revealed participant is pregnant; ineligible for vaccine.	Observation	NA	Resolved 20/8/20	NA
Systemic adverse event									
11123 UMCU NL	F	1	18/08/2020 PHx: No BCG	D1	From the day of vaccination until day 3: urticaria on the left arm. On day 3 generalized pruritis (punctum max vaccination site), could not sleep due to itchiness. Started on day 4 with desloratadine (antihistamine), itchiness decreased slowly, on day 6 itchiness resolved. Vaccination site: no redness at vaccination site, no regional lymph nodes.	Antihistamine	Possible	Resolved D6	NA
11311 POW	F	2	07/09/2020 PHx: 1 BCG, >5yo	D1	Low grade fever to 37.7. Feels systemically well. No intercurrent illness. No lymphadenopathy. 2cm redness at injection site.	Symptomatic management	Possible		
10300 Westmead	F	3	21/07/2020 Phx: no BCG	D9	"Bouts of dizziness". Reviewed by Infectious Diseases team, examined well.	Observation	Unlikely		
14994 MS Brazil	M	4	13/11/2020 PHx: 1BCG, >5y ago	D9 22/11/2020	Episode of high fever, mental confusion, psychomotor agitation - febrile delirium? He is a doctor and was working in the emergency room. he was attended by colleagues, collected exams. vaccine scar - ok the cause of the fever has not been clarified, due to symptoms and complementary exams	Observed	Unlikely	Resolved	

Participant ID number	Sex	Report no.	Date of vaccination and PHx of BCG	Onset following vaccination	Description of adverse event	Treatment	Relationship to vaccine *	Outcome	Local reaction Grade
Local adverse event									
Abscess at injection site									
9037 Epworth	F	1	21/05/2020 PHx: 1 BCG, >5y ago	D17	Local reaction started D3-D4. Increased injection site redness, swelling from D17 (~6/6/20), max ~1.5cm diameter, discharged pus, some tenderness. Crusty core came off D20. Reviewed in ID clinic D22.	Observation	Definite	Resolved D29	Abscess
10293 Westmead	F	2	14/07/2020 PHx: 1 BCG in 1995	D5	Redness from D3, swelling from D5, pain from D8, on D10 was ~1cm and 'pointing' with no discharge. Concerned & requesting review. Systemically well. Significant discharge on D16. **Max size 2cm**	ID review	Definite	**Resolved D49**	Abscess 3 (tenderness)
9843 CHW	F	3	23/06/2020 PHx: No BCG	D27	Swelling since ~D27, worsened from D33-D37, discharge of pus on D37, presented to ED and was swabbed + commenced flucloxacillin. Size 3cm diameter.	ED presentation: flucloxacillin	Definite	**Resolved D115**	Abscess
15905-2 UMCU NL	F	4	04/08/2020 PHx: No BCG	D14	New onset of swelling, tenderness and burning sensation at vaccination site (after initial local site reaction to vaccination was almost over). No regional lymphadenopathy. On day 17, localized swelling at vaccination site, 2x3cm in size, red, warm, firm and tender to touch. No systemic symptoms. On day 19, discharge of pus. Symptoms improved thereafter.	Analgesia and cooling	Definite	Resolved D57	Abscess 3 (tenderness)
11410 Randwick	F	5	31/8/20 Phx: 1 BCG, >5y ago	D5	Injection site abscess, tender and small amount of discharge on D7. No lymphadenopathy. Size 1.5cm diameter	Observation	Definite	Resolved **D19**	Abscess
9744 CHW	M	6	23/6/20 Phx: 1 BCG, > 5y ago	D2	Reports abscess 1.5cm, seen by external doctor and drained, treated with 10/7 cefazolin. Now well healed.	Oral flucloxacillin **and drainage**	Definite	Resolved **D22**	Abscess
12354 Antonius NL	M	7	15/09/2020 PHx: No BCG	D38	New onset of an abscess-like lesion at the vaccination site on day 38. Lesion was warm, tender to touch, and about 1.5-2 cm in diameter. Around day 58, lesion discharged spontaneously. Currently (day 72), the wound is still red and oozing pus. No swollen lymph nodes, no systemic symptoms. No antibiotics used, but participant did use non-narcotic pain killers.	Observation and analgesia	Definite	Resolved **D77**	Abscess
13939 MS Brazil	M	8	04/11/2020 PHx: 1BCG, >5y ago	D26	PAIN, redness and swelling in the first day 1/12/20. Swelling fluctuant day 3 - evaluated in person and the process in resolution, diameter 2 cm. Spontaneous drainage day 4	Observation	Definite	Resolved D30	Abscess
14318 HU Marques	F	9	19/11/2020 PHx: No BCG,	D14	D14 Participant reports pain, tenderness, redness 5 cm, swelling 3cm. Picture showing abscess.	Observation and analgesia	Definite	Resolved D90	Abscess 3 (tenderness)

Participant ID number	Sex	Report no.	Date of vaccination and PHx of BCG	Onset following vaccination	Description of adverse event	Treatment	Relationship to vaccine *	Outcome	Local reaction Grade
Valdecilla, SP					Consulted medical doctor (site PI) and is being followed up at primary care. Contacted D30, still some discharge but improving.				
11955 Rijnstate NL	F	10	03/09/2020 PHx: No BCG	D22	D22 Three weeks after vaccination start of abscess and swelling. Abscess stopped 10 December. Now dry and red color. No pain. 1 cm.	Observation	Definite	Resolved D43	Abscess
18760 Rio Brazil	M	11	28/01/2021 PHx: 1 BCG, >5y ago	D**7** 02/02/2021	Significant local reaction with abscess onset D6, with severe deep pain radiating into muscle, preventing participant from moving arm and performing daily activities. Max abscess size 1.5cm (erythema, swelling). He used local warm compress, leading to spontaneous discharge after 12hr. Continues without pain, swelling, only with ulcerated lesion with purulent secretion.	Observation	Probable	**Resolved D108 (16/05/2021 pus drainage ceased)**	Abscess 3 (pain),3 (swelling/induration)
14460 MS Brazil	F	12	11/11/2020 PHx: 1BCG, >5y ago	D**17** **27**/11/2020	PAIN, redness and swelling in the first day, Swelling fluctuant day 3. Spontaneous drainage day 3. sought medical service and performed wound cleansing. 2cm diameter.	Observation	Definite	Resolved D22	Abscess
13900 MS Brazil	F	13	11/11/2020 PHx: 1BCG, >5y ago	D29 11/12/2020	PAIN, redness and swelling in the first day, Swelling fluctuant day 3. Spontaneous drainage day 5. 2cm diameter.	Observation	Definite	Resolved D34	Abscess
15485 Mutua Terrassa, SP	F	14	19/11/2020 PHx: no BCG,	D20 09/12/2020	Fluctuant erythema, pain. 1x1.5 cm. Surgical drainage.	Surgical excision and amoxicillin+clavulanic acid	Definite	Resolved D**82**	Abscess
Lymphadenopathy									
9250 Epworth	F	1	22/05/2020 PHx: 1 BCG, >5y ago	D5	Developed 1cm lymph node left axilla, not tender, not red, no discharge. No concerns with her vaccination site.	Observation	Probable	Resolved D11	LA, left axilla
9495 Monash	F	2	04/06/2020 PHx: 1 BCG, >5y ago	D4	Onset D4 left axilla tender LA (max 0.3cm diameter), left submandibular LA (max 0.1cm diameter) , self-resolved by D7. No concerns with her vaccination site.	Observation	Probable	Resolved D7	LA, left axilla and left submandibular area
9425 Monash	F	3	02/06/2020 PHx: No BCG	D4	Onset D4 left axilla mild tender LA (max 3cm diameter), self-resolved D11. Also initial significant discomfort at rest at vaccine site D3-D5 (especially at night time unable to sleep on left side), no pain medications, self-resolved	Observation	Probable	Resolved D11 (LA) and D5 (Gr3 tenderness at vaccine site)	LA, left axilla and 3 (tenderness) at vaccine site
9469 Monash	F	4	02/06/2020 PHx: 1 BCG, >5y ago	D12	Onset D12 left cervical lymph node (max 1cm diameter), self-resolved within a day.	Observation	Possible	Resolved D13	LA, left cervical
9812 CHW	F	5	19/06/20 PHx: 1 BCG, 1-	D2	Axillary LA 4cm with associated pain, self-resolved within a day. Seen by GP	Observation	Probable	Resolved D3	LA, left axilla

Participant ID number	Sex	Report no.	Date of vaccination and PHx of BCG	Onset following vaccination	Description of adverse event	Treatment	Relationship to vaccine *	Outcome	Local reaction Grade
			5y ago						
9766 CHW	F	6	18/06/2020 PHx: No BCG	D3	Axillary LA 2cm, 1cm ISR. LA resolved over a week	Observation	Probable	Resolved D7	LA, left axilla
10378 Westmead	M	7	22/07/20 PHx: 1 BCG in childhood	D2	Reported axillary LA 1cm, achy arm, felt tired on D3, small ISR. Symptoms all improving now.	Observation	Probable	Resolved D5	LA, left axilla
10327 CHW	M	8	22/07/20 PHx: No BCG	D1	Cervical LA 1cm, fully resolved in a couple of weeks	Observation	Probable	Resolved D14	LA, left cervical
10647 RCH	F	9	06/08/2020 PHx: No BCG	D3	Left cervical LA, maximum 1 cm diameter onset D3, neck felt a bit tender, associated with some fatigue; fully resolved D4. Vaccine site following expected reaction.	Observation	Probable	Resolved D4	LA, left cervical
15905-3 UMCU NL	F	10	04/08/2020 PHx: No BCG	D3	Left axilla, 2 cm in diameter, tender. No discharge, no redness. Self-limiting, no need for treatment/ medication. No impact on daily life. Redness of vaccination site, max 6 cm in diameter.	Observation	Probable	Resolved D7	LA, left axilla (Vaccine site redness: grade 2)
10667 UMCU NL	F	11	05/08/2020 PHx: 1 BCG, >5y ago	D8	Cervical lymph node, max 1cm in diameter, behind left ear. Tender to touch, but no oozing, no redness. On day 20: lymph node still tender, but not swollen anymore	Observation	Probable	Resolved D22	LA, left cervical
10593 RCH	M	12	03/08/2020 PHx: No BCG	D10	Left cervical and Left axilla LA, maximum 2 cm diameter onset D10, until D12 (2 day duration), not tender, coinciding with slight ooze at vaccine site. He was just actively checking for LA as had been advised may occur. He reports he may not have noticed LA otherwise. Vaccine site following expected reaction.	Observation	Probable	Resolved D12	LA, left cervical and left axilla
11084 Rijnstate NL	F	13	17/08/2020 PHx: No BCG	D2	Noticed on day 2 swollen lymph node on the left side of the neck, not tender, not red, no pus. On the same day also swollen lymph node in the left axilla, and this one was also not painful or red or discharged pus. On day 4 the lymph nodes were not remarkable anymore. Self-limiting. Did not use any medication. Vaccination site: minimal swelling, otherwise unremarkable.	Observation	Probable	Resolved D4	LA, left cervical and left axilla
11092 Rijnstate NL	F	14	17/08/2020 PHx: No BCG	D5	Noticed swollen lymph node on day 5 on the left side of the neck, at max 1.5cm in diameter, no redness, no tenderness, no pus. Swollen lymph node resolved on day 11. Did not use any medication. Vaccination site: redness and a bit of swelling, minimal itching.	Observation	Probable	Resolved D11	LA, left cervical
10870 UMCU NL	F	15	11/08/2020 PHx: No BCG	D2	Noticed swollen lymph node on the left side of the neck, max <1 cm in diameter, no redness, no tenderness, no pus. Resolved on its own 2 days later.	Observation	Probable	Resolved D4	LA, left cervical

Participant ID number	Sex	Report no.	Date of vaccination and PHx of BCG	Onset following vaccination	Description of adverse event	Treatment	Relationship to vaccine *	Outcome	Local reaction Grade
					Vaccination site: redness and swelling, no pus, max diameter 1 cm.				
12457 Rijnstate NL	F	16	17/09/2020 PHx: No BCG	D5	Noticed swollen lymph node in the left axilla, max 10 mm in diameter, no redness, no tenderness, no pus. Resolved on its own. Vaccination site: some redness, max 1 cm, no tenderness, no pus.	Observation	Probable	Resolved D9	LA, left axilla
11448 Rijnstate NL	F	17	25/08/2020 PHx: no BCG	D18	Noticed swollen lymph node in left axilla because arm movement became painful, lymph node max 2 cm in diameter, no redness, no tenderness, no pus. Self-limiting. Vaccination site: was oozing pus at the beginning, but has now healed into a small scar.	Observation	Probable	Resolved D23	LA, left axilla Grade 2 (tenderness)
12352 Antonius NL	F	18	15/09/2020 PHx: No BCG	D16	Swollen lymph node at the left side of the neck, max 2cm in diameter, no concomitant lymphadenitis. Vaccination site: unremarkable	Observation	Probable	Resolved D20	LA, left cervical
12924 NWZ NL	F	19	01/10/2020 PHx: No BCG	D2	Noticed swollen lymph node in the left axilla and right side of the neck, lymph node in the axilla was very deep. Participant does not remember how big the lymph nodes were. Swelling resolved after 2 days without any treatment.	Resolved	Probable	Resolved D5	LA, left axilla Right cervical
10022 Westmead	M	20	06/07/2020 PHx: 1 prev BCG > 5 years ago	D5	Mild left axillary, bilateral cervical and inguinal lymphadenopathy, all small. Lasted 2 weeks. No associated fever, malaise. Associated with injection site pustule which drained for 1-2 weeks, then small ulcer.	Resolved	Possible	Resolved after 2 weeks	LA, left axilla, bilateral cervical, inguinal
12261 POW	F	21	20/09/2020 PHx: No BCG	D2	Bilateral cervical lymphadenopathy for a few days post vaccination, associated with sore throat, cough. Fully resolved.	Resolved	Unlikely	Resolved D7	LA, bilat cervical
12864 Radboud NL	F	22	29/09/2020 PHx: No BCG	D2	Unilateral cervical lymphadenopathy on the left side, swollen lymph node +/- 5 cm in diameter, no pain or redness. Resolved on its own.	Observation	Possible (no local site reactions)	Resolved D7	LA, left cervical
12271 Amphia NL	F	23	17/09/2020 PHx: No BCG	D4	Bilateral cervical lymphadenopathy, sore throat, flu-like symptoms. Covid test negative. Lymphadenopathy resolved on its own.	Observation	Possible	Resolved D 11	LA, bilateral cervical

Participant ID number	Sex	Report no.	Date of vaccination and PHx of BCG	Onset following vaccination	Description of adverse event	Treatment	Relationship to vaccine *	Outcome	Local reaction Grade
12367 Antonius NL	M	24	15/09/2020 PHx: No BCG	D4	Swollen lymph node left side of the neck, max 1 cm in diameter. Resolved on its own. Significant discomfort at rest at vaccine site D4-7	Observation	Probable	Resolved within a week	LA, left cervical 3 (tenderness)
12227 Amphia NL	F	25	08/10/2020 PHx: No BCG	D24	New onset of subfebrile temp (37.8), headache and nausea and noticed swollen lymph node just under the left ear, approximately 1.5 cm in diameter. No redness, pain, or pus. Swollen node resolved on its own. Other symptoms resolved over the weekend (31/10 - 1/11)	Observation	Unlikely	Resolved D27	LA, posterior auricular
14083 Amphia NL	F	26	29/10/2020 PHx: No BCG	D7 within	Noticed swollen lymph node on the left side of the neck, 1 x 2 cm in size, not clear when lymphadenopathy arose. Lymph node still swollen. No -itis. Vaccination site: some redness and swelling, no pain. Other symptoms: rhinitis and dyspnoea, rapid corona test negative, PCR pending. 01/12: lymph node still swollen, no tenderness.	Observation	Possible	Resolved D62	LA, left cervical
14858 Torquay UK	F	27	18/11/20 PHx: 1 BCG 17yrs ago	D3 20/11/20	Swollen lymph node in midline neck around thyroid cartilage. No redness or pus. No analgesia required. Self-resolved in 2 days. Some swelling and redness around vaccine site.	Resolved	Probable	Resolved D5	LA, midline neck
13266 Exeter UK	F	28	4/11/20 PHx: 1 BCG 38yrs ago	D6 (approx) 10/11/20	Swollen LN left sided anterior chain, midway up neck. Max size 1cm, non tender. No overlying erythema/ discharge. Systemically well.	Resolved	Probable	Resolved D14	LA, left neck midline
13486 Exeter UK	F	29	27/10/20 Phx: 1 BCG >5 yrs ago.	D13 8/11/20	Swollen lymph node left axilla, max size 2cm. Some tenderness, no redness. Attended GP on 17/11/20 and lymphadenopathy had fully resolved.	Resolved	Probable	Resolved D22	LA, left axilla
13965 MS Brazil	F	30	27/10/2020 PHx: 1 BCG, >5y ago	D3 30/10/2020	Developed 0.5cm lymph node right axilla, not tender, not red, no discharge. No concerns with her vaccination site.	Observation	Probable	Resolved D5	LA, right axilla
14001 MS Brazil	F	31	05/11/2020 PHx: 1 BCG, >5y ago	D14 20/11/2020	Developed 0.5cm lymph node right axilla, not tender, not red, no discharge. No concerns with her vaccination site.	Observation	Probable	Resolved D16	LA, right axilla
14046 MS Brazil	F	32	20/11/2020 PHx: 1 BCG, >5y ago	D1 21/11/2020	Developed 0.5cm lymph node right collar bone, not tender, not red, no discharge. No concerns with her vaccination site.	Observation	Probable	Resolved D2	LA right collar bone
14100 MS Brazil	F	33	27/10/2020 PHx: 1 BCG, >5y ago	D30 26/11/2020	Developed 1cm lymph node right axilla, not tender, not red, no discharge. No concerns with her vaccination site.	Observation	Probable	Resolved D33	LA, right axilla

Participant ID number	Sex	Report no.	Date of vaccination and PHx of BCG	Onset following vaccination	Description of adverse event	Treatment	Relationship to vaccine *	Outcome	Local reaction Grade
14383 MS Brazil	F	34	30/10/2020 PHx: 1 BCG, >5y ago	D3 03/11/2020	Developed 2cm lymph node right axilla, not tender, not red, no discharge. No concerns with her vaccination site.	Observation	Probable	Resolved D6	LA, right axilla
14576 MS Brazil	F	35	3/11/2020 PHx:No	D7 10/11/2020	Developed 2cm lymph node right axilla, not tender, not red, no discharge. No concerns with her vaccination site.	Observation	Probable	Resolved D9	LA, right axilla
14633 MS Brazil	F	36	4/11/2020 PHx: 1 BCG, >5y ago	D4 08/11/2020	Developed 1cm lymph node right axilla, not tender, not red, no discharge. No concerns with her vaccination site.	Observation	Probable	Resolved D6	LA, right axilla
15368 MS Brazil	F	37	17/11/2020 PHx: 1 BCG, >5y ago	D3 20/11/2020	Developed 1cm lymph node right axilla, not tender, not red, no discharge. No concerns with her vaccination site.	Observation	Probable	Resolved D5	LA, right axilla
15438 HU Cruces SP	F	38	26/11/2020 PHx: 1 BCG, >5y ago	D4 30/11/2020	Reported 1 cm lymph node left axilla, no discharge. Redness and swelling in vaccination site maximum 1cm, no further complaints, normal scarring. Swollen lymph node was self-reported by participant. When explored by local PI had already disappeared.	Observation	Probable	Resolved D10	LA, left axilla
11834 POW, NSW	F	39	07/09/2020 PHx: No BCG	D4	Developed 2cm left axillary lymph node within a few days of vaccination, not red, no discharge, resolved within a few days. No concerns with her injection site	Observation	Probable	Resolved D7	LA, left axilla
16449 MS Brazil	F	40	5/11/2020 PHx: 1 BCG, >5y ago	D2 7/11/2020	Developed 1cm lymph node right axilla, not tender, not red, no discharge. No concerns with her vaccination site.	Observation	Probable	Resolved D3	LA, right axilla
16747 MS Brazil	F	41	8/12/2020 PHx: 2 BCG, >5y ago	D1 8/12/2020	Developed 0.5cm lymph node right axilla, not tender, not red, no discharge. No concerns with her vaccination site.	Observation	Probable	Resolved D3	LA, right axilla
17148 MS Brazil	F	42	22/12/2020 PHx: 2 BCG, >5y ago	D3 22/12/2020	Developed 1cm lymph node right axilla, not tender, not red, no discharge. No concerns with her vaccination site.	Observation	Probable	Resolved D4	LA, right axilla
17539 MS Brazil	F	43	23/12/2020 PHx: 2 BCG, >5y ago	D2 26/12/2020'	Developed 0.5cm lymph node right axilla, not tender, not red, no discharge. No concerns with her vaccination site.	Observation	Probable	Resolved D4	LA, right axilla
16607 HU Marques Valdecilla, SP	F	44	17/12/2020 PHx: No BCG	D30 18/01/2021	Reports lymph node ipsilateral and contralateral at cervical (above collar bone) location. 0.5-1 cm. No concerns with vaccination site, redness and swelling less 1cm.	Observation	Probable	Resolved D67	LA, bilateral, cervical

Participant ID number	Sex	Report no.	Date of vaccination and PHx of BCG	Onset following vaccination	Description of adverse event	Treatment	Relationship to vaccine *	Outcome	Local reaction Grade
					Contact 30-01-21 Lymphadenopathies ongoing, no discharge, no pain. Submandibular appearing later on. Discharge from the vaccination site on 29-01-21. The participant has informed on 11-02-21 that received COVID specific vaccine on12-01-21 (D26) and 02-02-21. The submandibular ones did grow and were painful just after second dose and now improving				
18530 HUGTIP, SP	M	45	21/01/2021 PHx: No BCG	D8 29/01/2021	Self reported lymph node left axilla 2cm. Not tender, not red, no discharge. No concerns with vaccination site.	Observation	Probable	Resolved D10	LA, left axilla
14284 MS Brazil	F	46	30/10/2020 PHx: 1 BCG, >5y ago	D6 06/11/2020	Developed 0.5cm lymph node right axilla, not tender, not red, no discharge. No concerns with her vaccination site.	Observation	Probable	Resolved D8	LA, right axilla
18606 MS Brazil	F	47	23/01/2021 PHx: 1 BCG, >5y ago	D2 24/01/2021	Developed 2 cm lymph node right collar bone, not tender, not red, no discharge. No concerns with her vaccination site.	Observation	Probable	Resolved D3	LA right collar bone
15896 Rio Brazil	F	48	25/11/2020 PHx: 2 BCG, >5y ago	D3 27/11/2020	Swollen lymph node right axilla, painful, max size 0.5cm. No redness or drainage, very little pain on palpation, onset D3, resolution D7.	Observation	Probable	Resolved 1/12/2020	LA, right axilla
16664 Rio Brazil	F	49	25/11/2020 PHx: 2 BCG, >5y ago	D6 5/12/2020	Swollen lymph node right axilla, painful, max size 0.5cm. No redness or drainage, very little pain on palpation, onset D3, resolution D7. Subsequent left axilla lymph node D15, already with improvement, but without complete resolution	Observation	Probable	Resolved 8/12/2020	LA, right axilla
16819 Rio Brazil	F	50	30/11/2020 PHx: 1 BCG, >5y ago D15 14/12/2020	D2 10/12/2020	Swollen lymph node axilla, painful. He felt an enlarged lymph node D2, not very painful to move, of a maximum of 1cm, without redness or drainage, resolved spontaneously D6.	Observation	Definite	Resolved 14/12/2020	LA, right axilla
17696 Rio Brazil	F	51	4/01/2021 PHx: 1 BCG, >5y ago	D2 5/01/2021	Swollen lynph node submandibular max size 0.4cm. Participant reports having sore throat at the time of lymph node appearance. In addition, the participant tested positive on the nasal swab performed for coronavirus screening by RT-PCR on the day of randomization.	Observation	Unlikely	Resolved 7/01/2021	LA, submandibular

Participant ID number	Sex	Report no.	Date of vaccination and PHx of BCG	Onset following vaccination	Description of adverse event	Treatment	Relationship to vaccine *	Outcome	Local reaction Grade
18573 Rio Brazil	F	52	23/01/2021 PHx: 2 BCG, >5y ago	D6 28/01/2021	Significant local pain radiating to the right breast, axilla and neck, without resolution after use dipyrone. She used a cold compress, followed by spontaneous drainage of pustule and immediate pain relief. Also right axillary lymphadenopathy, max 1.5cm, resolved 02/02/21	Dipyrone	Probable	Resolved D11 02/02/2021	LA, right axilla 3 (pain), 3 (swelling/induration)
13613 UK	F	53	28/10/2020 PHx; 1BCG >5yrs ago	D15 11/11/2020	Reported on 3m questionnaire. Participant said she noticed a swollen node in the left side of the neck from around day 14-17. Minimal tenderness and self-resolved.	Observation	Probably	Resolved D17 14/11/2020	LA, left cervical
16255 Rio Brazil	F	54	01/12/2021 PHx: No BCG	D30 30/12/2020	Persistent lymph node enlargement palpated in the right axilla, max size 2cm, oedema up to the right breast, painful, preventing daily activities. 23/2/21: Ultrasound; oedema armpit region, no lymphadenopathy; axilla pain and arm pain resolved.	Cefalexin and Ibuprofen	Possible	Resolved D52 22/02/2021	LA, right axilla
15937 Rio Brazil	F	55	25/11/2020 PHx: 1 BCG, > 5 y ago	D8 02/12/2020	Right axilla lymphadenopathy, painful, max size 1.5cm, lasting 2 weeks. D8 to D22	Observation	Possible	Resolved D 22 16/12/2021	LA, right axilla
14476 HU Marques Valdecilla, SP	F	56	17/11/2020 PHx: No BCG	D78 04/02/2021	Participant refers in 3MQ appearance of right cervical lymphadenopathy one week after COVID specific vaccination and more than 2 months after randomisation. However it was contralateral (study vaccination right arm, COVID specific left arm). Also reports cold sore episode simultaneously. Maximum 0.5 cm.	Self-resolved	Unlikely	Resolved D97 23/02/2021	LA, right cervical
15502 HU Marques Valdecilla, SP	M	57	24/11/2020 PHx: No BCG	D67 31/01/2021	Participant reported swollen gland in 3MQ, not mentioned in vaccine diary and was contacted for additional information. Randomisation 24-11-20. Reports swollen gland left cervical at the end of january D67, maximum 2x1cm and self resolved, no discharge. Vaccination site with redness and swelling but within normal scarring. COVID specific vaccine received 24th february right arm.	Self-resolved	Unlikely	Resolved D81 14/02/2021	LA, left cervical
14351 HU Marques Valdecilla, SP	F	58	17/12/2020 PHx: 1 BCG, > 5 y ago	D69 26/02/2021	Participant reported swollen gland in 3MQ, not mentioned in vaccine diary and was contacted for additional information. Not any issues with vaccination site. Randomisation 17-12-20. Reports swollen gland left axillar day after second dose COVID specific vaccination 25-02-21, D69, received same arm. Maximum 0.8cm and self resolved in one week, no discharge, only some pain.	Self-resolved	Unlikely	Resolved D76 06/03/2021	LA, left axilla

Participant ID number	Sex	Report no.	Date of vaccination and PHx of BCG	Onset following vaccination	Description of adverse event	Treatment	Relationship to vaccine *	Outcome	Local reaction Grade
14769 MS Brazil	F	59	09/11/2020 PHx: 1 BCG, >5y ago	D2 10/11/202	Developed 1 cm lymph node right NECK, not tender, not red, no discharge. No concerns with her vaccination site.	Observation	Probable	Resolved D4	A, right side of the neck
14282 MS Brazil	F	60	30/10/2021 PHx: 1 BCG, >5y ago	D7 05/11/2021	Developed 2 cm lymph node right axilla, not tender, not red, no discharge. No concerns with her vaccination site	Observation	Probable	Resolved D9	LA, right axilla
14187 MS Brazil	M	61	31/10/2021	D7 06/11/2021	Developed 1 cm lymph node right axilla, not tender, not red, no discharge. No concerns with her vaccination site	Observation	Probable	Resolved D9	LA, right axilla
17400 HU Cruces SP	F	62	22/12/2020 PHx: 1 BCG, >5y ago	D77 11/03/2021	Swollen gland appeared 24h after second dose COVID specific vaccination that took place 10th march (D77). Detected by echography after an altered mamography. No redness, not swelling, no discharge. No concerns with vaccination site.	Observation	Unlikely	Resolved around D84, does not remember exactly	LA, left axilla
17523 MS Brazil	F	63	23/12/2020 PHx: 1 BCG, >5y ago	D5 28/12/2020	Developed 0.5cm lymph node right axilla, not tender, not red, no discharge. No concerns with her vaccination site.	Observation	Probable	Resolved D7	LA, right axilla
17534 MS Brazil	M	64	23/12/2020 PHx: 1 BCG, >5y ago	D3 26/12/2020	Developed 0.5cm lymph node right axilla, not tender, not red, no discharge. No concerns with her vaccination site.	Observation	Probable	Resolved D5	LA, right axilla
18911 Amazonas Brazil	F	65	30/01/2021 PHx: 1 BCG, >5y ago	D12	Developed 1.2cm left axillar lymph node without discharge or concern about the vaccination site. Self-limited by 6 days post onset.	Observation	Probable	Resolved D18	LA, left axilla
18942 Amazonas Brazil	F	66	30/01/2021 PHx: 1 BCG, >5y ago	D2	Developed 1cm, self-limited left axillar lymph node without discharge or concern about the vaccination site. Self-resolved by 3 days post onset.	Observation	Possible	Resolved D5	LA, left axilla
19033 Amazonas Brazil	F	67	03/02/2021 PHx: 2 BCG, >5y ago	D2	Complaint of unmeasured axillar lymphadenopathy probably non related to vaccine.	Observation	Unlikely	Resolved D7	LA, left axilla
19251 Amazonas Brazil	F	68	11/02/2021 PHx: 1 BCG, >5y ago	D3	Developed 1.0cm left axillar lymph node without discharge or concern about the vaccination site. Self-limited by 6 days post onset.	Observation	Probable	Resolved D9	LA, left axilla

Participant ID number	Sex	Report no.	Date of vaccination and PHx of BCG	Onset following vaccination	Description of adverse event	Treatment	Relationship to vaccine *	Outcome	Local reaction Grade
19281 Amazonas Brazil	F	69	11/02/2021 PHx: unknown BCG	D4	Developed 1.0cm left axillar lymph node without discharge or concern about the vaccination site. Self-limited by 11 days post onset.	Observation	Probable	Resolved D15	LA, left axilla
18497 Rio Brazil	F	70	18/01/2021 PHx: 2 BCG, 32y ago	D2	Right axilla and neck lymphadenopathy max 1cm diameter, not painful. Resolved by 27/01/2021	Observation	Probable	Resolved D10	LA, right axilla, right neck
18560 Rio Brazil	F	71	21/01/2021 PHx: 2 BCG, 10y ago	D3 23/01/2021	Right axilla lymphadenopathy max 1cm diameter, not painful. Resolved in 3 days.	Observation	Probable	Resolved D6	LA, right axilla
19003 Rio Brazil	F	72	01/02/2021 PHx: 1 BCG, 48y ago	D40 12/04/2021	Right neck lymphadenopathy max 2cm diameter, not painful.	Observation	Probable	Resolved D43 15/04/2021	LA, right axilla
19061 Rio Brazil	F	73	03/02/2021 PHx: 2 BCG, 28y ago	D30 03/03/2021	Right axilla and neck lymphadenopathy max 1cm diameter, not painful.	Observation	Probable	Resolved D33 06/03/2021	LA, right axilla, right neck
14936 MS Brazil	F	74	13/11/2020 PHx: 1 BCG, >5y ago	D2 15/11/2020	Developed 0.3cm lymph node right axilla, not tender, not red, no discharge. No concerns with her vaccination site.	Observation	Probable	Resolved D4	LA, right axilla
17418 MS Brazil	F	75	22/12/2020 PHx: 2 BCG, >5y ago	D3 24/12/2020	Developed 1 cm lymph node right axilla, not tender, not red, no discharge. No concerns with her vaccination site	Observation	Probable	Resolved D4	LA, right axilla
18743 Amazonas Brazil	M	76	30/01/2021 PHx: 1 BCG, 26y ago	D15 13/02/2021	Developed 1.2cm left (ipsilateral) axillary lymph node without discharge or concern about the vaccination site. Self-limited by 2 days post onset.	Observation	Probable	Resolved D17	LA, left axilla
17217 MS Brazil	F	77	13/11/2020 PHx: 1 BCG, >5y ago	D5 17/11/2020	Developed 0.5cm lymph node right axilla, for 1 week, tender for 10 days, no discharge Significant discomfort at rest at vaccine site D1-D5	Observation and analgesia (Dorflex) 1 day	Definite	Resolved D12	LA right axilla 3 (tenderness)
Large ulcer (>1.5cm diameter)									
~~13221 UK~~	~~F~~	~~1~~	~~14/10/2020 No BCG previously~~	~~D 15 29/10/2020~~	~~Reported on 3m questionnaire an ulcer of greater than 1.5cm. Followed up with participant and she reports an ulcer of 1.5cm with some discharge. Self-resolved~~	~~Observation~~	~~Definite~~	~~Resolved D 95~~	Ulcer not greater than 1.5cm.
Keloid scar									

Participant ID number	Sex	Report no.	Date of vaccination and PHx of BCG	Onset following vaccination	Description of adverse event	Treatment	Relationship to vaccine *	Outcome	Local reaction Grade
9766 CHW	F	1	18/06/2020 PHx: No BCG		Keloid scar reported in 3M questionnaire. Participant has a history of keloid scarring. Photo appears consistent with small keloid scar.	Observation	Definite		Keloid scar
14922 MS Brazil		3	13/11/2020 PHx: 1 BCG, >5y ago	01/03/2021	Keloid scar in right arm	Observation	Definite		Keloid scar
Other									
9567 WCH	F	1	20/05/2020 PHx: 1 BCG, >5y ago	D2	Pain at rest at injection site, onset D2, 24 hours duration. 1.5cm redness and swelling at injection site; appearance unremarkable. Also experienced diarrhoea on D2 of 24 hours duration, self-resolved.	Single dose of opioid analgesia (codeine/paracetamol) on D2	Definite (pain) Unlikely (diarrhoea)	Resolved D3	3 (pain)
10714 UMCU NL	M	2	06/08/2020 PHx: No BCG	D14	Started on day 14 with a nummular rash on the right upper arm, in the following days the rash extended to cover the chest, left upper arm and back, buttocks and groin area. No itchiness, no pain. On day 16 video consultation with GP, probably ringworm rash. Vaccination site: unremarkable, also no regional lymphadenopathy	GP review: Miconazole cream	Unrelated	Resolved D28	NA
11054 RCH	F	3	20/05/2020 PHx: 1 BCG, >5y ago	D3	Significant discomfort at rest at vaccine site for a few days; subsequently resolved- oral ibuprofen. No current concerns with vaccine site.	Ibuprofen for 2 days	Definite	Resolved D7	3 (tenderness)
12131 Randwick	F	4	21/09/2020 PHx: No BCG	D14	Please refer to specialist clinic visit entry in Table 3	Primapore dressing	Definite	Resolved D32	3 (pain)
9932 Randwick	F	5	7/7/20 PHx: No BCG	D4	Please refer to specialist clinic visit entry in Table 3	Observation	Definite	Resolved D18	3 (pain)
12810 Radboud NL	F	6	29/9/2020 PHx: No BCG	D1	Significant discomfort at rest at vaccination site, no medication used	Observation	Definite	Resolved D5	3 (tenderness)
12825 Amphia NL	F	7	08/10/2020 PHx: 1 BCG >5y ago	D2	Significant discomfort at rest at vaccination site, no medication used	Observation	Definite	Resolved D3	3 (tenderness)
13383 UK	F	8	21/10/2020 PHx: 1 BCG 1979	D1	Significant discomfort at rest at vaccination site, no medication used	Observation	Definite	Resolved D7	3 (pain)
13304 UK	F	9	03/11/2020 PHx: 1 BCG 1979	D1	Significant discomfort at rest at vaccination site, no medication used	Observation	Definite	Resolved D2	3 (tenderness)
12741	F	10	20/10/2020	D30	Intermittent tingling from left shoulder to elbow,	Observation	Possible	Resolved D44	NA

Participant ID number	Sex	Report no.	Date of vaccination and PHx of BCG	Onset following vaccination	Description of adverse event	Treatment	Relationship to vaccine *	Outcome	Local reaction Grade
St Vincents Sydney			PHx: 1 BCG, >5y ago		lasted 2-3 weeks. Resolved spontaneously				
13752 MS Brazil	F	11	20/10/2020 PHx: 1 BCG, >5y ago	D10 30/10/2020	Significant discomfort at rest at vaccine site for a few days; No current concerns with vaccine site.	Observation	Definite	Resolved D13	3 (tenderness)
14042 MS Brazil	F	12	12/11/2020 PHx: 2 BCG, >5y ago	D2 14/11/2020	Significant discomfort at rest at vaccine site for a few days; No current concerns with vaccine site. She needed help from a doctor and took non-opioid painkillers and lasted only 1 day.	Dipirona for 1 day	Definite	Resolved D3	3 (tenderness)
14183 MS Brazil	F	13	28/10/2020 PHx: 1 BCG, >5y ago	D43 10/12/2020	itching and papules in different part of the body. participant saw another doctor who treated her as scabies and allergy	Treatment for scabies and allergy	Possible	Follow up	Itch (3)
16105 MS Brazil	F	14	28/10/2020 PHx: 1 BCG, >5y ago	D12 10/12/20202	Itching and sores in different part of the body. participant saw another doctor who treated her as allergy	Treatment for allergy	Possible		Itch (3)
15091 HU Cruces, SP	F	15	19/11/2020 PHx: 1BCG, >5y ago	D6 23/11/2020	Redness and swelling maximum 1 cm. At D6 participant expresses significant discomfort at rest. Contacted by PI, it was temporary, D6 til D8. In follow up normal scarring.	Observation	Definite	Resolved D8	3 (tenderness)
15297 HU Cruces, SP	F	16	01/12/2020 PHx: 1BCG, >5y ago	D6 7/12/2020	Redness 2cm and swelling 3 1 cm. At D6 participant expresses significant discomfort at rest. and a vesicle that discharged. Contacted by PI, it was temporary, D6 til D9. In follow up normal scarring.	Observation	Definite	Resolved D9	3 (tenderness)
16379 MS BRAZIL	F	17	01/12/2020 PHx: 1 BCG, >5y ago	D4 05/12/2020	Redness across the circumference of the arm at the vaccine site	Observation	Definite	Resolved D9	3 (redness)
16295 MS Brazil	F	18	02/12/2020 PHx: 1 BCG, >5y ago	D3 05/12/2020	Significant discomfort at rest at vaccine site for a few days; No current concerns with vaccine site.	Dipirona for 1 day	Definite	Resolved D6	3 (tenderness)
16433 MS Brazil	F	19	02/12/2020 PHx: 1 BCG, >5y ago	D 2 04/12/2020	Significant discomfort at rest at vaccine site for a few days; No current concerns with vaccine site.	Observation	Definite	Resolved D5	3(tenderness)
16468 MS Brazil	F	20	03/12/2020 PHx: 1 BCG, >5y ago	D1 03/12/2020	Significant discomfort at rest at vaccine site for a few days; No current concerns with vaccine site.	Observation	Definite	Resolved D5	3 (tenderness)
16800 MS Brazil	F	21	09/12/2020 PHx: 1 BCG, >5y ago	D1 09/12/22020	Significant discomfort at rest at vaccine site for a few days; No current concerns with vaccine site.	Observation	Definite	Resolved D3	3 (tenderness)

Participant ID number	Sex	Report no.	Date of vaccination and PHx of BCG	Onset following vaccination	Description of adverse event	Treatment	Relationship to vaccine *	Outcome	Local reaction Grade
16851 MS Brazil	F	22	10/12/2020 PHx: 1 BCG, >5y ago	D1 10/12/2020	Significant discomfort at rest at vaccine site for a few days; No current concerns with vaccine site.	Observation	Definite	Resolved D4	3 (tenderness)
17163 MS Brazil	F	23	17/12/2020 PHx: 1 BCG, >5y ago	D3 19/12/2020	Significant discomfort at rest at vaccine site for a few days; No current concerns with vaccine site.	Observation	Definite	Resolved D5	3 (tenderness)
17198 MS Brazil	F	24	17/12/2020 PHx: 1 BCG, >5y ago	D1 17/12/2020	Significant discomfort at rest at vaccine site for a few days; No current concerns with vaccine site.	Observation	Definite	Resolved D3	3 (tenderness)
17235 MS Brazil	F	25	18/12/2020 PHx: 1 BCG, >5y ago	D1 18/12/2020	Significant discomfort at rest at vaccine site for a few days; No current concerns with vaccine site.	Observation	Definite	Resolved D8	3 (tenderness)
17343 MS Brazil	M	26	19/12/2020 PHx: 1 BCG, >5y ago	D1 19/12/2020	Significant discomfort at rest at vaccine site for a few days; No current concerns with vaccine site.	Observation	Definite	Resolved D5	3 (tenderness)
17382 MS Brazil	F	27	20/12/2020 PHx: 2 BCG, >5y ago	D2 21/12/2020	Significant discomfort at rest at vaccine site for a few days; No current concerns with vaccine site.	Observation	Definite	Resolved D5	3 (tenderness)
11907 Rijnstate NL	F	28	02/09/2020 PHx: No BCG	D30 02/10/2020	Vaccine diary redness and swelling less than 1 cm, only 1 day of pain. But reports in 3 month questionnaire pain and discomfort with movement between D30 and D60. No medication but severe pain to touch, Used local bands.	Observation	Probable	Resolved D60	3 (tenderness)
17975 MS Brazil	M	29	07/01/2021 PHx: 2 BCG, >5y ago	D9 16/01/2021	Significant discomfort at rest at vaccine site for one day; No current concerns with vaccine site.	Observation	Definite	Resolved D10	3 (tenderness)
18195 MS Brazil	F	30	11/01/2021 PHx: 1 BCG, >5y ago	D2 12/01/2021	Significant discomfort at rest at vaccine site for one day; No current concerns with vaccine site.	Observation	Definite	Resolved D4	3 (tenderness)
18303 MS Brazil	F	31	13/01/2021 PHx: 1 BCG, >5y ago	D9 21/01/2021	Significant discomfort at rest at vaccine site for one day; No current concerns with vaccine site.	Observation	Definite	Resolved D10	3 (tenderness)
18343 MS Brazil	F	32	14/01/2021 PHx: 1 BCG, >5y ago	D3 16/01/2021	Significant discomfort at rest at vaccine site for one day; No current concerns with vaccine site.	Observation	Definite	Resolved D5	3 (tenderness)
18336 MS Brazil	F	33	13/01/2021 PHx: 1 BCG, >5y ago	D3 15/01/2021	Significant discomfort at rest at vaccine site for one day; No current concerns with vaccine site.	Observation	Definite	Resolved D5	3 (tenderness)

Participant ID number	Sex	Report no.	Date of vaccination and PHx of BCG	Onset following vaccination	Description of adverse event	Treatment	Relationship to vaccine *	Outcome	Local reaction Grade
18343 MS Brazil	F	34	14/01/2021 PHx: 1 BCG, >5y ago	D3 16/01/2021	Significant discomfort at rest at vaccine site for one day; No current concerns with vaccine site.	Observation	Definite	Resolved D5	3 (tenderness)
13840 MS Brazil	F	35	21/10/2020 PHx: 1 BCG, >5y ago	D2 22/10/2020	Significant discomfort at rest at vaccine site for one day; No current concerns with vaccine site.	Observation	Definite	Resolved D3	3 (tenderness)
13982 MS Brazil	F	36	06/11/2020 PHx: 1 BCG, >5y ago	D1 06/11/2020	Significant discomfort at rest at vaccine site for one day; No current concerns with vaccine site.	Observation	Definite	Resolved D5	3 (tenderness)
14059 MS Brazil	F	37	30/10/2020 PHx: 1 BCG, >5y ago	D2 31/10/2020	Significant discomfort at rest at vaccine site for one day; No current concerns with vaccine site.	Observation	Definite	Resolved D4	3 (tenderness)
14162 MS Brazil	F	38	30/10/2020 PHx: 2 BCG, >5y ago	D1 30/10/2020	Significant discomfort at rest at vaccine site for one day; No current concerns with vaccine site.	Observation	Definite	Resolved D5	3 (tenderness)
14189 MS Brazil	F	39	06/11/2020 PHx: 1 BCG, >5y ago	D1 06/11/2020	Significant discomfort at rest at vaccine site for one day; No current concerns with vaccine site.	Observation	Definite	Resolved D5	3 (tenderness)
14284 MS Brazil	F	40	30/10/2020 PHx: 2 BCG, >5y ago	D1 30/10/2020	Significant discomfort at rest at vaccine site for one day; No current concerns with vaccine site.	Observation	Definite	Resolved D4	3 (tenderness)
14286 MS Brazil	F	41	30/10/2020 PHx: 2 BCG, >5y ago	D1 30/10/2020	Significant discomfort at rest at vaccine site for one day; No current concerns with vaccine site.	Observation	Definite	Resolved D5	3 (tenderness)
14393 MS Brazil	F	42	30/10/2020 PHx: 2 BCG, >5y ago	D3 02/11/2020	Significant discomfort at rest at vaccine site for one day; No current concerns with vaccine site.	Observation	Definite	Resolved D6	3 (tenderness)
14656 MS Brazil	F	43	17/11/2020 PHx: 2 BCG, >5y ago	D3 19/11/2020	Significant discomfort at rest at vaccine site for one day; No current concerns with vaccine site.	Observation	Definite	Resolved D5	3 (tenderness)
14662 MS Brazil	F	44	06/11/2020 PHx: 1 BCG, >5y ago	D1 06/11/2020	Significant discomfort at rest at vaccine site for one day; No current concerns with vaccine site.	Observation	Definite	Resolved D5	3 (tenderness)
18522 MS Brazil	F	45	20/01/2021 PHx: 1 BCG, >5y ago	D2 21/11/2020	Significant discomfort at rest at vaccine site for one day; No current concerns with vaccine site.	Observation	Definite	Resolved D5	3 (tenderness)
18552 MS Brazil	F	46	21/01/2021 PHx: 1 BCG, >5y ago	D2 22/11/2020	Significant discomfort at rest at vaccine site for one day; No current concerns with vaccine site.	Use of non-narcotic pain reliever	Definite	Resolved D5	3 (tenderness)

Participant ID number	Sex	Report no.	Date of vaccination and PHx of BCG	Onset following vaccination	Description of adverse event	Treatment	Relationship to vaccine *	Outcome	Local reaction Grade
15821 Rio Brazil	M	47	24/11/2020 PHx: 2 BCG, >5y ago	D5 28/11/2020	Significant local reaction: Single episode of fever 39.3 on 28/11/20, associated with chills and body pain, resolved after Dipirone 1g. Pain from application of vaccine and was unable to perform activities with the ipsilateral arm that needed to pick up weights. In 24 hours, pain improved, without the need for analgesics (used only once Dipirone), with the ability to perform usual daily activities, including work. Denies other symptoms. Denies flu-like symptoms.	Dipirone	Possible	Resolved 29/11/2020	3 (pain)
15882 Rio Brazil	F	48	25/11/2020 PHx: 1 BCG, >5y ago	D2 26/11/2020	Significant local reaction. Significant discomfort at rest from D2 to D4, resolved without medication.	Observation	Definite	Resolved 28/11/2020	3 (tenderness)
17282 Rio Brazil	F	49	18/12/2020 PHx: 1 BCG, >5y ago	D3 20/12/2020	Significant discomfort at rest D3 to D8. Did not use pain medication.	Observation	Definite	Resolved 25/12/2020	3 (pain)
17445 Rio Brazil	F	50	21/12/2020 PHx: No BCG	D2 22/12/2020	Significant local reaction. Much pain at the vaccine site, even at rest, preventing daily activities, required medication (dipyrone 500mg and ibuprofen), with little relief. No swelling or redness. Start D2, keeping on D8. Grade 3 local pain reaction. Improvement of pain in D12.	Dipirona and Ibuprofen	Definite	Resolved 1/01/2021	3 (pain)
17502 Rio Brazil	F	51	22/12/2020 PHx: 1 BCG, >5y ago	D3 24/12/2021	Pain at the vaccine site from D2 to D7, used dipyrone for pain for 5 days, reported significant discomfort at rest. Also presented with local swelling up to 13 cm at site, which has already improved. Grade 2 pain, grade 3 sensitivity, grade 3 swelling	Dipirone	Definite	Resolved 27/12/2020	3 (tenderness) and 3 (swelling)
18091 Rio Brazil	F	52	8/01/2020 PHx: 1 BCG, >5y ago	D1 09/01/2021	Significant local reaction. Discomfort at rest in right arm, started on D2, on D3 was better. Did not use medication.	Observation	Definite	Resolved 9/01/2021	3 (tenderness)
17649 UK	F	53	6/01/2021. PHx: BCG summer 2014	D11 17/01/2021	Swelling and feeling generally unwell prior to discharge from site. Tenderness Grade 3 for 12 hours. Able to go to work. Self managed pain with paracetamol	Paracetamol Observation	Definite	Resolved D18 24/01/2021	3 (tenderness)
18724 Rio Brazil	F	54	27/01/2021 PHx: 2 BCG, >5y ago	D2 28/01/2021	Significant discomfort at rest from D2 to D4.	Observation	Probable	Resolved D4 30/01/2021	3 (tenderness)

Participant ID number	Sex	Report no.	Date of vaccination and PHx of BCG	Onset following vaccination	Description of adverse event	Treatment	Relationship to vaccine *	Outcome	Local reaction Grade
19307 Rio Brazil	M	55	12/02/2021 PHx: No BCG	D2 13/02/2021	Significant generalised itch. Antihistamine commenced D16 for 5 days	Antihistamine 5 days	Probable	Resolved D21 04/03/2021	3 (itch)
16515 Rio Brazil	F	56	03/12/2020 PHx: 1 BCG, > 5 y ago	D20 22/12/2020	Significant local reaction from D20 to D23. Pain, hyperemia and edema, with significant discomfort at rest from D20 to D22, improvement from D23. He did not use medication.	Observation	Probable	Resolved D23 25/12/2020	3 (pain,tenderness and induration)
19427 Rio Brazil	F	57	22/02/2021 PHx: 0 BCG	D7 28/02/2021	Significant local reaction (significant tenderness/pain at rest) from D7 to D 10.	Observation	Probable	Resolved D10 03/03/2021	3 (tenderness)
16117 Rio Brazil	F	58	27/11/2020 PHx: 1 BCG, >5y ago	D16 12/12/2020	Significant local reaction. Onset of pain at the vaccine sites since D3. The pain worsened after D16 (significant discomfort at rest) and was maintained daily, requiring the use of common analgesic often for more than 2 days. D110 ongoing pain. Requested a face-to-face visit to assess the site, which will be scheduled. Still feels some pain but has no local inflammatory reaction. There was healing of the injection site.	Observation. Analgesic.	Probable	Resolved by 29/04/2021	3 (pain and tenderness)
19640 Rio Brazil	F	59	10/03/2021 PHx: 1 BCG, >5y ago	D4 13/03/2021	Significant local reaction (D4 to D8). Intense pain, could not move arm, prevented daily activity with right arm. Used dipyrone. Subsequent improvement with pustule rupture and spontaneous drainage of yellowish discharge.	Dipyrona	Probable	Resolved 17/03/2021	3 (pain)
19642 Rio Brazil	F	60	10/03/2021 PHx: 2 BCG, >5y ago	D2 11/03/2021	Significant pain at rest from D2 (11 / Mar / 2021) to D6 (15 / Mar / 2021). Did not need to use medication, nor did it hinder his usual activities. Spontaneous resolution after drainage of secretion.	Observation	Definite	Resolved 15/03/2021	3 (tenderness)
15899 MS Brazil	F	61	26/11/2020 PHx: 1 BCG, >5y ago	D4 30/11/2020	Significant discomfort at rest at vaccine site for one day; No current concerns with vaccine site.	use of non-narcotic pain reliever	Definite	Resolved D9	3 (tenderness)
19483 Amazonas Brazil	F	62	28/02/2021, PHx, 1 BCG, 33y ago	D2	Significant discomfort (swelling) at rest at vaccine site for a few days, prevented daily activities; subsequently resolved with no interventions. No current concerns with vaccine site.	Observation	Probable	Resolved D6	3 (swelling)
19162 Amazonas Brazil	F	63	07/02/2021, PHx, 1 BCG, >5y ago	D2	Significant discomfort (tenderness) at rest at vaccine site for a few days; subsequently resolved with no interventions. No current concerns with vaccine site.	Observation	Probable	Resolved D61	3 (tenderness)

Participant ID number	Sex	Report no.	Date of vaccination and PHx of BCG	Onset following vaccination	Description of adverse event	Treatment	Relationship to vaccine *	Outcome	Local reaction Grade
18827 Amazonas Brazil	F	64	30/01/2021, PHx, 2 BCG, >5y ago	D2	Significant discomfort (tenderness) at rest at vaccine site for a few days; subsequently resolved with no interventions. No current concerns with vaccine site.	Ibuprofen for 4 days	Probable	Resolved D7	3 (tenderness)
18926 Amazonas Brazil	F	65	31/01/2021, PHx, 1 BCG, >5y ago	D2	Significant discomfort (tenderness) at rest at vaccine site for a few days; subsequently resolved with no interventions. No current concerns with vaccine site.	Observation	Probable	Resolved D5	3 (tenderness)
18981 Amazonas Brazil	F	66	01/02/2021, PHx, 2 BCG, 16y ago	D6	Significant discomfort (tenderness) at rest at vaccine site for a few days; subsequently resolved with no interventions. No current concerns with vaccine site.	Observation	Probable	Resolved D60	3 (tenderness)
19162 Amazonas Brazil	F	67	07/02/2021, PHx, 1 BCG, >5y ago	D2	Significant discomfort (tenderness) at rest at vaccine site for a few days; subsequently resolved with no interventions. No current concerns with vaccine site.	Observation	Probable	Resolved D22	3 (tenderness)
19242 Amazonas Brazil	F	68	11/02/2021, PHx, 1 BCG, >5y ago	D1	Significant discomfort (tenderness) at rest at vaccine site for a few days; subsequently resolved with no interventions. No current concerns with vaccine site.	Observation	Probable	Resolved D110	3 (tenderness)
19281 Amazonas Brazil	F	69	11/02/2021, PHx: unknown BCG	D11	Significant discomfort (tenderness) at rest at vaccine site for a few days; subsequently resolved with no interventions. No current concerns with vaccine site.	Ibuprofen for 3 days	Probable	Resolved D14	3 (tenderness)
19326 Amazonas Brazil	F	70	13/02/2021, PHx, 1 BCG, 19y ago	D14	Significant discomfort (tenderness) at rest at vaccine site for a few days; subsequently resolved with no interventions. No current concerns with vaccine site.	Observation	Probable	Resolved D15	3 (tenderness)
17737 Brazil Rio	F	71	04/01/2021 PHx: 1 BCG, 40y ago	D3 06/01/2021	Significant discomfort (tenderness) at rest at vaccine site. Duration two days. Pain, redness, tenderness and swelling at the vaccination site, no need for medication, only hot compress at the site.	Observation and hot compress	Definite	Resolved D5	3 (tenderness)
18075 Brazil Rio	M	72	08/01/2021 PHx: 1 BCG, 10y ago	D1 08/01/2021	Significant discomfort at rest (tenderness) at vaccine site. Redness, swelling and tenderness on D1. There was no interference in daily activities. Did not use medications. Tenderness at vaccine site lasted 40 days (when touching arm), resolved.	Observation	Definite	Resolved D2	3 (tenderness)

Participant ID number	Sex	Report no.	Date of vaccination and PHx of BCG	Onset following vaccination	Description of adverse event	Treatment	Relationship to vaccine *	Outcome	Local reaction Grade
18385 UK	F	73	18/01/2021 PHx: 1 BCG, >5y ago	D3 20/01/2021	Tenderness grade 3: significant discomfort at rest during 3 days (day 2-4 post vaccination)	Observation	Definite	Resolved D6 (23/01/2021)	3 (tenderness)
8938 RAH South Australia	F	74	19/05/2020 PHx: 1 BCG, >5y ago	D9	Tenderness grade 3: significant discomfort at rest during first few weeks (D9-D28). Resolved by 4 weeks.	Observation	Definite	Resolved D28	3 (tenderness)
9872 Westmead NSW	F	75	14/07/2020 PHx: 1 BCG, >5y ago	D1	Tenderness grade 3: significant discomfort at rest first 10 days. Developed large tender pustule, very tender for about 10 days, then burst, pain was relieved after that. Wasn't able to sleep on that side nor wear tight clothing over that arm. Otherwise no impact on daily function. No meds taken	Observation	Definite	Resolved D10	3 (tenderness)
11655 PoW NSW	F	76	07/09/2020 PHx: 1 BCG, >5y ago	D1	Significant injection site pain first 4 days. Did not interfere with daily activity. No medications. There was a pustule present for 'quite some time', over several weeks it would intermittently discharge especially in shower, but was not painful for that whole duration, only first few days	Observation	Definite	Resolved D4	3 (tenderness)
12954 NL	F	77	01/10/2020 PHx: No BCG	D4	Significant discomfort at rest D4-D8	Observation	Definite	Resolved D8	3 (tenderness)
14740 MS Brazil	F	78	06/11/2020 PHx: 1 BCG, >5y ago	D2	Significant discomfort at rest D2-4	Observation	Definite	Resolved D4	3 (tenderness)
13373 StVincent NSW	F	79	27/10/2020 PHx: No BCG	D7	Significant discomfort at rest D7-D14	Observation	Definite	Resolved D14	3 (tenderness)
14797 MS Brazil	F	80	10/11/2020 PHx: 2 BCG, >5y ago	D3	Significant discomfort at rest D3-5 and pain preventing daily activity D4-5. Used analgesia for three days.	Observation and analgesia (Dorflex) for 3 days (D2-4)	Definite	Resolved D5	3 (tenderness) 3 (pain)
15312 MS Brazil	F	81	17/11/2020 PHx: 1 BCG, >5y ago	D1	Significant discomfort at rest D1-3	Observation	Definite	Resolved D3	3 (tenderness)

Participant ID number	Sex	Report no.	Date of vaccination and PHx of BCG	Onset following vaccination	Description of adverse event	Treatment	Relationship to vaccine *	Outcome	Local reaction Grade
15514 Rio Brazil	F	82	19/11/2020 PHx: 1 BCG, >5y ago	D2	Significant discomfort at rest D2-4.	Observation and analgesia (Dorflex) for 1 day	Definite	Resolved D4	3 (tenderness)
15699 MS Brazil	F	83	23/11/2020 PHx: 1 BCG, >5y ago	D1	Significant discomfort at rest D2-4.	Observation and analgesia (Dorflex) for 3 days	Definite	Resolved D4	3 (tenderness)
16481 MS Brazil	F	84	02/12/2020 PHx: 2 BCG, >5y ago	D1	Significant discomfort at rest D1-3	Observation and analgesia (Dipirona) for 3 days	Definite	Resolved D3	3 (tenderness)
17927 Rio Brazil	M	85	05/01/2021 PHx: 2 BCG, >5y ago	D2	Significant discomfort at rest D2-7, difficulty moving arm for two days, discomfort to sleep 7 days.	Observation	Definite	Resolved D7	3 (tenderness)
18373 MS Brazil	F	86	13/01/2021 PHx: 2 BCG, >5y ago	D3	Significant discomfort at rest D3-5	Observation	Definite	Resolved D5	3 (tenderness)
18405 Rio Brazil	M	87	14/01/2021 PHx: 1 BCG, >5y ago	D5	Significant discomfort at rest D5, duration 1 day	Observation	Definite	Resolved D5	3 (tenderness)
19076 Rio Brazil	F	88	03/02/2021 PHx: 1 BCG, >5y ago	D3	Significant discomfort at rest D3-6	Observation	Definite	Resolved D6	3 (tenderness)
9671 CHW NSW	F	89	19/06/2020 PHx: No BCG	D1	Significant discomfort at rest D1. Subsequent ongoing tenderness (discomfort with movement) until D90	Observation	Definite	Resolved D2	3 (tenderness)

Table 3: Summary report participants reviewed in Specialist Immunisation Clinic/Specialist Clinic; 14 May 2020 to 16 March 2022

Participant ID number	Sex	Report no.	Date of vaccination and PHx of BCG	Onset following vaccination	Description of adverse event	Treatment	Relationship to vaccine *	Outcome	Local reaction Grade (if applicable)
9037 Epworth	F	1	21/05/2020 PHx: 1 BCG, >5y ago	D17	Local reaction started D3-D4. Increased injection site redness, swelling from D17 (~6/6/20), max ~1.5cm diameter, discharged pus, some tenderness. Crusty core came off D20. Reviewed in Alfred ID clinic D22 (Dr Cheng); site red but dry, no local tenderness. Systemically well, no LA. Site consistent with small localised abscess that is resolving. Stopped discharging D29	Observation	Definite	Resolved D29	Abscess
12131 Randwick	F	2	21/09/2020 PHx: no prev BCG	D14	Increasing pain at the injection site starting from day 14, affecting ability to work (paramedic), notices is worse on work days. Exquisitely tender when things brush against it. No worsening of redness/swelling. No other assoc symptoms. Has taken paracetamol but prefers not to take analgesia. Update 22/10: pain much improved with Primapore. Still tender.	Primapore dressing	Definitie	Resolved D32	3 (pain)
9932 Westmead	F	3	7/7/20 PHx: no prev BCG	D4	Local pain affecting ability to work (hydrotherapy) and causing her to miss an exercise class. Could not sleep on that side. Avoided anything brushing against it. Took single dose of paracetamol, no narcotic pain relief. Pain lasted ~2 weeks, then settled. No indication of abscess, pustule only.	Observation	Definite	Resolved D18	3 (pain)

Abbreviations

AEFI	Adverse event following immunisation	LTBI	Latent tuberculosis infection
BCG	Bacille Calmette-Guérin	MET	Medical Emergency Team
BD	Twice daily	MMC	Monash Medical Centre, Victoria
BPM	Beats per minute	NA	Not applicable
CHW	Children's Hospital at Westmead, New South Wales	NAD	No abnormality detected
CXR	Chest X-ray	NL	Netherlands
D	Day	NSAID	Non steroid anti-inflammatory drugs
Diam	diameter	PHx	Past history
ECG	Electrocardiograph	POW	Prince of Wales Hospital, New South Wales
ED	Emergency Department	RCH	Royal Children's Hospital Melbourne, Victoria
FSH	Fiona Stanley Hospital, Western Australia	RR	Respiratory rate
Gr	Grade	SAE	Serious adverse event
GSC	Glasgow Coma Scale	SAEFVIC	Surveillance of Adverse Events Following Vaccination In the Community
GP	General practitioner	SCH	Sir Charles Gairdner Hospital, Western Australia
Hx	Medical history	SIS	Special immunisation clinic
ISR	Injection site reaction	WA	Western Australia
IV	Intravenous	WAVSS	Western Australian Vaccine Safety Surveillance system
LA	Lymphadenopathy	WCH	Women's and Children's Hospital, South Australia

UK	United Kingdom	w/o	Without
UMCU	University Medical Center Utrecht		

***Definition of relationship to the intervention**

- Unrelated (The AE is clearly NOT related to intervention)
- Unlikely (The AE is doubtfully related to the intervention)
- Possible (The AE may be related to the intervention)
- Probable (The AE is likely related to the intervention)
- Definite (The AE is clearly related to the intervention)

Overview of all local reactions

Local reaction to vaccination are monitored using standardised diary completed by the participant up to 14 days after vaccination(s). The diary is sent to participants to complete just after randomisation, with reminders sent at day 5, 10, and 15 after vaccination(s).

Participants also complete a questionnaire at 3 months after vaccination(s) asking similar questions. These data are used to complete participants' previous answers with events that occurred beyond the 14-day period, and for those who did not complete the 14-day standardised diary.

A toxicity grading scale is used to categorise the reports (Food and Drug Administration 2007):

Local reaction	**Grade 0** None	**Grade 1** Mild	**Grade 2** Moderate	**Grade 3** Severe	**Grade 4** Potentially life threatening
Pain	None	Does not interfere with activity	Repeated use of nonnarcotic pain reliever > 24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	Emergency room visit or hospitalization
Redness	None	2.5 - 5 cm	5.1 - 10 cm	>10 cm	Necrosis or exfoliative dermatitis
Tenderness	None	Mild discomfort to touch	Discomfort with movement	Significant discomfort at rest	Emergency room visit or hospitalization
Swelling / induration	None	2.5 - 5 cm and does not interfere with activity	5.1 - 10 cm or interferes with activity	>10 cm or prevents daily activity	Necrosis
Itch	None	Itching localised to injection site that is relieved spontaneously or in <48 hours of treatment	Itching beyond the injection site that is not generalised OR Itching localised to injection site requiring ≥48 hours of treatment	Generalised itching causing inability to perform usual social & functional activities	Not applicable

Food and Drug Administration. (2007). "Guidance for Industry: toxicity grading scale for healthy adult and adolescent volunteers enrolled in preventive vaccine clinical"
Retrieved 08.04.2020, from
https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Vaccines/ucm091977.pdf.

Participants reporting any concern, or an event greater than moderate are contacted by phone.
As 16 March 2022, **3965** participants have logged-in to report local reaction (99.4%). A total of 102 participants reported a local reaction event greater than moderate (2.6%)

During this reporting period, **3990** participants are at least one week post vaccination(s). The following tables summarise the local reaction to BCG or placebo vaccines in the first 3 months after vaccination(s) among the **3965** participants who are at least one week post-vaccination and have provided answer. This represents a 99.4 % response rate.

Vaccination site (BCG or Placebo)	**Total**	**No previous BCG**	**Previous BCG**
N	3965	912	3053
Pain	1118 (28.2%)	166 (18.2%)	952 (31.2%)
None	2847 (71.8%)	746 (81.8%)	2101 (68.8%)
Grade 1	988 (24.9%)	143 (15.7%)	845 (27.7%)
Grade 2	122 (3.1%)	20 (2.2%)	102 (3.3%)
Grade 3	7 (0.2%)	3 (0.3%)	4 (0.1%)
Grade 4	1 (<0.1%)	0 (0.0%)	1 (<0.1%)
Duration [day]	5 (2-8)	3 (2-10)	5 (3-8)
Apparition day	2 (1-3)	2 (1-6)	2 (1-2)
Redness	1903 (48.0%)	403 (44.2%)	1500 (49.1%)
None	2062 (52.0%)	509 (55.8%)	1553 (50.9%)
Grade 1	1850 (46.7%)	393 (43.1%)	1457 (47.7%)
Grade 2	52 (1.3%)	10 (1.1%)	42 (1.4%)
Grade 3	1 (<0.1%)	0 (0.0%)	1 (<0.1%)
Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)
Duration [day]	13 (9-14)	14 (10-60)	13 (9-14)
Apparition day	1 (1-2)	2 (1-2)	1 (1-2)
Maximal diameter [cm]	1.5 (1.0, 2.0)	1.0 (1.0, 2.0)	1.5 (1.0, 2.0)
Tenderness	1384 (34.9 %)	356 (39.0%)	1028 (33.7%)
None	2581 (65.1%)	556 (61.0%)	2025 (66.3%)
Grade 1	1059 (26.7%)	294 (32.2%)	765 (25.1%)
Grade 2	241 (6.1%)	51 (5.6%)	190 (6.2%)
Grade 3	83 (2.1%)	11 (1.2%)	72 (2.4%)
Grade 4	1 (<0.1%)	0 (0.0%)	1 (<0.1%)
Duration [day]	6 (4-12)	7 (2-21)	6 (4-11)
Apparition day	2 (1-2)	2 (1-3)	1 (1-2)
Swelling	1647 (41.5%)	338 (37.1%)	1309 (42.9%)
None	2318 (58.5%)	574 (62.9%)	1744 (57.1%)
Grade 1	1516 (38.2%)	311 (34.1%)	1205 (39.5%)
Grade 2	126 (3.2%)	26 (2.9%)	100 (3.3%)
Grade 3	5 (0.1%)	1 (0.1%)	4 (0.1%)
Grade 4	0 (0.0%)	0 (0.0%)	0 (0.0%)
Duration [day]	9 (5-13)	13 (5-30)	9 (5-13)
Apparition day	2 (1-3)	2 (1-3)	2 (1-2)
Maximal diameter [cm]	1.0 (0.5, 1.5)	1.0 (0.5, 1.5)	1.0 (0.5, 1.5)
Lymph node	63 (1.6%)	19 (2.1%)	44 (1.4%)

PROTOCOL

RCH HREC/protocol no: 62586

NCT04327206

BCG vaccination to Reduce the impact of COVID-19 in healthcare workers (BRACE) Trial

Version 12.0, 17May2022

Statement of Compliance

This clinical trial will be conducted in compliance with all stipulation of this protocol, the conditions of the ethics committees' approvals, and the Integrated Addendum to ICH E6 (R1): Guideline for Good Clinical Practice E6 (R2), dated 9 November 2016.

In Australia, this trial will also be conducted in compliance with with the NHMRC National Statement on Ethical Conduct in Human Research (2007 and all updates), the Integrated Addendum to ICH E6 (R1): Guideline for Good Clinical Practice E6 (R2), dated 9 November 2016 annotated with TGA comments and the NHMRC guidance Safety monitoring and reporting in clinical trials involving therapeutic goods (EH59, 2016).

This clinical trial is not sponsored by any pharmaceutical company or other commercial entity.

CONTENTS

PROTOCOL SYNOPSIS

TITLE	*BCG vaccination to Reduce the impact of COVID-19 in healthcare workers (BRACE) Trial*
TRIAL DESCRIPTION	Phase III, two group, multicentre, randomised placebo-controlled trial in up to 7244 healthcare workers to determine if BCG vaccine reduces incidence and the severity of COVID-19 during the 2020 SARS-CoV-2 pandemic. The trial includes a pre-planned meta-analysis with data from the 2834 participants recruited in first stage of this study which followed the same protocol but where participants were randomised between BCG and no BCG at the time of receiving an influenza vaccination, with a total sample size of 10078. Randomisation and immunisation will occur at each participating site. Participants will be randomised to receive BCG vaccine or 0.9% NaCl placebo. Participants will be followed-up for 12 months with notification from a smartphone application (up to daily when ill) or via phone calls, electronic messages, home visits and surveys to identify and detail suspected COVID-19 infection. Additional information on severe disease will be obtained from hospital medical records and/or government databases. Blood samples will be collected prior to randomisation, at 3 and 6 months, and in a sub-set of participants at 9 and 12 months to determine SARS-CoV-2 exposure. Where required swab/blood samples will be taken at illness episodes to assess SARS-CoV-2 infection.
OBJECTIVES	Primary objectives 1. To determine if BCG vaccination (Intervention) compared with placebo (Comparator) reduces the incidence of symptomatic COVID-19 (Outcome) measured over the 6 months following randomisation (Time) in healthcare workers (Participants). 2. To determine if BCG vaccination (Intervention) compared with placebo (Comparator) reduces the incidence of severe COVID-19 (COVID-19-related death, hospitalisation, or non-hospitalised severe disease, defined as 'non-ambulant' for ≥ 3 consecutive days OR Unable to work for ≥ 3 consecutive days) (Outcome) measured over the 6 months following randomisation (Time) in healthcare workers (Participants). SECONDARY OBJECTIVES 3. To determine if BCG vaccination (Intervention) compared with placebo (Comparator) reduces the incidence of symptomatic COVID-19 (Outcome) measured over the 12 months following randomisation (Time) in healthcare workers (Participants). 4. To determine if BCG vaccination (Intervention) compared with placebo (Comparator) reduces the incidence of severe COVID-19

	(non-hospitalised severe disease, hospitalisation or death) (Outcome) measured over the 12 months following randomisation (Time) in healthcare workers (Participants). 5. To determine if BCG vaccination (Intervention) compared with placebo (Comparator) prolongs the time to first COVID-19 episode (Outcome) measured over 6 and 12 months following randomisation (Time) in healthcare workers (Participants). 6. To determine if BCG vaccination (Intervention) compared with placebo (Comparator) reduces the severity of COVID-19 (Outcome) measured over 6 and 12 months following randomisation (Time) in healthcare workers (Participants). 7. To determine if BCG vaccination (Intervention) compared with placebo (Comparator) reduces the rate and severity of illness (fever or at least one sign or symptom of respiratory disease) measured over 12 months following randomisation (Time) in healthcare workers (Participants). 8. To determine if BCG vaccination (Intervention) compared with placebo (Comparator) reduces absenteeism (days off work) measured over 6 and 12 months following randomisation (Time) in healthcare workers (Participants). 9. To evaluate the safety of BCG vaccination in healthcare workers. Planned exploratory analyses 10. To determine in a subgroup of adults with recurrent cold sores whether BCG vaccination compared with placebo reduces herpes simplex recurrences (such as cold sores). 11. To determine the BCG vaccination induces changes in the immune system that are associated with protection of healthcare workers from non-tuberculous infectious diseases including COVID-19. 12. To determine and compare changes in the immune system induced by vaccination of healthcare workers. 13. To identify factors (e.g. age, sex, chronic conditions such as diabetes and cardiovascular disease, smoking, asthma, prior BCG vaccination, genetics, other vaccinations including COVID-19-specific vaccines, latent TB, immunological/molecular factors) that influence immune responses, infection and COVID-19 risk. 14. *(Brazil specific) To identify biomarkers for diagnosing TB infection*

OUTCOMES AND OUTCOME MEASURES	Primary outcomes: 1. Symptomatic COVID-19 defined as: • a positive SARS-CoV-2 test (PCR, RAT or serology) over the 6 months following randomisation PLUS • fever (using self-reported questionnaire)OR • at least one sign or symptom of respiratory disease, including cough, sore throat, shortness of breath, respiratory distress/failure (using self-reported questionnaire) 2. Severe COVID-19 defined as: • a positive SARS-CoV-2 test (PCR, RAT or serology) over the 6 months following randomisation PLUS • Death (as a consequence of COVID-19) • Hospitalised (including mechanical ventilation and death), OR • Non-hospitalised severe disease, defined as Non-ambulant[1] for ≥ 3 consecutive days OR Unable to work[2] for ≥ 3 consecutive days [1] *"pretty much confined to bed (meaning finding it very difficult to do any normal daily activities"* [2] *"I do not feel physically well enough to go to work"* Secondary outcomes: All assessed at 6 and 12 months following randomisation unless otherwise indicated. - The following outcomes are for both COVID-19 and fever or respiratory illness: presence of disease, days unable to work, days confined to bed, of days with symptoms, pneumonia, need for oxygen therapy, admission to critical care, need for mechanical ventilation - Symptomatic or severe COVID-19, fever or respiratory illness - Time to first symptom of COVID-19, fever or respiratory illness - Deaths - Number of days of unplanned absenteeism - Type and severity of local and systemic adverse event over the 3 months following randomisation - Planned exploratory analyses: episodes of and time to first recurrence of herpes simplex recurrence, immunological studies
TRIAL POPULATION	7244 adult healthcare workers from Brazil, Europe and Australia (Victoria, Western Australia, South Australia and New South Wales) will be involved in the study, plus 2834 recruited in the earlier stage of this study. Key exclusion criteria are having BCG vaccine contraindication, previously had a SARS-CoV-2 positive test result and prior involvement in this trial at an alternate study site. Participants will be randomised at 1:1 ratio giving approximately 5039 per group.
DESCRIPTION OF SITES	Multiple sites will enrol healthcare workers in Brazil, Europe and Australia.

ENROLLING PARTICIPANTS	Australian sites involved in this study include the Royal Children's Hospital (RCH) VIC, Monash Health VIC, Epworth Healthcare VIC, Perth Children's Hospital WA, Fiona Stanley Hospital WA, Sir Charles Gairdner Hospital WA, the Royal Adelaide Hospital SA, Women's and Children's Hospital Adelaide SA, The Children's Hospital at Westmead NSW, Westmead Hospital NSW, Prince of Wales Hospital NSW, St Vincent's Hospital NSW and Sydney Children's Hospital, Randwick NSW. Recruitment and follow-up may occur on site or at centrally identified locations overseen by Regional and/or Site Investigators. In Brazil, the study will be carried out in three cities, Campo Grande-MS, Rio de Janeiro-RJ and Manaus-AM. In Campo Grande, the Faculty of Medicine of UFMS, State Regional Hospital of Mato Grosso do Sul, Municipal Health Units, CASSEMS Hospital, Santa Casa Hospital and Eyes Hospital of the Pantanal will participate. In Rio de Janeiro the Centro de Referência Professor Hélio Fraga (CRPHF) da Escola Nacional de Saúde Pública Sergio Arouca (ENSP), FIOCRUZ and Municipal Health Office of Rio de Janeiro. In Manaus, the Tropical Medicine Foundation and the State Health Department of Amazonas will participate. In the Netherlands the study will be carried out in Noordest Ziekenhuis Alkmaar, Rijnstate Hospital Arnhem, Amphia Hospital Breda, St Antonius Hospital Nieuwegein, Radboud UMC Nijmegen and Universitair Medisch Centrum Utrecht. In Spain the study will be carried out in University Hospital German Trias I Pujol Barcelona, Mutua Terrassa University Hospital Barcelona, University Hospital Cruces Bizkaia, Marqués de Valdecilla University Hospital Santander and University Hospital Virgen Macarena Sevilla. In the United Kingdom (UK) the study will be carried out in Teign Estuary Medical Group Devon, Ide Lane Surgery Exeter, Travel Clinic Exeter, St Leonard's Practice Exeter and Royal Devon and Exeter NHS Foundation Trust Exeter.
DESCRIPTION OF INTERVENTIONS	BCG vaccination group: BCG Denmark, 0.1 mL injected intradermal over the distal insertion of the deltoid muscle onto the humerus. Control group: 0.1 ml of 0.9% NaCl injected intradermal over the distal insertion of the deltoid muscle onto the humerus.
TRIAL DURATION	2.5 years
PARTICIPANT DURATION	13.5 months from randomisation to final follow-ups

GLOSSARY OF ABBREVIATIONS

ABBREVIATION	TERM
AE	Adverse Event
AR	Adverse Reaction
BCG	Bacillus Calmette–Guérin Vaccine
BRF	Biobank Registration Form (MCRI)
COVID-19	Coronavirus Disease 19
CPI	Chief Principal Investigator
CRF / eCRF	Case Report Form / Electronic Case Report Form
DSMB	Data Safety Monitoring Board
ED	Emergency Department
GCP	Good Clinical Practice
HCW	Healthcare Worker/s
HREC	Human Research Ethics Committee
ICH	International Conference on Harmonisation
ITT	Intention To Treat
MCRI	Murdoch Children's Research Institute
MERS	Middle East respiratory syndrome
NHMRC	National Health and Medical Research Council
NSE	Non-Specific Effects
NSW	New South Wales
PI	Principal Investigator
PPE	Personal Protective Equipment
QC	Quality Control
RAT	Rapid Antigen Test
RCH	Royal Children's Hospital (Melbourne)
RGO	Research Governance Office
RPI	Region Principal Investigator
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SOP	Standard Operating Procedure
SSI	Significant Safety Issue
SPI	Site Principal Investigator
SUSAR	Suspected Unexpected Serious Adverse Reaction
TB	Tuberculosis
TGA	Therapeutic Goods Administration
UAR	Unexpected Adverse Reaction
USM	Urgent Safety Measure

We use the following terminology with regards to the term 'investigators':

- ***Chief Principal-Investigator** – is used to describe the **overall trial level** Investigator for this multi-site trial: Prof Nigel Curtis of MCRI in Australia (Overall Sponsor)*
- ***Region Principal Investigator** – is used to describe **the region-level** Investigator (i.e. the Region Principal Investigator) responsible for an area including multiple sites in this multi-site trial.*
- ***Site Principal Investigator** – is used to describe **the site-level** Investigator at a participating site in a multi-site trial.*

For some trial sites, one investigator fulfils the role of both Region Principal Investigator and Site Principal Investigator.

INVESTIGATOR AGREEMENT

I have read the protocol entitled "*BCG vaccination to Reduce the impact of COVID-19 in healthcare workers BRACE) Trial*".

By signing this protocol, I agree to conduct the clinical trial, after approval by a Human Research Ethics Committee or Institutional Review Board (as appropriate), in accordance with the protocol, the principles of the Declaration of Helsinki and the good clinical practice guidelines [Integrated Addendum to ICH E6 (R1): Guideline for Good Clinical Practice E6 (R2), dated 9 November 2016].

Changes to the protocol will only be implemented after written approval is received from the applicable Human Research Ethics Committee or Institutional Review Board (as appropriate), with the exception of medical emergencies.

I will ensure that study staff fully understand and follow the protocol and evidence of their training is documented.

Name	Role	Signature and date
Prof Nigel Curtis	Chief Principal Investigator	
Prof Marc Bonten	Region Principal Investigator for the Netherlands and Spain	
Prof Peter Richmond	Region Principal Investigator for Western Australia	
Prof David Lynn	Region Principal Investigator for South Australia	
A/Prof Nicholas Wood	Region Principal Investigator for New South Wales, Australia	
Prof John Campbell	Region Principal Investigator for United Kingdom	
Prof Julio Croda	Region Principal Investigator for Mato Grosso do Sul, Brazil	
Prof Margareth Dalcolmo	Region Principal Investigator for Rio de Janeiro, Brazil	
Prof Marcus Vinicius Guimaraes de Lacerda	Region Principal Investigator for Manaus, Amazonas, Brazil	

1. ADMINISTRATIVE INFORMATION

1.1. Trial registration

This trial is registered on ClinicalTrials.gov, NCT04327206.

1.2. Overall Sponsor

Trial Sponsor	MCRI
Chief Principal Investigator Contact name	Nigel Curtis
Address	Royal Children's Hospital, 50 Flemington Road

On behalf of the Sponsor, MCRI, the Chief Principal Investigator leading the trial will undertake and/or oversee those Sponsor responsibilities delegated by the Sponsor.

1.3. Expected duration of study

The recruitment and IP administration period is expected to take place from March 2020 to March 2021. The individual's follow-up will be 13.5 months from randomisation.

1.4. Stakeholder involvement

Stakeholder
Murdoch Children's Research Institute (MCRI)
Melbourne Children's Trials Centre (MCTC)
Royal Children's Hospital (RCH)
Royal Children's Hospital Immunisation Service
Hospital directors and staff where participants (staff) will be recruited
Hospitals whose staff will be included as sites
Department of Health (for each state)
Australian Health Research Alliance (AHRA)

2. INTRODUCTION AND BACKGROUND

2.1. Trial rationale and aim

In recent months severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) has emerged as a novel human pathogen. With no pre-existing immunity against this virus, susceptibly among humans is presumed to be universal. Healthcare workers are at the frontline of novel infectious disease outbreaks such as this. Due to their contact with patients and production of aerosols during some medical procedures they have greater exposure and potentially risk of contracting newly emerged human pathogens. Current strategies to protect healthcare workers rely on the use (and sustained supply) of personal protective

equipment. Healthcare worker absenteeism due to infection with the outbreak pathogen or illness cause by another disease with similar symptoms, compounds the pressure already placed on the healthcare system.

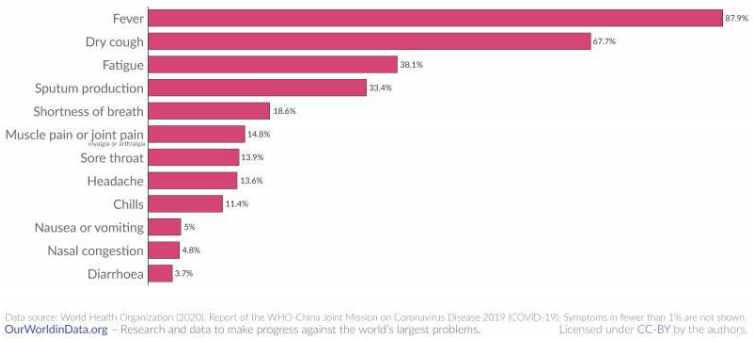
Prophylactic interventions to protect against emerging pathogens are needed, particularly for healthcare workers. The tuberculosis (TB) vaccine, Bacillus Calmette-Guérin (BCG) has beneficial off-target effects and has been shown to protect against non-TB infections[1]. This is proposed to result from BCG mediated boosting of early immune responses. As such, BCG vaccination represents a potential prophylactic intervention to provide protection against emerging pathogens such as SARS-CoV-2.

The aim of this trial is to determine whether in healthcare workers, BCG can reduce the incidence and severity of illness caused by the novel coronavirus, SARS-CoV-2.

2.2. Background

Since the emergence of coronavirus disease 19 (COVID-19) in China in December 2019, there have been over 18,000,000 cases disease and greater than 690,000 deaths caused by the disease globally[2] (as of August 2020). The causative agent of COVID-19 a novel coronavirus, severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2), has already spread to 108 countries (including over 200 cases in Australia) and it is predicted that up to 60% of the global population could become infected[3]. Following from SARS in 2002[4] and Middle East respiratory syndrome (MERS) in 2012[5], SARS-CoV-2 is the third coronavirus to make the jump from animals to humans and emerge as a serious human pathogen in less than 20 years.

In approximately 80% of cases COVID-19 results in mild to moderate disease with symptoms similar to common respiratory diseases such as influenza-like illnesses, with fever in the majority (87.9%) of cases, followed by dry cough (67.7%), fatigue (38.1%), sputum production (33.4%)[6]. In 14% of cases, SARS-CoV-2 causes severe disease requiring oxygen supplementation and/or mechanical ventilation, with a further 6% being critical cases that have respiratory failure, septic shock and/or organ failure.



There are worldwide efforts to reduce the peak of SARS-CoV-2 infection, in order to have enough hospital resources. However, with no vaccines or preventative interventions available to protect against COVID-19, current strategies rely on conventional control measures including travel restrictions, quarantines and increased hygiene practices. The overlap of COVID-19 symptoms with common respiratory diseases makes screening for SARS-CoV-2 infection difficult with diagnosis relying on microbiological confirmation of SARS-CoV-2 infection. Moreover, healthcare workers with these common respiratory symptoms are advised to be tested for SARS-CoV-2 infection prior to return to work. The loss of these healthcare workers with non-COVID-19 respiratory infections due to quarantine requirements places further pressure on the healthcare system during this critical time.

BCG, a vaccine given to over 120 million infants annually to protect against TB, represents a potential prophylactic intervention for the prevention of COVID-19. In addition to protecting against TB, BCG has beneficial off target (also termed 'heterologous' or 'non-specific') effects that protect against unrelated infections in children and adults[7-11].

The beneficial off-target effects of BCG vaccination have been most extensively studied in children. A world health organisation (WHO)-commissioned meta-analysis of 12 studies in high mortality settings concluded that BCG vaccination reduces all-cause mortality in children under 5-years of age by 30-53%[8]. This protection is evident within days of vaccination is proposed to be attributable to reduced deaths from infections other than TB, particularly respiratory tract infections and sepsis. Two large cohort studies in children similarly found that BCG reduces non-TB infections. The first, a 25-year retrospective study of over 150,000 children from 33 countries reported that BCG-vaccinated children had an up to 37% lower risk of acute lower respiratory tract infections[12]. The second, a study of paediatric hospitalisations in Spain, found that BCG-vaccinated children had a 41% lower risk of serious respiratory infection and 53% lower risk of sepsis not related to TB[13].

In adults, in a human challenge model, prior BCG vaccination reduced viraemia by over 70% and improved anti-viral immune responses to yellow fever vaccine virus[14]. Notably, yellow fever virus is a single-stranded, positive-sense RNA virus like SARS-CoV-2. Consistent with BCG mediated protection against infections, in two randomised control trials in adults, BCG vaccination reduced incidence of acute upper tract respiratory infections by 70-80%[15,16]. Several studies have also shown that BCG can reduce symptoms in human papilloma virus infection and herpes simplex virus infection adults[17].

A plethora of studies in animal models, have also shown that BCG protects against disease and mortality caused by a wide range of bacterial, fungal, protozoan and viral infections including infections with single-stranded, positive-sense RNA viruses[18-20].

The beneficial off-target effects of BCG are proposed to result from BCG induced changes in immune responses[1,14,19]. In adults, BCG vaccination increases immune responses to unrelated pathogens, an effect that is sustained for at least a year after vaccination[21]. BCG vaccination also boosts antibody responses to several vaccines including influenza vaccine[22-24]. Thus, in addition to protecting against viral infections, BCG provides further protection by increasing the efficacy of other vaccinations.

Therefore, by boosting the immune system, BCG vaccination may provide early protection against new human pathogens thus reducing their spread and severity. This will be of particular benefit among healthcare workers and high-risk groups for whom contraction of the disease would have the greatest impact.

This trial will determine whether BCG vaccination reduces the incidence and severity of COVID-19 but also whether BCG vaccination reduces other respiratory illnesses in healthcare workers. In this case of COVID-19, where symptoms overlap with common respiratory diseases and diagnostic tests currently take several days, the prevention of non-CODVID-19 respiratory illnesses will also reduce the strain on the healthcare system caused by the outbreak. This is particularly important in Australia and other countries in the southern hemisphere as the outbreak peak is expected to occur during the winter influenza season.

The results of this trial will establish whether, in future novel disease outbreaks, BCG vaccination could be implemented as an early intervention to protect healthcare workers and high-risk groups.

2.3. Risk/Benefit assessment

2.3.1. Known potential risks

This study involves minimal risk to participants.

HCWs randomised to receive BCG vaccine will have known potential risks associated with BCG vaccination. These risks are slightly increased for HCWs who have previously had BCG vaccine (revaccination), compared to HCWs receiving BCG vaccine for the first time (vaccine naïve).

There are additional known minimal risks for all HCWs re: blood tests and respiratory swabs.

<u>BCG vaccination</u>

Expected (common) reactions to BCG vaccination[25]:

- A small swelling, redness and tenderness (measuring 0.5-1.5 cm in diameter) at the injection site appears within 1-2 weeks at the injection site. The local lesion evolves into a small ulcer. The ulcer heals over several weeks to months, usually healing into a small flat scar.
- Slightly swollen lymph nodes in the axilla in up to 10% of recipients, and usually resolve spontaneously.

Revaccination is associated with an earlier, accelerated reaction which begins within 24–48 hours of vaccination with induration followed by pustule formation in 5–7 days and healing within 10–15 days[26] *(*https://www1.health.gov.au/internet/main/publishing.nsf/Content/cda-cdi3701h.htm)

Tuberculous skin lesions are more common in people over 15 years or with revaccination)[27,28].

Uncommon side effects of BCG vaccination (up to 1 in 100)[25,29-31]:

- Large ulcer, abscess at the injection site
- Keloid scar at injection site
- Swelling of lymph nodes in the armpit larger than 1 cm across

Rare side effects (up to 1 in 1000)

- Significant inflammation of lymph nodes in the axilla, sometimes with oozing ulcers, possibly abscess
- Infection with the bacteria from the vaccine can occur. The infection can spread throughout the body, including the bones (osteomyelitis)
- Allergic reaction or anaphylaxis (e.g.: redness of the face and neck, swelling of the face, throat or neck, skin rash, breathing difficulties and collapse)
- Fainting, seizures and convulsions (rare among patients receiving injections)

Very rare side effects (1–4 cases per million vaccinated people[25]):

- Disseminated BCG infection has been reported rarely after BCG vaccination, mainly in immunocompromised individuals (who are excluded from the trial).

Co-administration of vaccines:

- As indicated in the Australian immunisation handbook, BCG vaccine can be given at the same time as, or at any time after, other inactivated vaccines thus there is no additional risk for co-administration of influenza and BCG vaccines[25].

BCG vaccination in Europe (current recommendations) [32]

In Europe, recommendation for BCG vaccination varies among countries. In some, BCG is no longer recommended (e.g. Spain), whereas in others it is given routinely to all neonates (mainly Eastern Europe).[32] In the Netherlands it is limited to the children of parents from countries with a high incidence of tuberculosis (>50/100,000 people) and is not routinely recommended for healthcare workers.[33] In the UK, routine BCG vaccination of adolescents was stopped in 2005, with subsequent efforts focusing on high-risk groups for tuberculosis (UK 'Green Book' chapter 32).

BCG vaccination in Australia (current recommendations)

BCG vaccination in Australia is limited to selected high risk groups and is not routinely recommended for most healthcare workers (HCW)[26]. BCG vaccination is recommended for Aboriginal and Torres Strait Islander neonates in communities with a high incidence of TB; neonates and children 5 years of age and under who will be travelling or living in areas with a high prevalence of TB for extended periods; and neonates born to parents with leprosy. BCG should be considered in HCWs who may be at high risk of exposure to drug resistant cases. It is usually recommended that all individuals have a tuberculin skin test (TST) prior to BCG vaccination, except infants less than 6 months of age with no history of tuberculosis (TB) contact, and that BCG should not be given to an individual with a tuberculin reading of 5mm or more. Additionally, BCG revaccination is not recommended, regardless of TST reaction size[26].

BCG vaccination in Brazil (current recommendations)

In Brazil, BCG vaccination has been mandatory since 1976 in newborns. Revaccination in school-aged children (<6 years) was suspended in 2019. The REVAC trial evaluated adverse reactions resulting from BCG vaccination and revaccination in 71,347 Brazilian school-aged children. The authors concluded that the rate of adverse reactions associated with BCG revaccination is approximately twice the rate associated with vaccination, but this difference was not statistically significant. Similar results have been observed in previous studies that concluded that BCG revaccination is not associated with a higher rate of serious adverse events than primary BCG vaccination.[43,44]

Current contraindications of BCG vaccination

- BCG is contraindicated in immunocompromised individuals due to the risk of disseminated BCG infection[26]. This includes individuals immunocompromised by HIV infection, primary immunodeficiencies, corticosteroids or other immunosuppressive agents, and malignancies involving bone marrow of lymphoid systems.
- BCG is also contraindicated in individuals with any serious illness and those with generalised septic skin diseases and active skin conditions such as eczema, dermatitis and psoriasis near the site of vaccination[25].

- While BCG has not been shown to cause foetal damage the use of live vaccines is contraindicated in pregnancy [26].
- Individuals who have previously had tuberculosis or a large tuberculin (TST) reaction

In this study, HCWs will be excluded from the study if they are immunocompromised, have serious illness, skin disease at site of vaccination or are pregnant.

Global BCG recommendations and practices

The current World Health Organization (WHO) position is that BCG revaccination is not recommended for any person, as there is no evidence to support the role of BCG revaccination in protection against tuberculosis[34]. A number of countries have previously included BCG revaccination as part of their national immunisation policies[35]. In 1999, 30 countries in Europe and an additional 18 countries in the Middle East, South East Asia and the Western Pacific region reported using BCG revaccination. In several countries the national policy included BCG in infancy and again at school entry or leaving. In other countries, particularly in Eastern Europe, revaccination with BCG up to age five has been recommended. Some countries, such as Poland, recommended universal revaccination while others restrict revaccination to individuals without a BCG scar or those with a 'negative' TST. Criteria for TST negativity differs between countries [36,37]. ***In countries where BCG revaccination has been part of national immunisation practice, passive surveillance has not reported any particular issues, nor any cases of disseminated BCG in immunocompetent individuals.***

Pre-vaccination screening

TST and interferon gamma release assay (IGRA) screening aims to identify individuals with latent tuberculosis infection (LTBI)[38]. The diameter of induration following TST gives an indication of the likelihood of LTBI, however, positive results can also arise from previous BCG vaccination and exposure to environmental mycobacteria. This is in contrast to IGRA which are unaffected by previous BCG vaccination. A positive IGRA indicates either current or past infection with TB[38]. Screening of individuals using TST prior to BCG vaccination is recommended in Australia and other countries on the grounds that it may prevent complications due to pre-existing immunity due to previous exposure to mycobacterial antigens [28]. ***However, a large review of adverse effects of over 1.5 billion doses of BCG vaccine in adults and children showed that a positive TST did not increase the likelihood of complications from the BCG vaccine and did not predict the development of local skin reactions, abscesses or axillary lymphadenitis[27].***

Trials of BCG revaccination

Three large randomised controlled trials of BCG revaccination in children and adults in Malawi (n=54865), children in Guinea Bissau (n=2871) and adolescents in South Africa (n=990) did not show increased rates of serious adverse events among BCG revaccinated participants[15,39,40]. Participants in the Malawi study did not undergo any pre-randomisation screening with tuberculin skin test (TST) or interferon gamma release assay (IGRA)[39]. This study found a lower rate of leprosy amongst revaccinated participants but no difference in the rates of tuberculosis or death between the groups. Of the children in the Guinea Bissau

study, 3 of 6 children with a measurable TST (1-14mm) had increased rates of large local reaction compared to controls (18/388). Two months after revaccination all had healed vaccination scars with no axillary node enlargement, fever or suppurative lymphadenitis[40]. Participants in the South African study all had a negative IGRA at enrolment[15]. Among BCG revaccinated adolescents 93% reported mild local injection site reactions including swelling, induration, discharge, erythema, scab and ulceration. This was compared to 25% in the placebo group. The rates of moderate injection site reactions were similar between the BCG (5%) and placebo (6%) groups. There was 1 severe and 7 serious adverse events in each of the BCG and control groups. The serious adverse events reported in the BCG arm were not attributed to BCG revaccination and included gastroenteritis, chest injury, thermal burn, intentional self-injury, suicide attempt and small intestinal obstruction. The rate of upper respiratory tract infections was also lower in the BCG revaccinated group compared to placebo (2.1% compared to 7.9%, p<0.001).

Further studies looking at BCG revaccination in individuals with positive TST or IGRA do not show increased risk of significant adverse effects. A case-control study of 200 healthy nursing students in India included 28 participants with a positive IGRA who received BCG revaccination[41]. There were no serious side effects reported and no participants developed active tuberculosis during the follow-up study period. A randomised controlled trial of BCG revaccination in healthy adults with a positive TST (>15mm) with or without isoniazid pre-treatment (n=82) showed no difference in the rate of reactions between groups with only local injection site reactions (35-76%) and mild systemic adverse effects (19%) including headache, fever and nausea[42]. Among the 76% of participants who developed ulceration the median ulcer size was 5mm (IQR 4.0-6.0). Maximum ulcer diameter did not correlate with IGRA result prior to BCG vaccination in either group. There were no reports of regional lymphadenitis or serious morbidity.

Enhanced routine passive surveillance of BCG revaccinated school children in the BCG-REVAC trial in Brazil is available for 71718 individuals[43]. There are only 33 reported adverse events of which 60% were local cutaneous reactions and 28% axillary lymphadenopathy without suppuration. There were no deaths, permanent injuries or disseminated infections reported. In a case series of 13 children who experienced adverse events following BCG revaccination in Brazil all developed local ulceration or abscess formation with complete recovery following antimycobacterial therapy[44]. There were no cases of suppurative lymphadenitis or disseminated BCG. Further, an ongoing randomised trial in 150 participants in the US is giving repeat BCG (two vaccinations in the first year, then annually for 4 years) to adults aged 18-65 with type 1 diabetes to test if multiple BCG vaccinations can improve diabetic control and prevent complications[45]. They have reported variable local reactions but no increased risk of lymphadenopathy or disseminated BCG (Denise Faustman, personal communication).

The data presented above supports the WHO position that while BCG revaccination is not recommended due to a lack of evidence of efficacy against tuberculosis the risk of administering BCG vaccine to persons with positive tuberculin reactions due to either prior BCG vaccination or to natural infection is minimal.

One aim of the present study is to document the safety of BCG vaccination (and revaccination) in healthcare workers. The decision not to perform pre-vaccination TST screening in the study is pragmatic in order to reduce barriers to participation for already busy and stretched

healthcare workers during the current COVID-19 outbreak. While it does not align with current Australian vaccination guidelines it has been carefully considered upon systematic review of the literature presented above.

Risks related to Placebo injection

Having an injection can sometimes cause very minor pain from the needle or be uncomfortable. The 0.9% NaCl is an inert salt solution that will not cause any degree of local reaction. The placebo injection will be administered by a trained immunization nurse.

Risks related to blood sample collection

Having a blood test can sometimes cause some pain from the needle or be uncomfortable. Occasionally a small amount of bruising can occur on the skin where the blood was taken. Trained members of the study team will collect the blood samples from participants.

Risks related to respiratory swab collection

Having a respiratory swab can sometimes be uncomfortable. Trained members of the study team will collect the respiratory swabs from participants. Self-testing swab kits may be provided as required, with clear instructions to participants on safe self-swabbing technique.

2.3.2. Known potential benefits

In most places in the world, BCG is given to infants and children living in or travelling to TB endemic areas. In adults its efficacy is variable, and likely to have little effect in adults living in low prevalence settings (such as Australia, UK, Spain or the Netherlands) as their risk of TB is very low. BCG also protects against non-TB mycobacterial infections (e.g. leprosy, Buruli ulcer) but these are also rare in Australia and in Europe.

However, BCG also induce beneficial off target effects, and therefore BCG vaccination may reduce COVID-19 illness and other respiratory infections in study participants. In addition to the direct benefit this would give the participants by reducing disease, this would also benefit the healthcare facilities that they work at by reducing their need to be absent (symptom related quarantine or illness) and thus enabling them to continue working and supporting the healthcare system during this period of intense demand.

2.3.3. Assessment of potential risks and benefits

BCG vaccination has a well-established safety profile in healthy individuals. While there are known adverse reactions to BCG, serious adverse reactions are rare. BCG vaccination does also cause a scar in over 80% participants. Participants will be screened prior to BCG vaccination to ensure they have no known contraindications for BCG vaccination. Vaccination will be done by staff trained in intradermal injection to reduce the potential subcutaneous injection which can increase scarring. Blood tests and respiratory swabs will be done by trained staff. If necessary (e.g. insufficient testing capacity or personal protective equipment) participants may be asked to self-collect throat/nose swabs for later collection by study staff.

Given the minor risks of BCG vaccination, the potential benefits of BCG vaccination for the participants (by reducing COVID-19 and other respiratory infections), the healthcare system (by reducing absenteeism) during this current COVID-19 outbreak far outweigh them. In addition to this current outbreak, the findings of this study have major implications for future outbreak responses globally. If BCG vaccination is found to be effective at reducing COVID-19,

BCG vaccination could be implemented as an early preventative intervention in future outbreaks to protect healthcare workers globally. BCG vaccine is cheap and already administered to infants in over 80% of countries worldwide, therefore implementation of BCG vaccination campaigns during outbreaks is a feasible intervention to complement other preventative strategies.

We will be using BCG vaccine outside of its standard/recommended use, therefore, as per use of any intervention outside of standard regulations we will be assessing the reactogenicity and safety of BCG vaccination in vaccine naïve and previously vaccinated healthcare workers.

Risks will be continuously reviewed by continuously checking the literature and communicating with the other research group doing similar BCG trials. We have planned an interim analysis as well within our own cohort.

3 TRIAL OBJECTIVES AND OUTCOMES

3.1 Objectives

Two primary outcomes have been chosen for this study: occurrence of symptomatic COVID-19 and occurrence of severe COVID-19. Considering the number of unknown factors and the little knowledge of this new virus, we deemed it of clinical importance to have sufficient power to detect the potential effect of BCG vaccine compared to control for both outcomes (occurrence of symptomatic COVID-19, as well as occurrence of severe COVID-19). Our hypothesis is that, compared to control, the BCG vaccine will reduce both the number of cases of COVID-19 (increase the number of asymptomatic SARS-CoV-2 infections) and the number of severe cases of COVID-19. In other words, we have the hypothesis that BCG vaccine would be able to shift the "severity of COVID-19" curve down, i.e. to generally reduce the severity of the symptoms in healthcare workers. Because of the potential for multiplicity testing, the method of controlling type I error is explained in the sample size section (11.1).

3.1.1 Primary objective

1. To determine if BCG vaccination (Intervention) compared with placebo (Comparator) reduces the incidence of symptomatic COVID-19 (Outcome) measured over the 6 months following randomisation (Time) in healthcare workers (Participants).
2. To determine if BCG vaccination (Intervention) compared with placebo (Comparator) reduces the incidence of severe COVID-19 (COVID 19 related death, hospitalisation, or non-hospitalised severe disease (defined as Non-ambulant[1] for ≥ 3 consecutive days OR Unable to work[2] for ≥ 3 consecutive days) (Outcome) measured over the 6 months following randomisation (Time) in healthcare workers (Participants).

[1] "pretty much confined to bed (meaning finding it very difficult to do any normal daily activities"

[2]"I do not feel physically well enough to go to work"

3.1.2 Secondary objectives

3. To determine if BCG vaccination (Intervention) compared with placebo (Comparator) reduces the incidence of symptomatic COVID-19 (Outcome) measured over the 12 months following randomisation (Time) in healthcare workers (Participants).

4. To determine if BCG vaccination (Intervention) compared with placebo (Comparator) reduces the incidence of severe COVID-19 (non-hospitalised severe disease, hospitalisation or death) (Outcome) measured over the 12 months following randomisation (Time) in healthcare workers (Participants).
5. To determine if BCG vaccination (Intervention) compared with placebo (Comparator) prolongs the time to first COVID-19 episode (Outcome) measured over 6 and 12 months following randomisation (Time) in healthcare (Participants).
6. To determine if BCG vaccination (Intervention) compared with placebo (Comparator) reduces the severity of COVID-19 (Outcome) measured over 6 and 12 months following randomisation (Time) in healthcare workers (Participants).
7. To determine if BCG vaccination (Intervention) compared with placebo (Comparator) reduces the rate and severity of illness (fever or at least one sign or symptom of respiratory disease) measured over 12 months following randomisation (Time) in healthcare workers (Participants).
8. To determine if BCG vaccination (Intervention) compared with placebo (Comparator) reduces absenteeism (days off work) over 6 and 12 months following randomisation (Time) in healthcare workers (Participants).
9. To evaluate the safety of BCG vaccination in healthcare workers.

3.1.3 Planned exploratory analyses

10. To determine in a subgroup of adults with recurrent cold sores whether BCG vaccination compared with placebo reduces herpes simplex recurrences (such as cold sores).
11. To determine the BCG vaccination induces changes in the immune system that are associated with protection of healthcare workers from non-tuberculous infectious diseases including COVID-19.
12. To determine and compare changes in the immune system induced by vaccination of healthcare workers.
13. To identify factors (e.g. age, sex, chronic conditions such as diabetes and cardiovascular disease, smoking, asthma, prior BCG vaccination, genetics, other vaccinations including COVID-19-specific vaccines, latent TB, immunological/molecular factors) that influence immune responses, infection and COVID-19 risk.
14. *(Brazil specific) To identify biomarkers for diagnosing TB infection*

3.2 Outcomes

OBJECTIVE	OUTCOME & OUTCOME MEASURE
Primary	
1. To determine if BCG vaccination (Intervention) compared with placebo (Comparator) reduces the incidence of symptomatic COVID-19 (Outcome) measured over the 6 months following randomisation (Time) in healthcare workers (Participants).	Symptomatic COVID-19 by 6 months following randomisation defined as: Case definition • Positive SARS-CoV-2 test (PCR, RAT or serology), plus • Fever (using self-reported questionnaire), OR • At least one sign or symptom of respiratory disease including cough, sore throat, shortness of breath, respiratory distress/failure (using self-reported questionnaire)"
2. To determine if BCG vaccination (Intervention) compared with placebo (Comparator) reduces the incidence of severe COVID-19 (with COVID related hospitalisation, death, or non-hospitalised severe disease) (Outcome) measured over the 6 months following randomisation (Time) in healthcare workers (Participants).	Severe COVID-19 by 6 months following randomisation defined as Severe COVID-19 by 6 months following randomisation defined as: Case definition • Positive SARS-CoV-2 test (PCR, RAT or serology), PLUS • Death as a consequence of COVID-19, OR • Hospitalised as a consequence of COVID-19, OR • Non-hospitalised severe disease as a consequence of COVID-19, defined as non-ambulant[1] for ≥ 3 consecutive days or unable to work[2] for ≥ 3 consecutive days *[1] "pretty much confined to bed (meaning finding it very difficult to do any normal daily activities"* *[2] "I do not feel physically well enough to go to work" (excludes stay at home exclusively for quarantine/workplace restrictions)*
Secondary	
3. To determine if BCG vaccination (Intervention) compared with placebo (Comparator) reduces the incidence of symptomatic COVID-19 (Outcome) measured over the 12 months following randomisation (Time) in healthcare workers (Participants).	Symptomatic COVID-19 as defined above over the 12 months following randomisation
4. To determine if BCG vaccination (Intervention) compared with placebo (Comparator) reduces the incidence of severe COVID-19 (COVID related hospitalisation, death, or non-hospitalised severe disease) (Outcome) measured over 12 months following randomisation (Time) in healthcare workers (Participants).	Severe COVID-19 as defined above over the 12 months following randomisation
5. To determine if BCG vaccination (Intervention) compared with placebo (Comparator) prolongs the time to first COVID-19 episode (Outcome) measured over 6 and 12 months following randomisation (Time) in healthcare workers (Participants).	Time to first symptom of COVID-19 over the 6 and 12 months following randomisation.
6. To determine if BCG vaccination (Intervention) compared with placebo (Comparator) reduces the severity of COVID-19 (Outcome) measured over 6 and 12 months following randomisation (Time) in healthcare workers (Participants).	All the following measures will be assessed, over the 6 and 12 months following randomisation. • Number of episodes of COVID-19 disease as (defined above) • Asymptomatic SARS-CoV-2 infection (defined as:

	○ Evidence of SARS-CoV-2 infection (by seroconversion) and ○ Absence of any episodes of illness (using self-reported questionnaire) and ○ No evidence of exposure prior to randomisation • Number of days unable to work (using self-reported questionnaire) due to COVID-19 as defined above (excludes quarantine/workplace restrictions) • Number of days confined to bed (using self-reported questionnaire) due to COVID-19 as defined above • Number of days with symptoms due to for COVID-19 • Pneumonia cases (using self-reported questionnaire and/or medical/hospital records) due to COVID-19. • Need for oxygen therapy (using self-reported questionnaire and/or medical/hospital records) due to COVID-19 • Admission to critical care and duration of stay (using self-reported questionnaire and/or medical/hospital records) due to COVID-19. • Need of mechanical ventilation and duration (using self-reported questionnaire and/or medical/hospital records) • Hospitalisation and duration due to COVID-19 (using self-reported questionnaire and/or medical/hospital records) • Death due to COVID 19
7. To determine if BCG vaccination (Intervention) compared with placebo (Comparator) reduces the rate and severity of illness (fever or at least one sign or symptom of respiratory disease) measured over the 12 months following randomisation (Time) in healthcare workers (Participants).	All the following measures will be assessed, over the 12 months following randomisation For the following outcomes, fever or respiratory illness will be defined as: ○ fever (using self-reported questionnaire), or ○ at least one sign or symptom of respiratory disease including cough, sore throat, shortness of breath, respiratory distress/failure, or runny/blocked nose (in combination with another respiratory symptom or fever) fever or respiratory illness, as defined above • Severe fever or respiratory illness defined as: ○ Death, OR ○ Hospitalised, OR ○ Non-hospitalised severe disease, defined as non-ambulant[1] for ≥ 3 consecutive days or unable to work[2] for ≥ 3 consecutive days as a consequence of fever or respiratory illness, as defined above *[1] "pretty much confined to bed (meaning finding it very difficult to do any normal daily activities"* *[2] "I do not feel physically well enough to go to work" (excludes stay at home exclusively for quarantine/workplace restrictions)* • Number of episodes of fever or respiratory illness, as defined above • Number of days unable to work (using self-reported questionnaire) due to fever or respiratory illness, as defined above (excludes quarantine/workplace restrictions)

	• Number of days confined to bed (using self-reported questionnaire) due to fever or respiratory illness, as defined above • Number of days with symptoms due to fever or respiratory illness • Pneumonia within a febrile or respiratory illness (using self-reported questionnaire and/or medical/hospital records) • Need for oxygen therapy for a febrile or respiratory illness (using self-reported questionnaire and/or hospitalisation records) • Admission to critical care for a febrile or respiratory illness (using self-reported questionnaire and/or medical/hospital records) • Need of mechanical ventilation for a febrile or respiratory illness (using self-reported questionnaire and/or medical/hospital records) • Deaths as a consequence of an episode of fever or respiratory illness • Duration of hospitalisation for a febrile or respiratory illness (using self-reported questionnaire and/or medical/hospital records)
8. To determine if BCG vaccination (Intervention) compared with placebo (Comparator) reduces absenteeism (days off work) over 6 and 12 months in healthcare workers (Participants).	Number of days of unplanned absenteeism for an acute illness or hospitalisation (using self-reported questionnaire) within 6 and 12 months following randomisation
9. To evaluate the safety of BCG vaccination in healthcare workers.	Adverse events (AEs), over the 3 months following randomisation, by type, severity (graded using toxicity grading scale), relationship to intervention of adverse events (AEs) of interest. Serious Adverse Events, over the 3 months following randomisation
Exploratory analyses	
10. To determine in a subgroup of participants with recurrent cold sores whether BCG vaccination compared with placebo reduces herpes simplex recurrence (such as cold sores).	Herpes simplex recurrences (self-reported) over the 12 months following randomisation Number of episodes of herpes simplex recurrence (self-reported) over the 12 months following randomisation Time: to first of herpes simplex recurrence (self-reported) over the 12 months following randomisation
11. To determine the BCG vaccination-induced changes in the immune system that are associated with protection against non-tuberculous infectious diseases including COVID-19. 12. To determine and compare changes in the immune system induced by vaccination.	The immune system will be assessed by several methods including: - Cytokine levels in supernatants from whole blood stimulated with off-target pathogens (including BCG, *Staphylococcus aureus*, *Escherichia coli*) and Toll-like receptor (TLR) agonists, measured by multiplex - Cytokine production, activation and differentiation of immune cells (measured by flow cytometry) - Epigenetic modifications (e.g. histone methylation/acetylation and CpG methylation) measured by ChIP-Seq and/or microarray - Anti-vaccine and anti-pathogen (including SARS-CoV2) antibody levels measured by ELISA, multiplex or VirScan - RNA expression measured by qRT-PCR or RNA-Seq

13. To identify factors (e.g. age, sex, chronic conditions such as diabetes and cardiovascular disease, smoking, asthma, prior BCG vaccination, genetics, other vaccinations including COVID-19-specific vaccines, latent TB, immunological/molecular factors) that influence immune responses, infection and COVID-19 responses.	Association of demographic factors, exposure, genetic factors (e.g. single nucleotide polymorphisms) and immune factors (e.g. cell numbers, circulating cytokines, anti-vaccine/anti-pathogen antibodies) with the function of the immune system as described above and infection (including COVID-19) prevalence or severity as defined above
14. (Brazil specific) To identify biomarkers for diagnosing TB infection	Association of biomarkers (e.g. cytokines measured from QFT-Plus supernatants, whole blood transcriptional signature) with TB infection

4 TRIAL DESIGN

4.1 Overall design

This is a phase III, two group, multicentre, randomised placebo-controlled trial in up to 7244 frontline healthcare workers to determine if BCG vaccine reduces prevalence and the severity of COVID-19 during the 2020, SARS-CoV-2 pandemic. As part of this study, we plan to combine the data from this study in a pre-planned meta-analysis with data from the 2834 participants recruited in the first stage of this study which followed the same protocol but where participants were randomised between BCG and no BCG at the time of receiving an influenza vaccination, for a total sample size of 10078. Although we recognise that the first stage of this study was addressing a slightly different research question, we feel that it is important to combine data from the first stage of study as they both provide estimates of the efficacy of the BCG vaccination, which is critical to provide adequate power to determine the efficacy of the BCG vaccination. In Europe, there will be participating sites in the Netherlands, Spain and UK. The sites participating in the Netherlands are Noordest Ziekenhuis Alkmaar, Rijnstate Hospital Arnhem, Amphia Hospital Breda, St Antonius Hospital Nieuwegein, Radboud UMC Nijmegen and Universitair Medisch Centrum Utrecht. In Spain, University Hospital German Trias I Pujol Barcelona, Mutua Terrassa Univeristy Hospital Barcelona, University Hospital Cruces Bizkaia, Marqués de Valdecilla University Hospital Santander and University Hospital Virgen Macarena Sevilla. In United Kingdom, Teign Estuary Medical Group Devon, Ide Lane Surgery Exeter, St Leonard's Practice Exeter, Travel Clinic Exeter and Royal Devon and Exeter NHS Foundation Trust Exeter.

In Australia, participating sites are hospitals within Victoria, Western Australia, South Australia and New South Wales. Australian sites involved in this study include the RCH VIC, Monash Health VIC, Epworth Healthcare VIC, Perth Children's Hospital WA, Fiona Stanley Hospital WA , Sir Charles Gairdner Hospital WA, Royal Adelaide Hospital SA, Women's and Children's Hospital Adelaide SA, The Children's Hospital at Westmead NSW, Westmead Hospital NSW, Prince of Wales Hospital NSW, St Vincent's Hospital Sydney NSW and Sydney Children's Hospital, Randwick NSW.

In Brazil, there will be participating sites in Mato Grosso do Sul State, Rio de Janeiro and Amazonas. In Mato Grosso do Sul the principal site will the Faculty of Medicine of the Federal University of Mato Gross do Sul (UFMS) with additional locations: Regional Hospital of Mato Grosso do Sul, Hospital CASSEMS, Hospital Santa Casa and Municipal Health Units. In Rio de Janeiro the principal site will the Centro de Referência Prof Hélio Fraga (CRPFH) da Escola Nacional de Saúde Pública Sérgio Arouca (ENSP), FIOCRUZ and Municipal Health Office of Rio de Janeiro. Other sites in Rio de Janeiro and Mato Grosso do Sul will be identified. In

Amazonas the principal site will be Fundação de Medicina Tropical and Health State Office. Other sites in Brazil may be identified.

Recruitment may be held at participating sites or centrally identified locations with appropriate safety and privacy infrastructure.

Participants will be randomised to receive BCG or placebo.

During the first stage of the study in Australia, randomisation and immunisation coincided with the annual staff influenza immunisation roll out at each hospital. During the first stage of the study, influenza vaccine occurred at the same time as randomisation and BCG vaccination or no BCG for 2834 healthcare workers. During the second stage in locations where the annual influenza vaccine is available, participants are asked to confirm they have received the influenza vaccination a minimum of 72 hours prior to randomisation.

The control group will receive a placebo injection of 0.9% NaCl. Most people vaccinated with the BCG vaccine develop a papule/blister at the injection site around two-weeks after vaccination. Due to this, even using a placebo, it is not possible to completely blind participants to their treatment group allocation. The outcomes (symptomatic and severe COVID-19 or admission to hospital for COVID-19) are objective measures, it is however still plausible that participant's suspicion of their group allocation might bias the study results. This risk will be mitigated by using a placebo where an element of doubt over treatment allocation may persist even in the absence of scar formation. Members of the research team doing follow-up, data cleaning and analysis will be blinded to the group allocation (by the hiding of this variable and all other variables related to BCG from the dataset) until the formal detailed statistical analysis plan is confirmed and signed by all investigators and all data cleaning/preparation is complete.

Randomisation will be stratified for all factors that might influence the effectiveness of the intervention. For more details see section 6.

Follow-up for all participants will last 1-year. For each episode of fever with a respiratory symptom during the follow-up period, all participants complete a survey in a smartphone app, electronic message or by phone, and may have a home visit by members of the research team for sample collection (e.g. if the government ceases or limits COVID-19 testing; respiratory swab preferred, however blood sample will be taken if no swab testing kits are available). If necessary (e.g. insufficient testing capacity or personal protective equipment) participants may be asked to self-collect throat/nose swabs for later collection by study staff, or self-test a finger-prick blood sample and send a photo of the results to the study team.

4.2 Justification for dose

The dose and route of BCG administration are the standard accepted dosage for BCG vaccine when used to prevent TB. There is no justification to vary from this.

4.3 Trial population

4.3.1 Eligibility criteria

Participants will be assigned to a randomised trial treatment only if they meet all inclusion criteria and no exclusion criteria.

As soon as COVID-19-specific vaccine becomes available, for sites still recruiting participants into the BRACE trial, the site's study team will have to inform the participant before they provide consent, that there will be a delay in receiving their COVID-19-specific-vaccine by either (1) at least 7 days following BCG/placebo injection OR (2) in accordance with their relevant vaccine national guidelines whichever is the longest.

4.3.2 Inclusion criteria

- Over 18 years of age
- Healthcare worker
    - This is defined as anyone who works in a healthcare setting or has face to face contact with patients.
- Provide a signed and dated informed consent form
- Australian sites only: If annual influenza vaccination is available, receiving the influenza vaccine is an eligibility requirement. The influenza vaccine will be required a minimum of 3 days in advance of randomisation in the BRACE trial.
- Pre-randomisation blood collected

4.3.3 Exclusion criteria

- Has any BCG vaccine contraindication
    - Fever or generalised skin infection (where feasible, randomisation can be delayed until cleared)
    - Weakened resistance toward infections due to a disease in/of the immune system
    - Receiving medical treatment that affects the immune response or other immunosuppressive therapy in the last year.
        - These therapies include systemic corticosteroids (≥20 mg for ≥2 weeks), non-biological immunosuppressant (also known as 'DMARDS'), biological agents (such as monoclonal antibodies against tumour necrosis factor (TNF)-alpha).
    - People with congenital cellular immunodeficiencies, including specific deficiencies of the interferon-gamma pathway
    - People with malignancies involving bone marrow or lymphoid systems
    - People with any serious underlying illness (such as malignancy)
        - NB: People with cardiovascular disease, hypertension, diabetes, and/or chronic respiratory disease are eligible if not immunocompromised, and if they meet other eligibility criteria

- Known or suspected HIV infection,[11] even if they are asymptomatic or have normal immune function.
    - This is because of the risk of disseminated BCG infection[12,13]
- People with active skin disease such as eczema, dermatitis or psoriasis at or near the site of vaccination
    - A different adjacent site on the upper arm can be chosen if necessary
- Pregnant
    - Although there is no evidence that BCG vaccination is harmful during pregnancy, it is a contraindication to BCG vaccination. Therefore, we will exclude women who think they could be pregnant or are planning to become pregnant within the next month.
    - UK specific: Although there is no evidence that BCG vaccination is harmful during pregnancy, it is a contraindication to BCG vaccination. Therefore, we will exclude women of childbearing potential (WOCBP) who think they could be pregnant. See section 8.2 for definition of WOCBP and Appendix 3 for UK specific pregnancy test requirements.
    - Spain specific: If the patient is female, and of childbearing potential, she must have a negative pregnancy test (provided by Sponsor) at the time of inclusion and practice a reliable method of birth control for 30 days after receiving the BCG vaccination. See Appendix 6 for Spain specific requirements
- Another live vaccine administered in the month prior to randomisation
- Require another live vaccine to be administered within the month following BCG randomisation
    - If the other live vaccine can be given on the same day, this exclusion criteria does not apply
- Known anaphylactic reaction to any of the ingredients present in the BCG vaccine
- Previous active TB disease

- Currently receiving long term (more than 1 month) treatment with isoniazid, rifampicin or quinolone as these antibiotics have activity against *Mycobacterium bovis*
- Previous adverse reaction to BCG vaccine (significant local reaction (abscess) or suppurative lymphadenitis)
- BCG vaccine given within the last year

- Have previously had a SARS-CoV-2 positive test result (positive PCR on a respiratory sample or a positive SARS-CoV-2 diagnostic RAT test approved by the local jurisdiction's public health policy)
- Already part of this trial, recruited at a different site/hospital.
- Participation in another COVID-19 prevention trial
- Have previously received a COVID-19-specific vaccine

4.4 Lifestyle considerations

Not applicable

4.5 Screen failures

Screen failures are defined as participants who consent to participate in the trial but who are found, during the screening procedures, to be ineligible to continue into the trial. They therefore do not receive the intervention / are not randomised.

4.6 Recruitment and Consent

Potential participants will receive information (via email, healthcare facilities notice board and/or website/social media etc) about the trial. This will include a short blurb about the study and a link to a website where they can read further information contact details for further questions. Potential participants will be able to evaluate their eligibility online via the REDCap public link and having met the eligibility criteria access the site-specific participant information and consent form (PICF) prior to attending clinic.

Interested healthcare workers will be given the opportunity to talk with a member of the research team by phone or video conferencing if they have any questions (social distancing practices will still be applied wherever possible). The process will vary slightly between locations due to contextual adaptations, however, it will be built around the same core essentials:

- Providing accurate information regarding the trial through a combination of publicly available information and additional detailed explanation by trained study staff.
- Eligibility screening for all participants. If participants are ineligible no identifying information will be collected.
- Informed consent secured from all participants through signed (electronic or hard copy) PICFs. Consent will be voluntary and free from coercion.
- Study staff will confirm eligibility and consent with prospective participants.

The webpage text, PICFs (electronic or hard copy) and eligibility questionnaire will have prior approval of HREC before use.

In Australia, influenza vaccination 72 hours prior to randomisation is an inclusion criterion as outlined in 4.3.2. For sites outside Australia, the research team will provide recommendation to all participants not to have the influenza vaccine within the 72 hours prior or post randomisation.

For those who are eligible and provide informed consent, they will be asked to provide their contact details (including date of birth, healthcare card number or equivalent (except for Australia), name and other identifying details) and a baseline questionnaire on participant characteristic (demographics and environmental information) into either REDCap database or hard-copy forms based on national privacy regulations.

Participants will be told when completing eligibility check (before consenting) that pregnancy, or planning to become pregnant within the next month is a contraindication to getting BCG. We will ask that if they are unsure to do a home pregnancy test, and on the day of randomisation we will have pregnancy tests available that they can use to take away to self-test at the site before randomisation. In the UK and Spain completing a pregnancy test will be an eligibility requirement as outlined in Appendix 3 and 6. This will be done in a subtle way to limit the likelihood that other staff will be aware that they have requested a pregnancy test. We have structured it this way to allow people to test in the privacy of their homes rather than have a conversation with the researchers.

Because only 10,078 participants are to be recruited over multiple sites, it is possible that more staff will be interested in participating than can be included in the trial. Given there will likely be interested participants who complete e-consent (where relevant) but are not randomised (become sick, become ineligible, changed their mind) we will continue recruitment until we reach the required number of participants randomised (10,078 participants). Randomisation will cease on the day that 10,078 participants are randomised. On the consent form and other pre-information, interested participants will be informed that due to the limited numbers who can be included in the trial, despite consenting, we cannot guarantee they will be randomised.

Given the importance of finding an intervention that can be used early in future pandemics (before a disease-specific vaccine is available), we expect there will be significant interest from researchers to try and understand how BCG works to boost the immune system. To this end, we will include an optional consent for participants to indicate whether they are interested in being approached for other projects.

No identifying information will be provided to the hospital or recruiting sites regarding any staff who have consented to be part of the trial.

4.7 Pre-randomisation blood sample

To remain eligible for randomisation in BRACE a pre-randomisation blood sample must be provided. This blood sample will be taken at enrolment but can be taken up to 24 hours prior to randomisation. This sample cannot be taken after administration of the intervention or placebo.

4.8 Re-consent

As required, participants will be contacted through REDCap and sent appropriate and relevant information for re-consent. Re-consent materials will contain contact details for the study team so that participants can ask questions. Participants will be asked if they agree to the changes by signing the re-consent in either electronic or hard copy format depending on country specific ethics requirements. All participant information for re-consent will be approved by HREC prior to use.

5 INTERVENTION

5.1 Treatment arms

Intervention group: BCG vaccine
Comparator group: 0.9% Saline

5.2 Trial Intervention(s)

5.2.1 Description of trial investigational products

5.2.1.1 BCG vaccine SSI

	Freeze-dried powder: Live attenuated bacteria of the type *Mycobacterium bovis* BCG (Bacillus Calmette-Guerin), Danish strain 1331 0.1 ml vaccine contains between 2 to 8 x 10^5 colony forming units.
Active substance and excipients	Powder Excipient: Sodium glutamate Solvent for resuspension: magnesium sulphate heptahydrate, dipotassium phosphate, citric acid monohydrate, l-asparagine monohydrate, ferric ammonium citrate, glycerol 85%, and water for injections.
Trade or Generic name	BCG Vaccine SSI
Dosage form	Powder for Injection with solvent for resuspension
Route of administration	Intradermal

5.2.1.2 Placebo to match BCG vaccine SSI

Active substance and excipients	Sodium Chloride 0.9%.
Trade or Generic name	Sodium Chloride Injection BP or USP
Dosage form	Ampoule (10 mL)
Route of administration	Intradermal

5.2.2 Dosage

A single dose of BCG vaccine SSI or matched placebo will be given to all participants who are randomised. The adult dose is 0.1 mL (of BCG vaccine SSI or 0.9% NaCl) injected intradermally over the distal insertion of the deltoid muscle onto the humerus (approximately one third down the upper arm).

5.2.3 Dose modification

There are no allowable dose modifications

5.2.4 Storage and dispensing of BCG vaccine SSI

- Store between 2ºC - 8ºC
- Store in the original package in order to protect from light
- Do not freeze
- Do not use the vaccine after the expiry date which is stated on the carton as "EXP" and refers to the last day of the month listed
- Any unused vaccine at the end of the study, meaning vaccines unused after the last dosing of the last participant will be disposed of according to local regulations

Placebo – sodium chloride 0.9%

- Store less than 25ºC
- Do not use after the expiry date which is stated on the carton and ampoule as "EXP" and refers to the last day of the month listed
- Any unused sodium chloride 0.9% at the end of the study, unused ampoules after the last dosing of the last participant will be disposed of according to local regulations

5.2.5 Preparation

BCG Vaccine SSI

BCG Vaccine SSI consists of a powder and solvent for suspension for injection (2-8 x 10^5 CFU/0.1 mL dose).

Prior to reconstitution, the storage temperature of the BCG will be checked to ensure that the appropriate temperature has been maintained during storage, and transport (if applicable) unless the storage and transport has occurred in validated containers or conditions where the temperature is stable and the data readily available.

The rubber stopper must not be wiped with any antiseptic or detergent. In the eventuality of alcohol being used to swab the rubber stopper, it must be allowed to evaporate before the stopper is penetrated with the syringe needle. The BCG is re-suspended using the solvent provided according to the product directions then carefully inverted a few times to produce uniform resuspension of the lyophilised BCG. Study staff must not shake the vial. The study staff member who re-suspends the BCG will label the vial with the date, time of reconstitution and their initials.

To ensure a uniform suspension, and therefore dose, the vial will be gently swirled before drawing up each dose. When drawn up into the syringe the reconstituted vaccine should appear homogeneous, slightly opaque and colourless.

Each vial of BCG contains up to 10 adult doses. Study staff must NEVER administer the whole vial. Each vial can be kept for up to 4 hours after resuspension. During this time the vial is kept between 2-8°C. Each vial is discarded after 4 hours, or when the vial is empty, whichever occurs first.

Sodium Chloride 0.9% placebo

During each recruitment session sodium chloride 0.9% will be decanted using aseptic technique into an empty sterile amber glass vial or prepared in 0.1 mL dosing syringes as per local vaccination practices. The study staff member who prepares the sodium chloride for injection will record the date, time of the preparation and their initials.

The prepared sodium chloride for placebo can be kept for up to 24 hours. During this time the placebo is kept between 2-25°C. All prepared syringes or vials unused at the end of a vaccination session will be discarded.

5.2.6 Administration of trial drug

The vaccine or placebo will only be administered by clinician members of the study team trained in the intradermal vaccination technique.

The vaccinator will follow the vaccination SOP and relevant site safety requirements.

Administration of the BCG vaccine or placebo will take place in locations set-up by the study team prioritising participant safety for example ensuring appropriate facilities for management of any potential adverse event are available (e.g anaphylactic reaction, extremely rare). There will be space to allow for privacy for the participant if required (e.g. upper left/right arm not accessible due to clothing).

As per standard practice, participants will be required to remain at the site for 20 minutes after vaccination, in case an allergic reaction should occur, wearing a sticker “I have received the BCG vaccine at [time of vaccination]” for both BCG and placebo recipients.

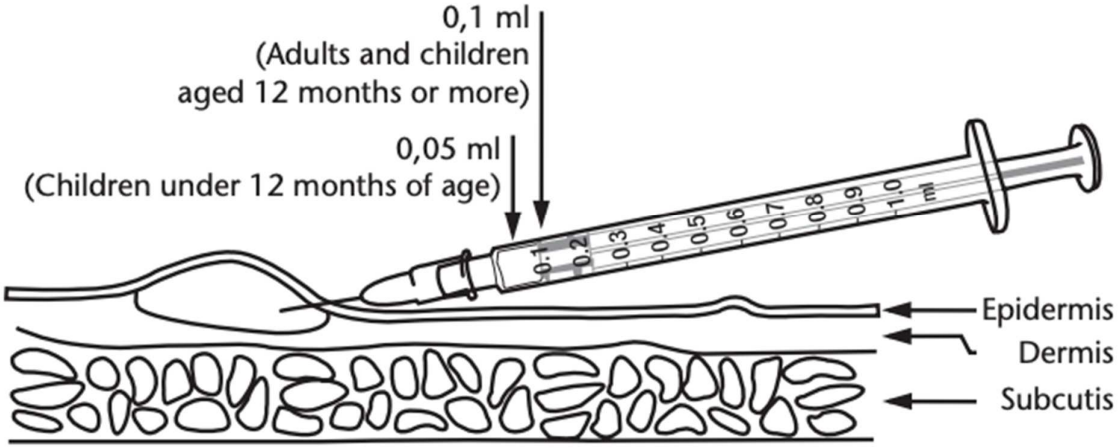
The time and date of resuspension of the vaccine vial, or placebo preparation, batch identifier, immunisation date/time, any issues with immunisation will be entered in the participants’ study record in REDCap Vaccinators database.

Route/method of administration

The injection site should be clean and dry using non-alcohol based antiseptic. Alcohol antiseptics should not be used prior to administration. If alcohol is used to swab the skin, it must be allowed to evaporate before the vaccine or placebo is injected. The vaccine or placebo must be given strictly intradermally, approximately one third down the upper arm corresponding to the area of the distal insertion of the deltoid muscle, as follows:

- The skin is stretched between thumb and forefinger
- The needle should be almost parallel with the skin surface and slowly inserted (bevel upwards), approximately 2 mm into the superficial layers of the dermis. The needle should be visible through the epidermis during insertion

- The vaccine or placebo should be given slowly



- The mixed vaccine should be administered with a syringe of 1 ml graduated into hundredths of millilitre (1/100) fitted with a short bevel syringe needle (Preference to use 25G or 26G, accepted up to 30G).
- You should feel considerable resistance as you give the injection. If there is no resistance, the needle may be in the subcutaneous tissues.
- If the injection is not intradermal, withdraw the needle and repeat at a new site.
- A raised, blanched papule/bleb of about 7 mm diameter (looks like orange peel) at the needle point is a sign of correct injection
- The injection site is best left uncovered to facilitate healing
- Jet injectors or multiple puncture devices should not be used to administer the vaccine.
- A photo of the bleb (with measuring tape or 10 cent coin used as scale (or equivalent in local currency)) should be uploaded in REDCap form.

Over/under dosage or incorrect administration

Overdose increases the risk of suppurative lymphadenitis and may lead to excessive scar formation. Gross over dosage increases the risk of undesirable BCG complications. Deep injections increase the risk of lymphadenitis and abscess formation.

The clinician members of the research team who administers BCG or placebo as part of this trial will be required to document whether the vaccination was given 'perfectly' with appropriate bleb. Any variations will be documented, and standard procedures followed regarding the need for re-administration, notification to RPI (or delegate).

Complications

All BCG-related complications will be referred to the SPI for advice regarding management. In the very unlikely event a participant has a systemic infection of *Mycobacterium bovis* or persistent local infection following vaccination the SPI will provide advice to the local treating team regarding management, including antibiotic treatment choice. Any serious adverse event or adverse event of interest occurring during the administration of the IP or the 20 minutes post administration will be documented appropriately according to the safety monitoring and reporting section of this protocol.

5.2.7 Product accountability

A pharmacy in each region will act as the study central pharmacy and coordinate the storage, distribution and maintain accountability records of the BCG vaccine and placebo supply in that region as appropriate. The RCH pharmacy will act as the study central pharmacy for Australia. The UMC Utrecht pharmacy will be the study central pharmacy in mainland Europe. A UK based pharmacy will act as the central study pharmacy should any UK sites be included in the trial. The LAC/UFMS will act as the central pharmacy in Mato Grosso do Sul, Brazil and a central pharmacy in Rio De Janeiro and Manus will be managed through the collaborating institution. Trial accountability of IP including documentation of storage, dispensation and destruction (if required) will be maintained in the pharmacy files at each region/site as appropriate. A pharmacy summary/manual will outline the specific processes for each region in line with local processes and regulations.

Any reason for departure from the expected dispensing regimen will be recorded. At the end of the trial, there will be final reconciliation of trial drug received, dispensed, used and returned. Any discrepancies will be investigated, resolved and documented by the study team.

5.2.8 Excluded medications and treatments

BCG vaccination may be given on the same day of any inactivated or live vaccines. If not given on the same day a period of not less than 4 weeks must pass before giving another live vaccine (although there is no real data supporting this precaution). There must be an interval of at least 3 months before a vaccination in the same arm can take place. Inactivated vaccine (such as the diphtheria-tetanus-pertussis vaccine) can be given in the other arm at any time before, during, or after BCG vaccination if needed.

Participants should not take part in any other COVID-19 preventative intervention clinical trials during the 6 month follow-up period.

5.2.9 Discontinuation from trial intervention

The trial intervention is a once-off vaccination. Due to this there is no possibility to 'discontinue the trial intervention'. If a participant changes their mind between randomisation and vaccination, deciding that they do not want to have the vaccination (but are happy to continue in the study for the follow-up period) they will be included in the analysis as intention to treat.

6 RANDOMISATION AND BLINDING

Once consent has been obtained, and following baseline assessment, eligible participants will be recruited and randomised on the day of the enrolment via REDCap. Randomisation will be to intervention or placebo group with an allocation ratio of 1:1, using a web-based randomisation procedure. The randomisation schedule and web-based service will be provided by an independent statistician from the Clinical Epidemiology and Biostatistics Unit (CEBU) at the Murdoch Children's Research Institute. Randomisation will be in randomly permuted blocks of variable length (2, 4, or 6). Randomisation will be stratified by stage of the study (prior to or post the addition of the placebo vaccination), study site, by age (<40 years; 40 to 59 years; >=60 years) and by presence of comorbidity (any of diabetes, chronic respiratory disease, cardiac condition, hypertension). Stratification by age is necessary for data analysis because

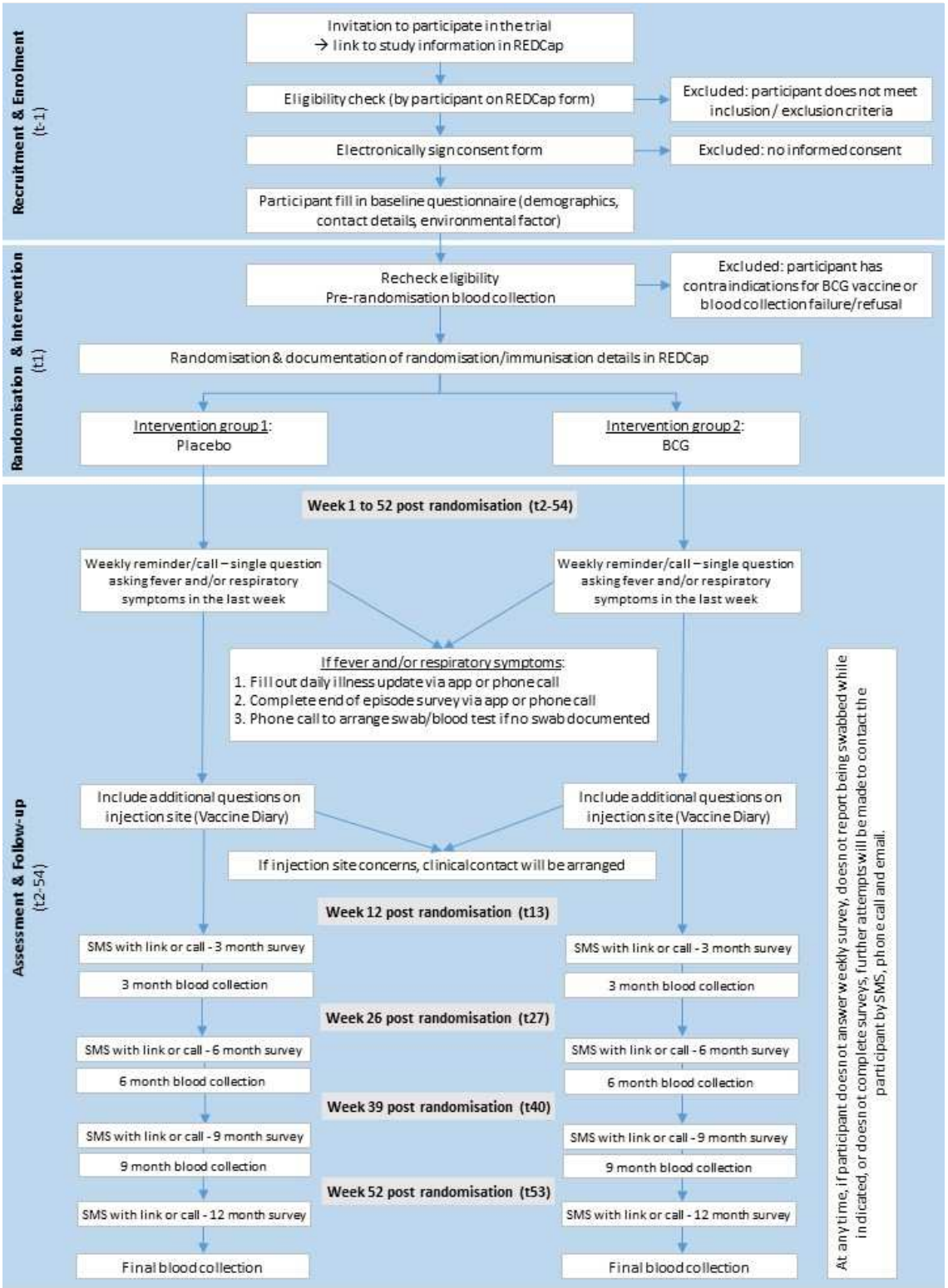
older ages are associated with a greater likelihood of developing severe COVID-19. Likewise, presence of comorbidity is associated with a greater risk of developing severe COVID-19. Each study site will have their own randomisation list stratified by study stage (where relevant), age and presence of comorbidity.

6.1 Concealment mechanism

The control group will receive a placebo of 0.9% NaCl. Most people vaccinated with the BCG vaccine develop a papule/blister at the injection site around two-weeks after vaccination. Due to this, even using a placebo, it is not completely possible to blind participants to their treatment group allocation. The outcomes (symptomatic and severe COVID-19 or admission to hospital for COVID-19) are objective measures, it is however still plausible that participant's suspicion of their group allocation might bias the study results. This risk will be mitigated by using a placebo where an element of doubt over treatment allocation may persist even in the absence of scar formation. Members of the study team, except immunisers, will be blinded to the group allocation (by the removal of this variable and all other variables related to BCG from the dataset) until the formal detailed statistical analysis plan is confirmed and signed by all investigators and all data cleaning/preparation is complete.

7 TRIAL VISITS AND PROCEDURES

7.1 TRIAL TIMELINE



7.2 Schedule of assessments

	TRIAL PERIOD									
	Pre-study	Inclusion & randomisation	Post-randomisation							
TIME POINT	t_{-1}	t_0	t_{1-12}	t_{13}	t_{14-25}	t_{26}	t_{27-38}	t_{39}	t_{40-51}	t_{52}
RECRUITMENT:										
Eligibility screen	X									
Informed consent	X									
Contact details	X									
Allocation to intervention		X								
INTERVENTIONS:										
BCG vaccine		X (BCG group)								
Saline injection		X (Placebo group)								
ASSESSMENTS:										
Baseline questionnaire	X	X								
Weekly survey			X	X	X	X	X	X	X	X
Instruction for swab testing *(if indicated by weekly survey)*			(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)
3-month survey				X						
6-month survey						X				
9-month survey								X		
12-month survey										X
*Clinical advice on injection site **			X	X						
*Blood collection***		X		X		X		X#		X#
*Baseline SARS-CoV-2 Test ****		X								

T=week (e.g. t1=first week). A 42day window period is accepted for the periodic survey and the blood collection timepoints
* In indicated Infectious Diseases clinician, or state-based organisation, as appropriate
** Optional consent for additional biological sample including blood sample when illness reported
*** Brazil only as outlined in Appendix 4
# Sub-set of participants

7.3 Description of procedures

The procedures related to recruitment, consent, eligibility confirmation, randomisation and intervention are described in sections 4 and 5 of this protocol. The procedure for blood collection is described in the relevant SOP. Capture of applicable adverse events is described in section 8.

In Brazil only, a baseline respiratory swab will be collected as outlined in appendix 4.

After randomisation there are two key aspects of the 1-year follow-up period; questionnaires and sample collections for SARS-CoV-2 identification (respiratory swabs or blood samples). Participants will be asked to complete a questionnaire using the smartphone application (app) designed for the trial, electronic messages or via phone calls to report symptoms, access SARS-CoV-2 testing through the public health system and if needed self-collect a respiratory swab each time they have a febrile illness or a respiratory symptom. Where app is utilised, participants will be trained on how to use the app on day of enrolment.

Questionnaires

Baseline

- Comorbidities: diabetes, cardiovascular disease, chronic respiratory disease, hypertension
- Risk factors: smoking, body mass index (calculated with weight and height)
- BCG/TB history: Prior BCG vaccination, ever positive TST
- Influenza immunisation: date of last influenza vaccine (if within influenza season)
- Exposure (presence of COVID-19 cases at workplace, average days working in hospital or other healthcare settings as appropriate)
- Other: Recurrent herpes infection (such as cold sores)

Regular (generally weekly) questionnaires on smartphone app, via phone call or via electronic messages

- Any symptoms of COVID-19: fever or at least one sign or symptom of respiratory disease such as sore throat, cough, shortness of breath, respiratory distress/failure (y/n)

For each episode of illness (via smartphone app, via phone call or via electronic messages)

- Which symptoms of COVID-19: fever, cough, shortness of breath and/or difficulty breathing, runny/blocked nose, sore throat, fatigue, muscle and/or joint ache, headache, nausea, vomiting and/or diarrhoea, loss of taste and smell
- Has a COVID-19 swab been taken? (if so what was the result)
- Date of/days since onset and cessation of symptoms
- Days absent from work (total number and number due to illness)
- ED presentations
- Hospital admission (oxygen, ICU admission, mechanical ventilation)
- Known test results
- If a swab has been taken for clinical purposes, who ordered it
- Impact on daily activities
- Days in bed
- Chest x-ray results

For local reaction to injection: the Vaccine Diary (daily diary for the two weeks following injection)

- Questionnaire collecting common reactions to the injection, including photograph of injection site

Periodic questionnaires (once every 3 months)

- Exposure (presence of COVID-19 cases at workplace, average days working in hospital or other healthcare settings as appropriate)
- Cold sore recurrence
- Request for participants to confirm the main episodes of illness experienced in the prior 3 months.
- Screening, exposure or treatment of TB

- Detail on other vaccinations
- Hospitalisation (any)
- Information regarding participation in any other COVID-19 preventative intervention clinical trials
- Injection site evolution and side effects (photo of injection site)
- Treatment that could influence COVID-19 outcome

Additional questions for 3rd month questionnaire only:

- Record any non-serious adverse event of interest, including Injection site evolution and side effects (photo of injection site), with onset between randomisation and 3 months post randomisation
- If relevant: Influenza vaccine side effects
- Record any serious adverse event with onset between randomisation and 3 months post randomisation

Swabs

- Where a participant has had a swab sample assessed outside the indication of the study (e.g. with non-respiratory symptoms or asymptomatic) results will be collected via self-report. All test results will also be obtained, where possible, from centralised SARS-CoV-2 testing government database.

Where a participant has symptoms of febrile or respiratory illness (cough, sore throat, shortness of breath) and a swab sample for SARS-CoV-2 is not collected through standard pathways (for example due to swab shortage, or government decision to restrict screening to high-risk patients), a sample collection study visit may be done. A respiratory swab/s may be collected from the participant at home and linked with the relevant public health testing and reporting systems. If respiratory swab/s are done by participant self-collection (e.g. nasal/throat swabs) they will receive full instructions on how to take the samples, when to take them and how to correctly store them until a member of the research team collects them.

Blood samples

- At randomisation, a blood sample will be taken for later assessment of seroconversion (production of specific anti-SARS-CoV-2 antibodies). This will identify participants who had SARS-CoV-2 exposure and immunity prior to commencement of the study.
    - The baseline blood samples will be analysed in batch months after randomisation, so there will be no clinically actionable results. We will provide individualised results to participants via email after completion of the trial. This email will be sent to the applicable HRECs to review before being sent out to any participant.
    - In Brazil, IGRA testing will be completed on pre-randomisation and 12-month blood samples as outlined in appendix 4.
- At 3 months and 6 months (+ 42 days) post randomisation, the study team will coordinate to collect study blood samples from participants and in a subset of participants at 9 and 12 months (+ 42 days) post randomisation. This will identify

participants who had an immune response to SARS-CoV-2 (surrogate marker of infection) during the study. This is needed to determine asymptomatic SARS-CoV-2 infections.

- Blood samples will also be taken for assessment of the immune system. This will be used to meet the planned exploratory analyses related to vaccine induced changes in the immune system. These blood samples will be taken at the same time as blood collection for serum or plasma samples (i.e. at randomisation and post randomisation)
- In the eventuality that it is unfeasible to collect swab samples to confirm SARS-CoV-2 infection at the time of febrile or respiratory illness episodes (or conduct a validated RAT test), seroconversion may be used to associate episodes of febrile or respiratory illness with SARS-CoV-2 infection. Therefore, for episodes of febrile or respiratory illness where a swab sample cannot be taken, 1 month after the onset of symptoms (expected peak post-infection antibody production), participants may be asked to come to the hospital to provide a blood sample. If rapid point-of care testing is available, these tests may be distributed to participants to self-test. Should these alternative methods of testing become required, an amendment will be submitted to HRECs to outline the process and submit any information for participants. This testing will not be conducted without further consultation with and approval from the HRECs, including providing the HRECs with details of the test and its efficacy.

For blood sample collection for serum/plasma plus analysis of the immune system, a venous blood sample (up to 10ml or up to 35ml depending on the study site) will be taken by a trained member of the study team and labelled with participant ID, date/time collected, study timepoint, year of birth (no identifying information). Samples will be transported to the site's designated laboratory for the trial. Samples will be processed for serum/plasma separation and analysis of the immune system and stored at -80˚C or in liquid nitrogen for later assessment.

A self-collected dried blood spot may be requested from participants instead of a venous blood sample collection. These may be stored in a locked cabinet prior to elution and storage at -80˚C. If blood samples are done by participant self-collection of dried blood spot, participants will receive full instructions on how to take the samples, when to take them and how to correctly store them until they are returned to the study site.

Data Retrieval

Data retrieval is further described in Section 9 of this Protocol.

The present study expects that it will acquire some research data from existing administrative and service data sources. In Victoria, for example, this would include obtaining details from the Victorian Department of Health and Human Services (VDHHS) who collects information about presentations to hospitals and emergency departments for medical care in Victoria. Similar processes will be followed in other Australian states. In mainland Europe and Brazil, participants will be required to consent to provide access to their medical records by study staff. In the UK self –reports from participants may be supplemented by tracking of participants using their NHS number or other relevant unique identifiers (provided by

participant), drawing on Hospital Episode Statistics and Office of National Statistics data to track health service use (admissions) and deaths.

7.4 Notes on specific trial visits

7.4.1 Unscheduled visit

If participants have any concerns related to side effects or the injection site evolution or scarring, they can call or email the study team for advice and if necessary, they will be seen by a clinician member of the study team or delegate. Reassurance, appropriate management or referral for medical care will be done according to best practice. Documentation of adverse event will be done as indicated in section 8.

7.5 Procedure discontinuation, participant withdrawals and losses to follow up

7.5.1 Discontinuation of blood collection - participant remains in trial for follow up

Participants that decline further blood collection may still continue in all other aspects of the study.

7.5.2 Withdrawal of consent - participant withdraws from all trial participation

Participants are free to withdraw from the trial at any time upon their request. Withdrawing from the trial will not affect their access to standard treatment or their employment as their participation will not be shared with their employer.

For the safety of all participants withdrawing from the trial, reasonable efforts should be made to undertake protocol-specified safety evaluations.

A dedicated Case Report Form (CRF) page will be used to capture the date of participant withdrawal of consent, and the reason if offered.

7.5.3 Losses to follow-up

Due to the study taking place with healthcare workers during a pandemic, we expect that there may be periods that participants will ignore the smartphone app prompts, phone calls or electronic messages. This includes the eventuality that a participant has been admitted to hospital. The weekly smartphone app prompts will only ask whether the participant has had a fever or respiratory symptom since the last time they answered in the app (date provided). Alternatively, where appropriate, phone follow-up will be used (i.e., Brazil). We deem this very unlikely to annoy participants excessively as they can ignore the notification or call if they are too busy (or withdraw). This will give the project the best chance of having a complete dataset to analyse as they can answer 'Yes' when they get the opportunity and fill in the associated questionnaire. Therefore, we will continue to send out weekly notifications or calls for the entire study regardless of whether participants respond.

In Australia and Europe, if a participant does not answer 2 regular smartphone app prompts (2 consecutive weeks), further attempts will be made to contact them by electronic messages (maximal 3 attempts), phone call (maximal 3 attempts) and email (maximal 3 attempts). If there is still no response, and the participant is not found to have died on medical records, we will try to contact them later (when the workload is expected to have decreased).

In Brazil, if a participant does not answer 3 follow-ups phone contacts (phone call or electronic messages), a home visit may be carried out by study staff. If there is still no response, and the participant is not found to have died on medical records, we will try to contact them later (when the workload is expected to have decreased).

Where secondary contact provided, the study team will follow-up if unable to contact participants.

7.5.4 Replacements

Participants who have been randomised may NOT be replaced.

7.5.5 Trial Completion

A participant is considered to have completed the trial if he or she has completed all processes of the trial including the last visit or the last scheduled procedure shown in the Schedule of Assessments.

The end of the trial is defined as completion of the last visit or procedure shown in the Schedule of Assessments in the trial at all sites. At the end of the trial, the Sponsor-Investigator will ensure that all HRECs as well as all regulatory and funding bodies have been notified, if required.

This trial may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. If the trial is prematurely terminated or suspended, the Sponsor and Investigators will promptly inform trial participants, HRECs, the funding (where applicable) and regulatory bodies, providing the reason(s) for the termination or suspension.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of an unexpected, significant, or unacceptable risk to participants that meets the definition of a Significant Safety Issue (for the definition refer to Section 8.1).
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Demonstration of efficacy that would warrant stopping
- Determination that the primary endpoint has been met
- Determination of futility

In the case of concerns about safety, protocol compliance or data quality, the trial may resume once the concerns have been addressed to the satisfaction of the sponsor, HRECs, funding and/or regulatory bodies.

7.5.6 Continuation of therapy

As the treatment is ‘once-off’ there is no provision for continuation of therapy.

8 SAFETY MONITORING AND REPORTING

8.1 Definitions

Adverse Event (AE):

An AE is any untoward medical occurrence in a participant administered an investigational product and does not necessarily have a causal relationship with the study treatment. For this study, only certain adverse events are recorded, specifically serious adverse events as defined below, and non-serious adverse events of interest specified in section 8.2

Serious Adverse Event (SAE) :

Any serious adverse event (SAE) is an untoward medical occurrence that:

- Results in death; or
- Is life-threatening; or
- Requires hospitalisation or prolongation of existing hospitalisation;
    - Hospitalisation is to be considered an SAE only in the event of an overnight admission. Any elective hospitalisation does not constitute an SAE
- Results in persistent or significant disability/incapacity; or
- Is a congenital anomaly/birth defect

Note: Life-threatening refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.

Medical and scientific judgement should be exercised in deciding whether an adverse event should be classified as serious in other situations. Important medical events that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the participant or may require intervention to prevent one of the other outcomes listed in this definition should also be considered serious.

For this study, all SAE will be collected for the period from randomisation to 3 months post randomisation.

Suspected Unexpected Serious Adverse Reaction (SUSAR):

A SUSAR is an AE that meets all of the following criteria:

- The AE is serious (as defined above; an SAE); and
- The SAE is suspected adverse reaction to the investigational product, meaning it is judged by either the reporting investigator or the Sponsor as having a reasonable possibility of a causal relationship to a study vaccine (possibly, probably or definitely related), and
- The SAE is also unexpected: An unexpected serious adverse reaction is one for which the nature or severity of the reaction is not consistent with reference safety information (Which is comprised of the BCG vaccine Product Information and the *WHO information sheet: Observed rate of vaccine reactions Bacille Calmette Guerin Vaccine April 2012*).

Note that an event is instead considered 'expected' if it is listed in the Reference Safety Information and therefore cannot meet the definition of SUSAR.

Significant Safety Issue:
A significant safety issue is an issue that could adversely affect the safety of participants or materially impact on the continued ethical acceptability or conduct of the trial.
Comment: A significant safety issue is a new safety issue or validated signal considered by the Sponsor in relation to the study vaccines that requires urgent attention of stakeholders. This may be because of the seriousness and potential impact on the benefit-risk balance of the study vaccines, which could prompt regulatory action and/or changes to the overall conduct of the clinical trial, including the monitoring of safety and/or the administration of the study vaccines.

Urgent Safety Measure (USM):
A measure required to be taken in order to eliminate an immediate hazard to a participant's health or safety. Note: This is a type of significant safety issue that can be instigated by either the investigator or Sponsor and can be implemented before seeking approval from HRECs or institutions.

8.2 Capturing and eliciting adverse event information

For the period of randomisation to 3 months post randomisation only, the following are non-serious adverse events of interest for this study:

- At injection site:
    - Reaction (pain, tenderness, redness, swelling) of grade 3 (severe) or 4 (potentially life threatening)
    - Abscess
    - Large ulcer (>1.5 cm diameter)
    - Keloid scar
    - Unusual local reaction
- Lymphadenopathy (in region of injection site)
- BCG osteitis/osteomyelitis
- Disseminated BCG infection (BCG-osis)
- Allergic reaction due to IP
- Fainting episode, seizures and convulsions following IP administration (recorded on the day of IP administration only)

Only these non-serious AE and all SAE, occurring between randomisation and 3 months post randomisation, will be recorded for this study. If applicable, for the remainder of the follow-up period, sites may additionally document participants' AE as required to meet reporting requirements of the applicable HREC/s and/or regulatory authority.

8.2.1 SAE capture

SAE are captured on the day of IP administration, as recorded by the site personnel. Information on any SAE since randomisation will be solicited from participants at the 3-month questionnaire. SAE may also be captured via participant notification, in the period

between randomisation and the 3-month questionnaire, such as through spontaneous contact by the participant via call or email, data entered in the Vaccine Diary or the study smartphone app (or equivalent, e.g. weekly phone calls). In cases where a participant does not respond to multiple attempts at contact, over several weeks, the participant's secondary contact will be contacted to confirm their status and record fatal SAE if applicable.

For this study, all SAE will be collected for the period from randomisation to 3 months post randomisation.

8.2.2 Non-Serious AE Capture

Non-serious AE of interest are captured:

- On the day of IP administration, recorded by the site personnel
- Within the Vaccine diary (which triggers an alert to the site personnel to contact the participant)
- Through the 3-month questionnaire (questions on injection site evolution)
- Through spontaneous contact (e.g. phone call, electronic message or email) from the participant to the site team.

8.3 Documentation of AEs

For the purposes of this study the investigator or delegate is responsible for recording the applicable Adverse Events, regardless of their relationship to study vaccines.

The documentation of each applicable AE on the REDCap CRF will include:

- A description of the AE
- The onset date, duration, date of resolution
- Severity
- Seriousness (SAE or not)
- Any action taken (e.g. treatment, follow-up tests)
- The outcome (recovery, death, continuing)
- The likelihood of the relationship of the AE to the trial treatment

All AEs will be followed to resolution or stabilisation, where possible.

8.4 Assessing the relatedness (causality) of a participant's AE

All non-serious AE of interest and SAE must have their relationship to the trial intervention assessed by the SPI (or delegate) who evaluates the AE based on temporal relationship and their clinical judgment. The degree of certainty about causality will be graded using the categories below.

The relationship of the event to the trial intervention will be assessed as follows:

Code	Causal Relationship	Description
1	Unrelated	The AE is clearly NOT related to the intervention
2	Unlikely	The AE is doubtfully related to the intervention
3	Possible	The AE may be related to the intervention
4	Probable	The AE is likely related to the intervention
5	Definite	The AE is clearly related to the intervention

8.5 Assessing the severity of a participant's AE

The SPI (or delegate) will be responsible for assessing the severity of an AE. The determination of severity for all AE should be made by the investigator based upon medical judgment and the severity categories of Grade 1 to 5 as defined in the first table below, with the following exceptions: injection site pain, redness, tenderness and swelling/induration are assigned severity grades using the specific toxicity grade specified in the second table below.

Grade	Severity	Description
Grade 1	Mild	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2	Moderate	Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL)
Grade 3	Severe	Severe or medically significant but not immediately life-threatening; hospitalisation or prolongation of hospitalisation indicated; disabling; limiting self-care ADL
Grade 4	Life Threatening	Life-threatening consequences; urgent intervention indicated
Grade 5	Fatal	Death related to AE

Toxicity grading scale

Local reaction to vaccination are monitored using Vaccine diary completed by the participant up to 14 days after vaccination. A toxicity grading scale is used to categorise the reports (Food and Drug Administration 2007):

Local reaction	**Grade 0** None	**Grade 1** Mild	**Grade 2** Moderate	**Grade 3** Severe	**Grade 4** Potentially life threatening
Pain	None	Does not interfere with activity	Repeated use of nonnarcotic pain reliever > 24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	Emergency room visit or hospitalization
Redness	None	2.5 - 5 cm	5.1 - 10 cm	>10 cm	Necrosis or exfoliative dermatitis
Tenderness	None	Mild discomfort to touch	Discomfort with movement	Significant discomfort at rest	Emergency room visit or hospitalization
Swelling / induration	None	2.5 - 5 cm and does not interfere with activity	5.1 - 10 cm or interferes with activity	>10 cm or prevents daily activity	Necrosis
Itch	None	Itching localised to injection site that is relieved spontaneously or in <48 hours of treatment	Itching beyond the injection site that is not generalised OR Itching localised to injection site requiring ≥48 hours of treatment	Generalised itching causing inability to perform usual social & functional activities	Not applicable

Food and Drug Administration. (2007). "Guidance for Industry: toxicity grading scale for healthy adult and adolescent volunteers enrolled in preventive vaccine clinical"
Retrieved 08.04.2020, from
https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Vaccines/ucm091977.pdf.

8.6 Reporting of safety events

Site Principal Investigator Reporting Procedures:

The SPI (or delegate) is responsible for expedited reporting (within 24 hours of becoming aware of the event) to the Sponsor the following:

- USMs
- All SAEs (including SUSAR)

SAE reports should be submitted using the REDCap SAE form, or by alternative means specified in the Safety Reporting Plan.

At MCRI, the CPI (or delegate) will determine whether or not each SAE meets the definition of SUSAR and will notify all RPI in a timely manner.

The RPI and SPI will be notified of USM and other significant safety issues in a timely manner following MCRI first knowledge of the event/s.

In each country, USM, other significant safety issues, SUSARs and other SAE, will be reported to the applicable regulatory authorities and HRECs in accordance with the requirements.

Further details of event reporting responsibilities and processes are documented in the Safety Reporting Plan.
For safety reporting requirements specific to Brazil, refer to Appendix 4.

9 DATA AND INFORMATION MANAGEMENT

9.1 Overview

The Site Principal Investigator is responsible for storing essential trial documents relevant to data management and maintaining a site-specific record of the location(s) of the site's data management-related Essential Documents.

The Site Principal Investigator is responsible for maintaining adequate and accurate files of any relevant source documents that include observations or other data relating to participants at their site. Source data will be attributable, legible (including any changes or corrections), contemporaneous, original, accurate, complete, consistent, enduring and available. Changes to source data (hardcopy and electronic) must be traceable, must not obscure the original entry, and must be explained where this is necessary.

The Site Principal Investigator will also maintain accurate case report forms (CRFs) (i.e. the data collection forms) where applicable and be responsible for ensuring that the collected and reported data is accurate, legible, complete, entered in a timely manner and enduring. To maintain the integrity of the data, any changes to data (hardcopy and electronic) must be traceable, must not obscure the original entry, and must be explained where this is necessary.

Any person delegated to collect data, perform data entry or sign for data completeness will be recorded on the delegation log and will be trained to perform these trial-related duties and functions.

9.2 Data management

9.2.1 Data generation (source data)

In this study, the following types of data will be collected:

- personal identifying information (names, dates of birth, contact details; NHS number in UK, SUS CARD and CPF in Brazil)
- sensitive information including health data (medical history, participant eligibility, adverse reactions and other notes as appropriate)
- participant completed electronic questionnaires
- de-identified data from laboratory assays

Source document plan

Much of the data for this trial will be collected electronically directly from participants. There will be a limited number of source documents for this study; recorded data from automated instruments, laboratory reports and the signed information and consent forms (in REDCap or hard copy). Each site participating in the trial will maintain a site-specific Source Document Plan that will document the source, i.e. original recording, for each data discrete item/ category of items collected for the study. This Source Document Plan, signed and dated by

the Site Principal Investigator, will be prepared prior to recruitment of the first participant and will be filed in the site's Investigator Site File.

9.2.2 Data capture methods and data use, storage, access and disclosure during the trial

Data collection methods

Data for this trial will be collected and entered using electronic database REDCap and a smartphone application developed for this trial. REDCap is a secure, web-based application for building and managing online surveys and databases. The trial smartphone application stores participant information directly in the REDCap database. In line with local privacy regulations, identifying or personal data may be maintained in complementary site level information management systems as required.

Use of the data

The data will be used for the analyses specified in the protocol and Statistical Analysis Plan.

Following the completion and analysis of the trial, the data will be retained long-term following the mandatory archive period for use in future research projects.

Storage and access

Hard copy data will be stored by collaborators in a locked cabinet in a secure location, accessible to the research team only.

Electronic data maintained on REDCap database will be securely stored in MCRI's 'network file servers, which are backed up nightly. Electronic or hard copy files containing private or confidential data will be stored only in locations accessible only by appropriate designated members of the research team.

REDCap is hosted on MCRI infrastructure and is subject to the same security and backup regimen as other systems (e.g. the network file servers). Data is backed up nightly to a local backup server, with a monthly backup taken to tape and stored offsite. REDCap maintains an audit trail of data create/update/delete events that is accessible to project users who are granted permission to view it. Access to REDCap will be provided via an MCRI user account or (for external collaborators) via a REDCap user account created by the MCRI system administrator. The permissions granted to each user within each REDCap project will be controlled by, and will be the responsibility of, the study team delegated this task by the Principal Investigator. REDCap has functionality that makes adding and removing users and managing user permissions straightforward. All data transmissions between users and the REDCap server are encrypted. The instructions for data entry to REDCap must be read and the training log signed prior to personnel commencing data entry on REDCap.

Authorised representatives of the sponsoring institution as well as representatives from the HREC, Research Governance Office and regulatory agencies may inspect all documents and records required to be maintained by the CPI for the participants in this trial. The trial site will permit access to such records.

Disclosure

The trial protocol, documentation, data and all other information generated will be held in

strict confidence. No information concerning the study or the data will be released to any unauthorised third party, without prior written approval of MCRI. Clinical information will not be released without written permission of the participant, except as necessary for monitoring by the HREC, Research Governance Office or regulatory agencies.

9.2.3 Data confidentiality

Data confidentiality

Participant confidentiality is strictly held in trust by the CPI, participating investigators, research staff, and the MCRI and their agents. This confidentiality is extended to cover testing of biological samples in addition to the clinical information relating to participating participants.

To preserve confidentiality and reduce the risk of identification during collection, analysis and storage of data and information, the following will be undertaken:

(1) The number of private/confidential variables collected for each individual has been minimised. The data collected will be limited to that required to address the primary and secondary objectives.

(2) Participant data and samples will be identified through use of a unique participant study number assigned to the study participant ("re-identifiable").

The CPI is responsible for the storage in REDCap of a master-file of identifiable data with the participant ID; access is managed by restricting user permissions to members of the research team and authorised persons.

(3) Separation of the roles responsible for management of identifiers and those responsible for analysing content. The data will be analysed by members of the research team who will be provided with anonymised data identified only by the unique participant study ID.

9.2.4 Quality assurance

A REDCap data dictionary with range checks will be used to minimise data entry errors, such as out-of-range values. Data quality control checks (e.g. checking for invalid characters, invalid dates, data that are not consistent with data in other data fields) and data cleaning will be done by trained members of the research team on a regular basis. Any discrepancies will be reported to the CPI or delegate and addressed in a timely manner.

Quality control checks will be run by the data team, on a regular basis, who will highlight any queries to the CPI, RPI and SPI.

9.2.5 Archiving - Data and document retention

Upon completion of the study, data will be stored securely on MCRI server (restricted access) and/or locked in secure cabinet in MCRI laboratories (for hardcopy data) for at least 15 years after study completion, in accordance with the requirements of the Therapeutic Goods Administration and Health Privacy Principles and any other relevant regulatory authorities.

Prof Nigel Curtis (CPI) will be the custodian during the archive period, and members of the research team will have access to the stored data. If the CPI becomes unable to perform this

task all responsibilities of the custodian will fall to the sponsor (MCRI). At the end of the archival period, long-term retention of the data may occur.

Records should not be destroyed without the written consent of the Sponsor. The Sponsor will inform Site Principal Investigators when these documents no longer need to be retained.

9.2.6 Data sharing

Data sharing- Bill and Melinda Gates foundation requirements

Under the terms of the funding agreement with the Bill and Melinda Gates foundation, the BRACE trial has a data sharing agreement in place. Further information about the requirement can be found here: https://openaccess.gatesfoundation.org/how-to-comply/data-sharing-requirements/. The key actions undertaken are:

- Registration of the BRACE trial with clinicaltrials.gov and provided all required information (https://clinicaltrials.gov/ct2/show/NCT04327206)
- Executed an agreement and created an account with Vivli, a Clinical Trials Data Sharing Repository (https://search.vivli.org/studyDetails/5090da81-0953-464f-9e46-3260697d4f22)

An anonymised Individual Participant Data (IPD) dataset and a data dictionary will be provided to Vivli (https://vivli.org/) under the terms of the agreements with the Bill and Melinda Gates foundation grant and Vivli.

Participant consent to the data sharing requirements is a mandatory requirement in updated Master PICF v8. Participants consented under earlier versions (prior to v7) of the PICF will be advised about the updated data sharing requirements and given an opportunity to opt-out via email of the data sharing arrangement. Data will not be shared, where participants have specifically requested their data not be shared.

After database lock, a 12-month embargo period will be in place, to allow adequate time for analyses and publication outputs. Data transfer to Vivli should occur during the embargo period.

After database lock, the following may be made available long-term for use by future researchers from a recognised research institution whose proposed use of the data has been ethically reviewed and approved by an independent committee and who accept MCRI's conditions, under a collaborator agreement, for accessing:

- Individual participant data that underlie the results reported in our articles after de-identification (text, tables, figures and appendices)
- Study protocol, Statistical Analysis Plan, PICF

9.2.7 Long-term custodianship (after archive period finished)

Prof Nigel Curtis will be the long-term custodian following the archive period. If he is unable to perform this task the responsibility of custodianship will fall to the sponsor (MCRI).

9.2.8 Data retrieval

The present study expects that it will acquire some research data from existing administrative and service. Participant consent may allow retrieval of datasets as has usually been the case of other MCRI studies.

In Brazil, this data can be retrieved, if necessary, from the national government information systems, such as E-SUS, SIVEP-GRIPE, GAL and electronic medical records from SESAU / CG / MS (Municipal Health Secretariat of Campo Grande / MS, through unique identifiers of the participant (registration in the Individual Taxpayer Register - CPF and SUS CARD).

We anticipate data access will occur after the study recruitment period is complete, but the exact timing is yet to be determined.

9.2.9 Sample management: Additional data management considerations

Data and information for biospecimens will be managed as above with the additional considerations.
Data collection: de-identified sample data may also be stored in OpenSpecimen (restricted access stored on secured servers at each study laboratory site), other site-specific electronic laboratory information management systems (LIMS, restricted access) or hard copy . Where biospecimen data are stored in OpenSpecimen or site-specific LIMS, data will be transferred to the MCRI servers on a regular basis. Where biospecimen data is collected on hardcopy, data will be transcribed to REDCap on a regular basis.

9.2.10 Sample management: Specimen collection & storage.

Biospecimens will be processed, stored and data will be recorded at laboratory study sites. Samples will be identified using barcoded tubes or with the unique participant study ID, and year of birth. No identifying information will be stored on biospecimen labels. Biosamples will be stored securely at laboratory study sites in temperature-controlled freezers and liquid nitrogen tanks as appropriate for the sample type. Access to biosamples will be restricted to the study team. The samples will be used for the analyses specified in the protocol. Samples will be shipped from study sites to MCRI for long term storage. For tests that require equipment or technical expertise not available in Melbourne, select specimens may be sent to collaborating laboratories outside of Melbourne (interstate and/or overseas) for further testing. These samples may be shipped from MCRI or directly from study sites if they have not yet been shipped to MCRI. Shipment of samples to MCRI or collaborating laboratories doing testing will be done by International Air Transport Association (IATA) accredited staff with temperature control (e.g. ice pack, dry ice) as appropriate for the sample type.

The biosamples will be retained long-term according to the banking management detailed below. As per data, Prof Nigel Curtis (CPI) will be the custodian of the biosamples during the archive period.

9.2.11 Sample management: Specimen & Biobanking

All samples that are not used immediately for the laboratory assessments described in previous sections, may be cryopreserved for an indefinite period of time to enhance the possible benefit from this study, by providing a sample biobank that may be used for research related to immunology or infectious diseases, in the future. The biobank will be at MCRI laboratories

(Infectious Diseases Group) in Melbourne, (please see Appendix 1 for Biobank Registration Form). The biobank will be registered with the Melbourne Children's Bioresource Centre (MCBC). Written informed permission (extended consent) for banking of specimens and future use for study objectives without further consent will be obtained from the participant. These samples may be used for additional research studies related to immunology or infectious diseases. For tests that require equipment or technical expertise not available in Melbourne, select specimens may be sent to collaborating laboratories outside of Melbourne (interstate and/or overseas) for further testing.

Databank is defined as: "A systematic collection of data, whether individually identifiable, re-identifiable or non-identifiable" (NHMRC National Statement on Ethical Conduct in Human Research)

Biobank is defined as: ".... collections of human biological materials (biospecimens) linked to relevant personal and health information (which may include health records, family history, lifestyle and genetic information) and held specifically for use in health and medical research." (NHMRC Biobanks Information Paper 2010)

10 TRIAL OVERSIGHT

10.1 Governance structure

10.1.1 Trial Steering Committee (TSC)

The trial steering committee will be made up of representatives from the key stakeholders and the chief principal investigator along with independent content expert(s).

10.1.2 Independent Data and Safety Monitoring Board (DSMB)

An independent Data and Safety Monitoring Board (DSMB) will be convened three times during the study: at 3 and 9 months post initial recruitment, and once there have been 100 severe case of COVID-19.

The DSMB at 3 and 9 months will monitor safety (including number of deaths and number of ICU admissions), data completeness, and the general study conduct.
A third DSMB is planned once there have been 100 cases of severe COVID-19. This interim analysis will primarily be on a comparison of the number of cases of severe COVID-19 (primary outcome (2)) between the BCG group and the control group for participants recruited post the introduction of the placebo (second stage of the trial). The DSMB will be given a stopping rule, but since the pandemic is rapidly evolving, the global situation should be considered with the context of any apparent differences. More information of this efficacy interim analysis is explained in section 11.4 of this current Protocol and on the Statistical Analysis Plan for the interim analysis.

All the details of the DSMB analyses will be outlined in the DSMB charter.

The DSMB will be composed of individuals with the appropriate expertise, including at least three independent clinicians and/or biostatisticians who, collectively, have experience in the management of biostatistics and the conduct and monitoring of randomised controlled trials.

Members of the DSMB will be independent of trial conduct. The DSMB will review data from each intervention group of the trial in a semi-blinded fashion. The DSMB will provide its input to the CPI.

10.1.3 Independent Safety Monitor

During the start of the recruitment period until August 2020, an independent safety monitor will review a report of sae and specified non-serious adverse events of interest on a weekly basis and report any concerns to the sponsor-investigator. For the remainder of the recruitment period, the monitor will review such reports monthly until June 2021, after which the reports will be review every 3 monthly.

10.1.4 Quality control and quality assurance.

Both the Chief Principal Investigator and Site Investigators have responsibilities in relation to quality management.

The Chief Principal Investigator will ensure the development of procedures that identify, evaluate and control risk for all aspects of the study, e.g. study design, source data management, training, eligibility, informed consent and adverse event reporting. The Chief Principal Investigator will ensure the implementation of quality control (QC) procedures, which will include the data entry system and data QC checks. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

The Site Principal Investigator will be responsible to ensure the verification that the clinical trial is conducted and data are generated and biological specimens are collected, documented (recorded), and reported in compliance with the protocol, good clinical practice and applicable regulatory requirements. In some regions a subcontracted monitor may be engaged by MCRI as needed.

In the event of non-compliance that significantly affects human participant protection or reliability of results, the Chief Principal Investigator (or delegate) and/or Site Principal Investigator (or delegate) will perform a root cause analysis and corrective and preventative action plan (CAPA).

In addition, each clinical site will perform internal quality management of study conduct, data and biological specimen collection, documentation and completion. An individualised quality management plan will be developed to describe a site's quality management.

11 STATISTICAL METHODS

11.1 Sample Size Estimation

7244 healthcare workers will be enrolled in the trial outlined in this protocol, although data from this trial will be combined with the data from the 2834 participants enrolled into the first stage of this study which followed an identical protocol but where participants were randomised between BCG and no BCG which was given concurrently with the influenza vaccination, resulting in a total sample size of 10078 participants.

Participants will be randomly allocated in a 1:1 ratio to BCG vaccine group (n=3622, plus 1417 from the first stage who received influenza vaccine at time of randomisation), and to control (n=3622, plus 1417 from the first stage who received influenza vaccine at time of randomisation and no 0.9% NaCl placebo). This sample size was calculated based on the two primary outcomes of (1) symptomatic COVID-19 and (2) severe COVID-19. Since the study aims to assess two primary outcomes, an adjustment for multiplicity will be applied to maintain a global Type I error rate of 5% by splitting of this alpha.

For the primary outcome (1), symptomatic COVID-19 at 6 months: it is conservatively estimated that a proportion of 55% of subjects will be infected by symptomatic COVID-19 in the placebo group; applying a 1:1 ratio for randomisation, a total sample size of n=2016 (1008 group) will provide 95% power with 2-tailed 0.005 significance level (10% of the global significance level) for the Pearson chi-square test (with continuity correction) to detect an absolute difference of 10% between an incidence of symptomatic COVID-19 of 45% in the BCG vaccine group and 55% in the placebo group.

For the primary outcome (2), severe COVID-19 at 6 months, we powered the study to identify a risk ratio of 0.67 in the BCG compared with the placebo group for severe COVID-19 at 6 months (which is much more realistic than a risk ratio of 0.5 as per the original sample size). Assuming that 4% of subjects will be infected by severe COVID-19 by 6 months in the control group, a total sample size of n= 6076 (3038 per group) will provide 80% power with 2-tailed 0.04 significance level (80% of the global significance level) for the Pearson chi-square test to detect a risk ratio of 0.667, equivalent to an absolute difference of 1.3%. Note this calculation was conducted using an alpha of 0.04 to allow the remaining 0.01 to be spent on primary outcome (1) (alpha=0.005) and the interim analysis as originally planned (alpha=0.005, see section 11.4 for details of the interim analysis, total alpha for this outcome=0.045). Allowing for a 16% loss to follow up, it is planned that the study will recruit 7244 healthcare workers.

In the pre-planned meta-analysis, we will have a sample size of 10,078 participants (7244+2834), or 8062 participants allowing for an overall 20% loss to follow up. For the combined analysis it is expected that the drop-out will be slightly higher (20% instead of 16%) because it also includes participants recruited prior to the introduction of the placebo, i.e. not placebo controlled. Again assuming that 4% of subjects will be infected by severe COVID-19 by 6 months in the control group, a total sample size of n=8062 (4031 per group) will provide 90% power with 2-tailed 0.04 significance level for the Pearson chi-square test to detect a risk ratio of 0.667, equivalent to an absolute difference of 1.3%. This will be a secondary analysis of the final study report.

The original trial plan included a meta-analysis on all the outcomes (both COVID-19 and non-COVID-19 related outcomes) combining data from Stage 1 and Stage 2 participants. Stage 1 healthcare workers were recruited only in Victoria and Western Australia, both of which Australian states had almost negligible COVID-19 exposure risk during that trial period (30th Mar 2020 to 13th May 2020). In light of this, the overwhelming majority of Stage 1 blood samples are likely to be seronegative. Moreover, with a low prevalence of COVID-19, there is a high probability that positive SARS-CoV-2 serology results are false positive. For these reasons, in December 2021 the BRACE team has agreed that it is not justifiable to devote extra resources (time and costs) to the data cleaning of potential COVID-19 episodes and SARS-CoV-2 serology for all participants in Stage 1. As a consequence, the meta-analysis will

only be run on non-COVID-19 related outcomes and its main objective will be to determine if BCG vaccination compared with control reduces the rate and severity of febrile or respiratory illness over 12 months following randomisation in Stage 1 and Stage 2 healthcare workers.

11.2 Population to be analysed

The primary analysis of all outcome data will be an intention-to-treat (ITT) analysis including all randomised participants, regardless of whether they received trial drug.

11.2.1 Handling of missing data

For the primary analysis the imputation of missing data will only be considered if 10-20% of the primary outcome is missing and will be undertaken using multiple imputation (MI) models. Multiple imputation analysis will be performed on the ITT population. The frequency and patterns of missing data will be examined. Multiple imputation models will be conducted separately in the two treatment groups using chained equations applied to all outcomes, including baseline measures, as auxiliary variables. Fifty imputed datasets will be generated including all randomised subjects.

11.3 Methods of analysis

Data analysis for the study will be performed by CEBU at MCRI. Ms Francesca Orsini has been appointed for the trial.

Statistical analysis will follow standard methods for randomised trials and the primary analysis will be by intention to treat (ITT), including all randomised participants.

Categorical variables will be presented as the number and proportion in each category. Continuous variables will be presented as means and standard deviations (SDs), or medians and interquartile ranges for skewed data, and the range.

PRIMARY ANALYSIS. Comparison between the BCG and placebo groups in the proportions of participants with symptomatic COVID-19 (primary outcome 1), as well as in the proportions of participants with severe COVID-19 (primary outcome 2), will be presented as the absolute risk difference (RD) as well as the risk ratio (RR) at 6 months and their 95% confidence interval (CI), obtained using a generalised linear model, with adjustment for the strata (defined by site, age and presence of comorbidity) used in the randomisation. The same analysis will be repeated on the same outcomes at 12 months. As secondary analyses the same models will be run to include also the following covariates: gender, number and type of comorbidities, whether already vaccinated for BCG in the past, and any other factor that may show imbalance between the groups at baseline.

A secondary analysis will be performed as above on the total 10078 participants, comparing all the participants who were randomised to BCG (irrespective of whether they received influenza vaccine at randomisation) and those randomised to control (irrespective of whether they received influenza vaccine or placebo at randomisation). Analysis will be as described above, but also adjusted for being in the initial stage of the study. As part of this analysis we will conduct an exploratory analysis of whether the treatment effect varies between the two stages of the study (prior to and post the introduction of the placebo) by including an

interaction between treatment and study stage. Results will be interpreted with caution given that the study is underpowered for this comparison.

SECONDARY OUTOMES. According to the nature of the secondary outcomes to be analysed (binary, continuous or categorical) the appropriate generalised linear model (GLM) will be used to estimate the effect of the BCG vaccine on the outcome of interest compared to the control group. All analyses will be adjusted for the stratification factors used in the randomisation (site, age and presence of comorbidity). As secondary analyses the same models will be run to include the following covariates: sex, number and type of comorbidities, whether already vaccinated for BCG in the past, and any other factor that may show imbalance between the groups at baseline.

Survival analysis techniques will be adopted to analyse time to event data.

A secondary analysis will be conducted on the total 10078 participants using the same methodology but also adjusted for being in the initial stage of the study. We will conduct an exploratory analysis of whether the treatment effect varies between the two stages of the study by including an interaction between treatment and study stage.

Sub-group analyses will be undertaken on outcomes of those who:

- Had previous BCG vaccine before enrolling into the trial
- Had a positive serology to SARS-CoV-2 when enrolling into the trial

The full details for each variable will be included in the Statistical Analysis Plan (SAP).

11.4 Interim Analyses

As part of the interim monitoring there will be a single formal interim analysis of the efficacy data. This interim analysis will be on a comparison of the number of cases of severe COVID-19 (primary outcome (2)) between the BGG group and the control group for those recruited post the introduction of the placebo (second stage of the study). The timing of the interim analysis will be event driven, and will be conducted using a time-to-event analysis, censoring participants who have not had the event at the time of their last follow-up. This data will be used to provide Kaplan-Meier estimates of the survival curve in the BCG and control groups, which will be used to estimate the proportion with severe COVID-19 at 6 months. These proportions will be used to compare the two groups.

The timing of the interim analysis will be determined by the original sample size calculation. Under the original sample size calculation, with 1668 per group and an incidence of 4% in severe COVID-19 at 6 months in the control group and 2% in the intervention group, this would equate to 67 + 33 = 100 cases in total. We therefore planned to conduct a formal interim analysis of severe COVID-19 once there had been 100 cases of severe COVID-19.

The stopping rule to be used in the interim analysis will be based on an alpha spending function, where the threshold to identify efficacy is based on the amount of data available at the time of the interim analysis relative to the data available at the end of the trial. The threshold for the interim analysis and the remaining alpha for the final analysis if the study is not stopped at the interim will be calculated using the Group Sequential Test (GST) of Two Proportions in NQuery (PTT12-1) with an alpha-spending function based on the Pocock stopping rule. This calculation will be based on an overall alpha of 0.045 for the primary

outcome (2), and the amount of available information at the time of the interim analysis (calculated as the percentage of participants with outcome data on severe COVID by 6 months relative to the final sample size).

This interim analysis of severe COVID-19 will be performed on all of the participants randomised into Stage 2 of the trial up to the interim analysis time point, comparing all the participants who are randomised to BCG and those randomised to placebo.

A statistical analysis plan for the interim analysis will be written, shared with the DSMB and made publicly available prior to undertaking the interim analysis. This analysis plan will provide all the details of the interim analysis, including the threshold to be adopted for the interim analysis.

Given the dynamic nature of research in this field, the DSMB will be advised that this rule be used as a guideline rather than a formal rule, and should be interpreted in the context of external information and information on the efficacy of BCG vaccination on the incidence of symptomatic COVID-19.

12 ETHICS AND DISSEMINATION

12.1 Research Ethics Approval & Local Governance Authorisation

This protocol and the informed consent document and any subsequent amendments will be reviewed and approved by the applicable human research ethics committee (HREC) prior to commencing the research at each site. A letter of protocol approval by HREC will be obtained prior to the commencement of the trial, as well as approval for other trial documents requiring HREC review.

12.2 Amendments to the protocol

This trial will be conducted in compliance with the current version of the protocol. Any change to the protocol document or Informed Consent Form that affects the scientific intent, trial design, participant safety, or may affect a participants willingness to continue participation in the trial is considered an amendment, and therefore will be written and filed as an amendment to this protocol and/or informed consent form. All such amendments will be submitted to the HREC, for approval prior to being implemented.

12.3 Protocol Deviations and Serious Breaches

All protocol deviations will be recorded in the participant record (source document) and on the CRF and must be reported to the CPI or delegate, who will assess for seriousness.

Those deviations deemed to affect to a significant degree rights of a trial participant or the reliability and robustness of the data generated in the clinical trial will be reported as serious breaches. Reporting will be done in a timely manner (the CPI or delegate to review and submit to the approving HRECs within 7 days, or as required).

Where non-compliance significantly affects human participant protection or reliability of results, a root cause analysis will be undertaken and a corrective and preventative action plan prepared.

Where protocol deviations or serious breaches identify protocol-related issues, the protocol will be reviewed and, where indicated, amended.

13 CONFIDENTIALITY

Participant confidentiality is strictly held in trust by the participating investigators, research staff, and the sponsoring institution and their agents. This confidentiality is extended to cover testing of biological samples in addition to the clinical information relating to participating participants.

The trial data and all other information generated will be held in strict confidence. No information concerning the trial or the data will be released to any unauthorised third party, without prior written approval of the sponsoring institution. Authorised representatives of the sponsoring institution may inspect all documents and records required to be maintained by the Investigator. The clinical trial sites will permit access to such records.

All laboratory specimens, evaluation forms, reports and other records that leave the site will be identified only by the Participant Identification Number (SID) to maintain participant confidentiality.

Clinical information will not be released without written permission of the participant, except as necessary for monitoring by HREC or regulatory agencies.

14 PARTICIPANT REIMBURSEMENT

In Australia and Europe, participants will not be reimbursed for their involvement.

As outlined in appendix 4 in Brazil in line with federal legislation, expenses resulting from participation in the study, such as transportation to the place where the vaccination will be carried out will be reimbursed. The amount will not be considered substantial and reimbursement system will be designed to reduce risk of reimbursement being considered compensation or inducement to participant in the trial.

15 FINANCIAL DISCLOSURE AND CONFLICTS OF INTEREST

This is an investigator-initiated study, and the funders will have no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript. MCRI holds no commercial interest in the manufacture and trade of BCG.

16 DISSEMINATION AND TRANSLATION PLAN

The results of the trial will be reported to the participants after analysis is complete. The results of this trial will be submitted to peer reviewed journals, presented at conferences and may form part of student theses.

The Chief Principal Investigator holds primary responsibility for publication of the results of the trial.

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17.1 Appendix 1: Specimens for biobanking - completed biobank registration form

Document version & date	Version 1.1 24th Aug 2020
Name of the bank	BCG vaccine to prevent severe COVID-19 in healthcare workers (BRACE)
Custodian of the bank	Name: Prof Nigel Curtis
Purpose of the bank	To store data and samples collected in the ':BCG vaccination to Reduce the impact of COVID-19 in healthcare workers (BRACE)' trial so they can be used in future research related to infectious diseases and immunity.
Sample/data type(s) and where these will be accessed from and over what time period	Data will be collected from Questionnaires and test results obtained as part of the research project 'BCG vaccination to Reduce the impact of COVID-19 in healthcare workers (BRACE)', by members of the research team. Blood and/or swab samples will be obtained via this research project and stored for an indefinite period of time. The samples/data may be sent overseas for future research related to infectious diseases, immunology, or vaccines. Data stored includes: - Demographics (e.g. age, gender, date) - Environment (e.g. household members, exposure to SARS-CoV-2 positive people, role in the hospital, TB exposure, previous vaccinations) - Study outcome related data (e.g. SARS-CoV-2 test results, BCG and influenza vaccine reactions, illnesses during study period, data generated from the laboratory analysis of samples collected) Sample types stored: - Swabs - Plasma - Serum - Peripheral blood samples - Granulocytes and whole blood - Nucleic acid After data ceases to be collected directly from participants, data may be obtained/generated via access to their medical records, government data sets or as samples are analysed and the data are added back into the data/biobank.

Sample/data identifiability	Clinical data in 'BCG vaccination to Reduce the impact of COVID-19 in healthcare workers (BRACE)' will be collected and stored in a REDCap database; a secure password-encrypted online database, or similar electronic database hosted by MCRI. Data will be stored in re-identifiable format with the key held by the custodian or delegate. The REDCap database or comparable database will be hosted on the secure Murdoch Children's Research Institute (MCRI) server and backed up regularly by MCRI Information Technology. Only members of the research team involved in data collection or data management will have access to the project's REDCap database or similar electronic database. Samples will be stored (frozen) in re-identifiable format by using study ID number or tube barcodes. All data associated with sample storage location and tracking will be stored in a separate REDCap database or similar electronic database. Access to this database is limited to members of the research team working in data/sample management or sample processing. Laboratory generated data, any data collected outside of REDCap and data exported from REDCap or similar electronic database, will be stored in re-identifiable format by study ID. The data will be stored on the MCRI server in restricted folders on the Infectious Diseases group drive, as per MCRI policy. Samples/data stored in re-identifiable format can be linked by the custodian or delegate to participants' identifiable information if it is ethically appropriate and required.
Criteria for Bank participants	Consenting to the project includes allowing the participants' data and samples to be used as defined in the protocol. In addition there is an optional consent in the PICF for the storage of participants' biospecimens and participants' re-identifiable data for use in future research related to infectious diseases and immunity. Inclusion criteria for Bank participants - Recruited participant in the research project 'BCG vaccination to Reduce the impact of COVID-19 in healthcare workers (BRACE))' - Provided informed consent for their data and samples to be stored for future ethically approved research (extended consent) related to infectious diseases and immunity.

Access process for obtaining the samples/data	Researchers must discuss their research plan with a member of the research team of the project 'BCG vaccination to Reduce the impact of COVID-19 in healthcare workers: (BRACE))'. The following will be taking into consideration: - Scientifically justifiable hypothesis and aims - Study design is appropriate to achieve study aims - Inclusion/exclusion criteria for participants appropriate to answer question - If the research proposal is deemed to have merit, the researcher will complete a REDCap (or similar electronic database) access form detailing the proposed design, participants, data +/- samples that they would like access to. This will be reviewed by the custodian (or delegate) of the data who will need to take into account the following, before approval is granted: - Does the research plan involve research in the area of immunology or infectious diseases? If not, it is outside the scope of the data/biobank. To use the data one of the following will be required: o a new project approved by the RCH HREC and participants contacted for their consent o a new project approved by the RCH HREC and a waiver of consent granted - Is the planned analysis feasible with the data/samples available in the data/biobank? - Are there competing interests for the sample/data type in question? - Is another researcher already analysing the data in a similar way and would collaboration on the existing project be more appropriate? The access form for access to the data/biobank will be kept on the REDCap database or similar electronic database.
Sample and data input	Members of the research team working in data/sample management will input the data and samples to the data/biobank.
Location of the Bank	Samples will be stored in the MCRI freezer farm or in the Infectious Disease Group's freezers, and may be distributed to other collaborating laboratories where they may also be stored.

	Data will be stored in a REDCap online database or similar electronic database, hosted on the secure Murdoch Children's Research Institute (MCRI) server, as well as in restricted electronic folders on the MCRI Infection and Immunity group drive.
Confidentiality/security of samples/data	Members of the research team of the project 'BCG vaccination to Reduce the impact of COVID-19 in healthcare workers (BRACE)' involved in data/sample collection or management will have open access to the bank data/samples. No identifying data will be provided to researchers using data/samples from the biobank. To re-identify data/samples, the custodian (or delegate) will have access to the key, but will not pass this information onto researchers unless approved by ethics, or as required by law. Data stored on REDCap database or similar electronic database will be password protected, and hosted on the secure MCRI server. This is backed up regularly by MCRI Information Technology. The Bank will be secure against unauthorised access and passwords will be changed at regular intervals (as per MCRI policy). The custodian (or delegate) will ensure removal of access to data once a project is finished or a researcher leaves the project.
Destruction of samples/data	Destruction of samples/data will occur upon participant request. This will be managed by the custodian (or delegate).
Modifications to Bank Protocol	If a change of purpose/data type/type of samples is to be considered, the custodian (or delegate) is required to submit to the HREC for approval and either contact the participants to obtain consent, or a waiver must have been granted.

17.2 Appendix 2. Collection of stool samples from a subset of BRACE participants

Background and Rationale:

For reasons that are poorly understood, B and T cell responses to vaccination (including BCG vaccination) are highly variable between individuals and between different populations. While many host factors, such as genetics, can influence inter-individual variation in these responses, increasing evidence shows that the gut microbiota, a large and diverse group of microorganisms that colonise gastrointestinal tract (GIT), plays a key role in shaping immune responses to vaccination (reviewed Lynn & Pulendran, 2017). For instance, in human infants, the relative abundance of several bacterial species in the stool microbiota has been associated with vaccine-specific IgG and T cell proliferation responses (Huda et al., 2014). Similarly, the composition of the stool microbiota in infants from rural Ghana was correlated with responses to the oral rotavirus vaccine (Harris *et al.,* 2017). Interestingly, germ-free mice have also been found to have impaired antibody responses to immunization with the model antigen ovalbumin (Lamousé-Smith *et al.,* 2011) and to the non-adjuvanted influenza vaccine (Oh *et al.,* 2014). Moreover, one of the principal investigators involved in this trial has recently found that, in mice, dysregulation of the microbiota leads to significantly impaired B and T cells responses to five different adjuvanted and live vaccines (including BCG) that are routinely administered to infants worldwide (Lynn *et al.,* 2018). Restoring the commensal microbiota rescued impaired responses (Lynn *et al.,* 2018). These data strongly suggest that the composition of the gut microbiota plays an important role in specific immune responses to vaccination. Whether the gut microbiota also influences non-specific effects of vaccines is currently unknown.

Primary objective of exploratory sub-study:

In a subset of BRACE trial participants consenting for an optional stool sample collection at baseline, determine whether the composition or metagenome-encoded function of the stool microbiota is correlated with either specific or non-specific immune responses to the BCG vaccine.

Secondary objectives of exploratory sub-study:

- Assess whether the composition of the stool microbiota is associated with any of the other primary, secondary, or exploratory outcomes described in the study protocol.
- Characterise the composition of the stool microbiota in participants in the trial and investigate whether the composition of the microbiota is altered at 3 or 12 months later.
- Assess whether immunisation with BCG leads to an altered microbiota at 3 or 12 months compared to participants receiving the placebo.

Outcomes:

Microbiota composition, including identities and the relative abundance of the bacteria present and their encoded microbial genes.

Population:

BRACE trial participants consenting for an optional stool sample collection at baseline, 3 months and 12 months.

Study Duration:

As per the BRACE trial protocol – 2 years.

Participant Duration:

12 months from randomisation.

Sub-study Locations:

Optional inclusion for Australian sites.

Sub-study Principal Investigator:

Prof. David J. Lynn BA MSc PhD
EMBL Australia Group Leader, Precision Medicine Theme, South Australian Health & Medical Research Institute, Adelaide, SA 5001.
Professor, College of Medicine & Public Health, Flinders University, Bedford Park, South Australia.
Email: *david.lynn@sahmri.com*

Potential risks and benefits:

Known potential risks:

This sub-study involves minimal risk to participants. Appropriate collection containers will be provided to participants to facilitate stool sample collection, storage and transport. A small stool sample will be collected by the participants at home. The tube contains a reagent that stabilises DNA at room temperature for up to 14 days. Participants will return the sample via a pre-paid addressed envelope. There will be no financial cost to the participant.

Known potential benefits:

This sub-study is exploratory in nature and is not expected to provide any direct additional benefit to the participants. The findings of the study, however, may be of significant value for understanding the role of the microbiota in influencing responses to vaccination.

Sub-study design:

Consent:

An additional option has been added to the BRACE online consent form to allow participants to optionally consent for a stool sample collection at baseline, 3 months and 12 months. The BRACE participant information and consent form (PICF) has been also modified to explain to participants the process for collecting stool samples and why they are being collected. If a participant declines to consent for stool sample collection this will not affect their participation in the BRACE trial (assuming all other inclusion and exclusion criteria are met).

Sample collection process:

Participants consenting for a stool sample collection will be provided with a collection pack at existing study visits at baseline, 3 months, and 12 months. The provided pack will contain: Instruction sheet, gloves, pathology stool pot, stool specimen collector tube and spoon set, protective plastic carrying tube, specimen bag, labels for identification of samples and pre-paid addressed envelope (for return postage). Participants will take the collection pack home with them and follow the following instructions to collect and return the stool sample.

Collection instructions:

1. Wash hands thorough and apply gloves.

2. Collect stool sample into the pathology stool pot within 1-3 days of study appointment.
   Note: Method of collecting the stool sample must prevent stool from falling into toilet water to avoid sample contamination.

3. Unscrew the stool specimen collector tube cap and use the spoon to scoop two spoonsful of stool (approximately 2 gram or 2mL in volume) from the sample.

4. Place the sample in the stool specimen collector tube.

5. Tighten the cap and shake to mix the contents thoroughly (invert 10 times) to create a suspension. Note: Some stool material may be difficult to re-suspend. As long as the material is suspended, the sample is stabilized. Foaming/ frothing during shaking is normal.

6. Dispose of gloves, unused stool material and the pathology stool pot and wash hands thoroughly.

7. Place stool specimen collector tube into the protective plastic carrying tube.

8. Place carrying tube into specimen carrier bag.

9. Place the sealed specimen bag containing the sample into the provided postage-paid reply envelop and post within 7 days of sample collection.

10. Samples will be returned to the nearest BRACE site laboratory for storage at -80C.

What we will do with the sample:

Briefly, samples will be collected at home by the study participants into Zymo fecal collection tubes which contain a reagent to stabilise DNA at ambient temperature. Samples were returned by mail within 2 weeks and stored at -80^{o}C until processed. DNA will be extracted from pelleted samples using the appropriate DNA Isolation kit. We will perform 16S rRNA sequencing and/or metagenomic sequencing to profile the composition of the microbiota in the sample and the metagenome encoded by the microbiota. qPCR will be utilised to quantify bacterial load and quantify specific bacterial populations. We will then determine whether the composition or metagenome-encoded function of the stool microbiota is correlated with either specific or non-specific immune responses to the BCG vaccine. We will also assess whether the composition of the stool microbiota is associated with any of the other primary, secondary, or exploratory outcomes described in the study protocol. Furthermore, we will characterise the composition of the stool microbiota in participants in the trial and investigate whether the composition of the microbiota is altered at 3 or 12 months later. We will assess whether immunisation with BCG leads to an altered microbiota at 3 or 12 months compared to participants receiving the placebo.

References:

Lynn, D.J. and B. Pulendran, *The potential of the microbiota to influence vaccine responses.* J Leukoc Biol, 2017. **103**(2): p. 225-23

Huda, M.N., et al., *Stool microbiota and vaccine responses of infants.* Pediatrics, 2014. **134**: p. e362-72.

Harris, V.C., et al., *The infant gut microbiome correlates significantly with rotavirus vaccine response in rural Ghana.* J Infect Dis, 2017. **215**(1): p. 34-41.

Lynn, M.A., et al., *Early-Life Antibiotic-Driven Dysbiosis Leads to Dysregulated Vaccine Immune Responses in Mice.* Cell Host Microbe, 2018. **23**(5): p. 653-660 e5.

Oh, J.Z., *et al., TLR5- Mediated Sensing of Gut Microbiota Is Necessary for Antibody Responses to Seasonal Influenza Vaccination*. Immunity, 2014. ***41***: 478-492.

17.3 Appendix 3 UK Specific Requirements

In the UK, the Competent Authority (MHRA) required the following two UK specific requirements:

1. In the UK, a negative pregnancy test is required for all WOCBP to confirm eligibility for the trial.

2. In the UK, the responsibility to break the treatment code in emergency situations resides solely with the UK Principle Investigator and will not be delayed by requiring other study staff in Australia such as the Chief Investigator or medical monitor to be involved in the decision to un-blind. The study code will only be broken for valid medical or safety reasons e.g. in the case of a severe adverse event where it is necessary for a treating physician (Requester) to know which intervention the participant has received, in order to manage the participant's condition appropriately.

The Requester contacts the local Principal investigator (PI), or delegate, to discuss the pros and cons of breaking the code. If the consensus is to break the code, the Requester contacts the holder of the code break list. In the UK, this has been delegated to the UK based Data Manager who will provide the Requester with the information on allocated group on direction from the PI. On receipt of the allocation details the Requester deals with the participant's medical emergency as appropriate. Should this code-breaking protocol be activated, the Chief Investigator will be alerted at the earliest opportunity, and within 2 working days at the latest.

Woman of Child Bearing Potential:
For the purpose of this document, a woman is considered of childbearing potential (WOCBP), i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. However in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

17.4 Appendix 4 Brazil Specific Requirements

SARS-CoV-2 Screening test

Due to public interest in determining the extent of asymptomatic SARS-CoV-2 infection in healthcare workers in Brazil, the Brazilian investigators will use the BRACE participants to estimate this prevalence rate. Therefore after enrolment a baseline respiratory swab will be collected by the study nurse. The swab samples will be analysed by PCR for detection of SARS-CoV-2 and participants advised when results are confirmed. Participants who return a positive SARS-CoV-2 result on the baseline swab will remain in the trial. In Mato Grosso do Sul, the samples will be analysed in batch months after randomisation, so there will be no clinically actionable results. Results will be shared with participants approximately 3 months after randomisation, for participant who return a positive SARS-CoV-2 result, the site will be required to report the participant's positive SARS-CoV-2 results to the applicable health agencies. They will be told that they will not be informed of their result before then. In Rio de Janeiro, due to high transmission rates, samples will be tested immediately and reported to participants. PCR tests will be conducted by the study lab team and the results reported to health agencies by a system called e-SUS VS, which constitutes a database of several diseases, including COVID-19, which is mandatory.

IGRA

At randomisation, blood for anti-SARS-CoV-2 antibodies and IGRA will be taken for later assessment of seroconversion and TB infection. Therefore the initial blood sample in Brazil will be 35ml. This will identify participants who had TB exposure prior to commencement of the study. IGRA results will not exclude participants at consent & randomisation stage. Results will be shared with participants approximately 3 months after randomisation. A study doctor will follow-up with participants with positive IGRA to offer further assessment and treatment through government service provision.

At 12 months, blood for IGRA will be taken for later assessment to answer exploratory outcomes. Therefore the 12-month blood sample in Brazil will be 35 ml. This will identify participants who acquired TB during the study. Results will be shared with participants approximately 3 months after 12-month blood collection. A study doctor will follow-up with participants with positive IGRA to offer further assessment and treatment through government service provision.

Participant reimbursement

In Brazil, Resolution No. 466 of December 12, 2012 outlines the guidelines and regulatory standards for research involving humans in Brazil. This resolution outlines the requirement to provide reimbursement to participants and their companions, when necessary, such as transportation. In line with this requirement, participants in Brazil will receive reimbursement for relevant transportation costs for participation in the BRACE trial.

Safety Reporting

In Brazil, the RPI/s and SPI/s must comply with the safety reporting requirements of CEP/CONEP (defined in Circular Letter number 13). The HREC/s must be notified of all SAEs through the Brazil Platform (Notification), after the end of the event. The following timelines will be met for this study:

1. 30 days in case of fatal SAE occurring in a participant of the site in the jurisdiction of the HREC
2. 7 days in case of an SAE with a causal relationship with the investigational product, in a participant of the site in the jurisdiction of the HREC (Casual relationship means that the SAE is judged by either the reporting investigator or the sponsor as having a reasonable possibility of a causal relationship to a study vaccine).
3. 6 months for other SAE.

The RPI (or delegate) will notify SUSAR in Brazil to all investigators in their region, as appropriate. The RPI (or delegate) will report significant safety issues (including USM) to SPI in their region, the regulatory authority and applicable HREC/s in accordance with the requirements. The RPI (or delegate) will provide periodic reports of SAE (from Brazil trial sites) to the applicable regulatory authorities and/or HREC/s, as appropriate.

17.5 Appendix 5 The Netherlands Specific Requirements

The following changes will apply for the performance of the protocol in the Netherlands:

Statement of Compliance

This clinical trial will be conducted in compliance with all stipulations of this protocol, the conditions of the ethics committee approval, the NHMRC National Statement on ethical Conduct in Human Research (2007 and all updates), the Integrated Addendum to ICH E6 (R1): Guideline for Good Clinical Practice E6 (R2), dated 9 November 2016 annotated with TGA comments and the NHMRC guidance Safety monitoring and reporting in clinical trials involving therapeutic goods (EH59, 2016), and General Data Protection Regulation (GDPR) , as well as local laws and regulations, such as the Wet medisch-wetenschappelijk onderzoek met mensen (WMO).

2. Recruitment and consent

In Europe, due to ethics regulations, an electronic PICF will not be used and no information on eligibility nor any contact information will be collected prior to the informed consent process being finalized. When participants are interested in the study, they can verify their eligibility with the criteria listed on the website. Then, they will be shown a list of participating centers and advised to contact one of the centers directly to make an appointment for the first study visit. At this visit, the informed consent procedure will be completed in a face-to-face setting where the PICF will be read and signed by both participant and investigator. Exact date of birth will not be collected in the eCRF for the study due to GDPR constraints; instead, year of birth (or 01-01-yyyy) will be used in the eCRF.

3. Data capture methods and data use, storage, access and disclosure during the trial

Archiving will be in compliance with NFU requirements: study data, source documents and the Study File will be kept for 25 years.
EU protocol addendum page_V2.0_20200629

4. COVID-19 testing will be performed via the national testing policy and therefore, the General Practitioner will be notified of the results by the organisation that performs the testing: GGD or the hospital that performs the test.

5. Sharing of contact information

In order to send out the 3, 6, 9, and 12 month questionnaires, the participant's email address will be collected in the REDCap database. No other identifying information will be stored in the database for EU participants.

6. BCG vaccination is not expected to cause an exacerbation of the immune response with adverse consequences, because of 3 main arguments: • By activating anti-viral mechanisms, BCG decreases virus load and systemic inflammation (Arts et al, Cell Host Microbe 2018). Influenza pathophysiology is the same so if BCG had adverse effects, this would have been known for a long time. • Information is available on individuals vaccinated with BCG last year and no COVID19 complications were observed in this group.

17.6 Appendix 6 Spain Specific Requirements

The following changes will apply for the performance of the protocol in Spain:

1. Statement of Compliance

This clinical trial will be conducted in compliance with all stipulations of this protocol, the conditions of the ethics committee approval, the Integrated Addendum to ICH E6 (R1): Guideline for Good Clinical Practice E6 (R2), dated 9 November 2016 and General Data Protection Regulation (GDPR) , as well as local laws and regulations

2. Inclusion criteria

According to recommendations of the competent authority AEMPS (Agencia Española del Medicamento y Productos Sanitarios) If the patient is female, and of childbearing potential, she must have a negative pregnancy test (provided by Sponsor) at the time of inclusion and practice a reliable method of birth control for 30 days after receiving the BCG vaccination. - Woman of Childbearing Potential is defined as a premenopausal female who is capable of becoming pregnant.

3. Recruitment and consent

In Europe, due to ethics regulations, an electronic PICF will not be used and no information on eligibility nor any contact information will be collected prior to the informed consent process being finalized. When participants are interested in the study, they can verify their eligibility with the criteria listed on the website. Then, they will be shown a list of participating centers and advised to contact one of the centers directly to make an appointment for the first study visit. At this visit, the informed consent procedure will be completed in a face-to-face setting where the PICF will be read and signed by both participant and investigator.
Exact date of birth will not be collected in the eCRF for the study due to GDPR constraints; instead, year of birth (or 01-01-yyyy) will be used in the eCRF.

4. Data capture methods and data use, storage, access and disclosure during the trial

Archiving will be in compliance with NFU requirements: study data, source documents and the Study File will be kept for 25 years.

5. Sharing of contact information

In order to send out the 3, 6, 9, and 12 month questionnaires, the participant's email address will be collected in the REDCap database. No other identifying information will be stored in the database for EU participants.

17.7 Appendix 7 Optional Biological sample collection during episodes of illness

Assessment of immune responses during episodes of illness will provide crucial insights into the mechanisms by which BCG may protect against COVID-19. BCG is proposed to protect against unrelated infections by boosting the innate immune response[1] which can directly protect against infections and also shape the adaptive immune response[2-3]. Biological samples collected after infection provide meaningful insight into the long-lasting effects of the infection and immune memory. However, they do not provide information about the early immune response to infection that can promote early clearance, may impact disease severity and may define the long-lasting memory response. It is this part of the immune response where BCG vaccination may play a crucial role in protection against COVID-19 as well as non-COVID-19 respiratory infections.

Objectives of exploratory sub-study

The additional collection of biological samples from BRACE participants during episodes of febrile or respiratory illness will contribute to the planned subgroup exploratory analyses of BRACE:

11. To determine the impact of BCG vaccination on the immune system that are associated with protection of adult healthcare workers from non-tuberculous infectious diseases including COVID-19.
13. To identify factors (e.g. age, sex, chronic conditions such as diabetes and cardiovascular disease, smoking, asthma, prior BCG vaccination, genetics, influenza vaccination, immunological/molecular factors) that influence adult immune responses and COVID-19 responses.

It will also contribute to the following additional exploratory objectives:
In a sub-set of BRACE trial participants who consent for an optional biological sample to be collected during episodes of fever or respiratory illness:

- To characterise the immune response to SARS-CoV-2 infection
- To compare immune responses during an episode of respiratory illness (COVID-19 or non-COVID-19 illness) in BCG-vaccinated and non-BCG vaccinated participants

Outcomes:

Immune system characterisation and molecular markers of disease in episodes of COVID-19 or non-COVID-19 respiratory or febrile illness from BCG-vaccinated and non-vaccinated participants.

Population: A sub-group of the BRACE trial participants who consent to an optional biological sample to be collected during episodes of fever or respiratory illness.

Study Duration:

As per the BRACE trial protocol – 2 years.

Participant Duration:

12 months from randomisation.

Sub-study Locations:
Optional inclusion for Australian sites.

Sub-study Principal Investigator:
Dr Nicole Messina
Senior Research Officer, Infectious Diseases Group, Murdoch Children's Research Institute, The Royal Children's Hospital, 50 Flemington Road Parkville, 3052 Victoria, Australia
Honorary fellow, Department of Paediatrics at Melbourne Children's Melbourne Medical School, Faculty of Medicine, Dentistry and Health Sciences, The University of Melbourne
Email: nicole.messina@mcri.edu.au

Potential risks and benefits:
Known potential risks:
This sub-study involves minimal risk to participants. Having a blood test can sometimes cause some pain from the needle or be uncomfortable. Occasionally a small amount of bruising can occur on the skin where the blood was taken. Trained members of the study team will collect the blood samples from participants. Having a respiratory swab can sometimes be uncomfortable. Trained members of the study team will collect the respiratory swabs from participants. Self-testing swab kits may be provided as required, with clear instructions to participants on safe self-swabbing technique.

Known potential benefits:
This sub-study is exploratory in nature and is not expected to provide any direct additional benefit to the participants. The findings of the study, however, may be of significant value for understanding the immune response to COVID-19, the off-target effects of BCG vaccination on responses to COVID-19 and other respiratory infections and determinants of disease severity.

Sub-study design:
Consent:
An additional option has been added to the BRACE online consent form to allow participants to optionally consent additional biological sample collection during an episode of illness. The BRACE participant information and consent form (PICF) has been also modified to explain to participants the process for collecting these additional blood samples and why they are being collected. If a participant declines to consent for additional biological sample collection during an episode of illness this will not affect their participation in the BRACE trial (assuming all other inclusion and exclusion criteria are met).

Sample collection process:
Participants consenting for additional biological sample collection during an episode of illness may be contracted by the study team during any episode of respiratory or febrile illness that occurs during their involvement in the BRACE trial (i.e. up to 12 months from randomisation). Sample collection would occur during and up to one month after resolution of an episode of illness with fever or respiratory symptoms. The collection of samples will be done at a study

site (e.g. if they are inpatients or obtaining SARS-CoV-2 testing at a study site) or at the participant's home, depending on the location of the participant.

Samples to be collected are:

-a blood sample

and/or

- saliva/respiratory swab/s

All samples will be collected, processed and stored in accordance with the BRACE trial protocol section 7.3. We will aim to take these samples at the same time as any other clinical or research samples where possible to minimise the number of sample collections for each participant, minimise contact of research staff with infectious patients and to reduce the need for research staff to use vital personal protective equipment (PPE).

What we will do with the sample:

Samples will be processed for analysis of the immune system as detailed in BRACE trial protocol section 3.2. Where indicated, saliva/respiratory swab/s collected will be linked with the relevant public health testing and reporting systems as BRACE trial protocol section 7.3. In addition, samples will be included in the BRACE biobank if participants have also consented for their samples being placed in the BRACE biobank.

References

1. Novakovic B, Messina N, Curtis N. Chapter 6 - The Heterologous Effects of Bacillus Calmette-Guérin (BCG) Vaccine and Trained Innate Immunity. In: Faustman DL, editor. The Value of BCG and TNF in Autoimmunity (Second Edition). Second edition. ed: Academic Press; 2018. p. 71-90.
2. Arts RJW, Moorlag S, Novakovic B, et al. BCG Vaccination Protects against Experimental Viral Infection in Humans through the Induction of Cytokines Associated with Trained Immunity. Cell Host Microbe. 2018;23:89-100 e5.
3. Kleinnijenhuis J, Quintin J, Preijers F, et al. Long-lasting effects of BCG vaccination on both heterologous Th1/Th17 responses and innate trained immunity. J Innate Immun. 2014;6:152-8.

17.8 Appendix 8 Optional Sub-study: collection of blood samples to measure immune responses to COVID-19 specific vaccines.

Sub study locations:
Australia
Brazil

Overview:
COVID-19-specific vaccines are becoming increasingly available and healthcare workers, being at high risk of SARS-CoV-2 exposure, are prioritised for receipt of these vaccines. BCG vaccination alters immune responses to subsequence vaccinations[1,2] and therefore it is plausible that it may boost the immune response to COVID-19-specific vaccines. As healthcare workers, participants in the BRACE trial will be prioritised for receipt of COVID-19-specific vaccines in most regions and as a result will likely receive these vaccines during their involvement of the BRACE trial.

The type of COVID-19-specific vaccine given to BRACE trial participants will vary between sites and it is likely that more than one type of vaccine will be used in a given region. The number of doses given (one or two) and the recommended interval between the two doses are likely to vary as well but are likely to be consistent within a given region.

The BRACE trial exploratory outcomes already include assessment of the effects of vaccines on the immune system (including the effects of BCG-vaccination on immune response to COVID-19-specific vaccines).

To ensure we obtain samples at the optimal times before and after COVID-19-specific vaccination, in a subset of participants, we propose collecting blood samples at up to three additional time-points:

- (Visit 1, site specific) prior to receipt of the first dose of a COVID-19-specific vaccine.
- (Visit 2, site specific) after the first dose of a COVID-19-specific vaccine.
- (Visit 3) 28 days after the second dose of a COVID-19-specific vaccine.

These additional blood samples enable us to:

- screen for prior SARS-CoV-2 exposure (accounted for at analysis), and provide a baseline measure of the immune system prior to receipt of COVID-19-specific vaccines.
- measure the immune response (e.g. antibodies) to the first and second dose of COVID-19-specific vaccines, and other changes in the immune system induced by the COVID-19-specific vaccine.
- compare the vaccine responses to COVID-19-specific vaccines between the BCG and the control group to each COVID-19 specific vaccine.
- compare our findings to other studies on COVID-19-specific vaccines[3].

Determining if BCG vaccination can improve the immune response to COVID-19-specific vaccines have important implications for the potential of BCG vaccination to increase efficacy of COVID-19-specific vaccines and may also impact our interpretation of the outcomes of the BRACE trial. This is particularly important for the COVID-19-specific vaccines that have a lower efficacy.

Objectives of exploratory sub-study

The additional collection of blood samples from BRACE trial participants immediately prior to, and after each COVID-19-specific vaccination will contribute to the existing planned subgroup exploratory analyses of BRACE:

1. *To determine the impact of BCG vaccination on the immune system that are associated with protection of adult healthcare workers from non-tuberculous infectious diseases including COVID-19.*
2. *To determine and compare changes in the immune system induced by vaccination of adult healthcare workers.*
3. *To identify factors (e.g. age, sex, chronic conditions such as diabetes and cardiovascular disease, smoking, asthma, prior BCG vaccination, genetics, other vaccinations including COVID-19-specific vaccines, latent TB, immunological/molecular factors) that influence adult immune responses, infection and COVID-19 risk.*

Population: A sub-group of the BRACE trial participants who receive COVID-19-specific vaccines in regions taking part in the sub-study.

Outcomes: Immune system characterisation and molecular markers of immunity (including seroconversion to SARS-CoV-2) in response to COVID-19-specific vaccines in BCG-vaccinated and non-BCG-vaccinated participants.

Study Duration: As per the BRACE trial protocol – 2 years.

Participant Duration: Up to 4 months from sub-study inclusion

Sub-study Principal Investigator: Prof Nigel Curtis

Potential risks and benefits

Known potential risks

This sub-study involves minimal risk to participants. Having a blood test can sometimes cause some pain from the needle or be uncomfortable. Occasionally a small amount of bruising can occur on the skin where the blood was taken. Trained members of the study team will collect the blood samples from participants.

The amount of blood collected is too small to have any impact on the participants' health. This sub-study will not impact the setting up of COVID-19-specific vaccination clinic at the participating sites. It is not expected to have any negative interactions between the BCG and the COVID-19-specific vaccine.

Known potential benefits

This sub-study is exploratory in nature and is not expected to provide any direct additional benefit to the participants. The findings of the study, however, may be of significant value for understanding the immune response to COVID-19-specific vaccines and the off-target effects of BCG vaccination on responses to COVID-19-specific vaccines.

Sub-study design

Eligibility:

Inclusion Criteria

- Participant in the BRACE trial who has previously consented to be contacted for future ethically approved projects.
- Participant recruited to the BRACE trial at a site taking part in this sub-study.

Exclusion Criteria

- A previous positive SARS-CoV-2 test at any time (not applicable in Brazil).
- Expected inability to provide a blood sample in the indicated time window after: the first dose (visit 2) and/or the second dose (visit 3) of a COVID-19-specific vaccine.
- [site specific]: Inability to provide a blood sample in the indicated time window prior the first dose (visit 1) of a COVID-19-specific vaccine.

Recruitment

Potential BRACE participants will be informed of this sub-study and invited to participate as per their recruitment sites' existing communication approach. BRACE participants will evaluate their eligibility for the sub-study and will have access to the site-specific participant information and consent form (PICF) prior to enrolment in the sub-study.

Consent

An additional participant information and consent form (PICF) will be provided to participants to allow them to optionally consent to this sub-study. If a participant declines to consent for this sub-study it will not affect their participation in the BRACE trial.

Data collection

Participants interested in this sub-study will be contacted by the study team to arrange blood collection if:

- The BRACE trial study site from which they were recruited begins COVID-19-specific vaccinations of staff

Or

- if the participants inform the BRACE trial team that they will receive a COVID-19 specific vaccine.

At these additional sub-study visits, participants will be asked about:

- prior positive COVID-19 tests,
- any other vaccines received since randomisation in BRACE (type, dose, route, date)

- expected date of vaccination with COVID-19-specific vaccine and which vaccine
- episodes of febrile or respiratory illness since last visit (if not already collected as part of the BRACE trial)
- (after vaccination only) adverse reaction to the COVID-19-specific vaccine

After the expected COVID-19-specific vaccine administration date, participants will be contacted as per their recruitment sites' existing communication approach, to confirm which vaccine they have received, where and when they received it, as well as when is the second dose planned.

Sample collection process

Sample collection will occur:

- (Visit 1, site specific) On the day of (or in the 5 to 14 days preceding) the first dose of a COVID-19-specific vaccine.

  [site specific] *Note that for a participant who has already received their first dose of a COVID-19 specific vaccine, the participant's blood sample for the first timepoint will not need to be collected. However, blood samples for the remaining time points below will need to be collected.*
  It is planned to collect blood samples on the same day of vaccination, however we will accept bloods that are taken up to 5 days before the first dose of COVID-19 specific vaccine in all regions, or even up to 14 days before the first dose of COVID-19 specific vaccine in regions where the COVID-19 prevalence is low, are acceptable.

- (Visit 2, site specific) 1 to 28 days (±2) days after the first dose of a COVID-19-specific vaccine

  Note that where the second dose of the COVID-19 specific vaccine is given within 28 days in a given region, this sample will be taken at an earlier time point. Efforts will be made to standardise the interval between the first dose of COVID-19-specific vaccine and the blood sample for each type of COVID-19-specific vaccine within each given region, e.g. within 14 (±2) days after the first dose of COVID-19-specific vaccine if the two doses of COVID-19-specific vaccine are given 2 weeks apart, or within 21 (±2) days after the first dose of COVID-19-specific vaccine if the two doses of COVID-19-specific vaccine are given 3 weeks apart.

  In specific sites, an earlier time-point (<7 days) will enable the exploration of the initial gene expression responses to vaccination.

- (Visit 3) 28 (±2) days after the second dose of a COVID-19-specific vaccine

  Note that efforts will be made to standardise the interval between the COVID-19-specific vaccine doses and the blood collection for both blood collections, for each type of COVID-19-specific vaccine and within a given region.

Blood samples will be collected, processed and stored in accordance with the BRACE trial protocol section 7.3 with the exception that up to 40 mL of blood will be taken at each time point. Also, if this blood collection is done at the same time as a BRACE trial 3-monthly blood collection, an additional 10 mL of blood may be required for a total of 50 mL. The collection of blood samples will be done at a study site or at the participant's home, depending on the region. We will aim to collect these samples at the same time as the existing BRACE Trial 3-monthly blood samples where possible, to minimise the number of sample collections for each participant.

What we will do with the sample:

Samples will be processed for analysis of the immune system as detailed in BRACE trial protocol section 3.2. The immune system will be assessed by several methods, including:

a) measurement of antibodies to SARS-CoV-2 (to assess prior exposure/infection with SARS-COV-2) and their neutralisation ability
b) measurement of antibodies to COVID-19 specific vaccines (to determine seroconversion and antibody titres) and their neutralisation ability
c) characterisation of immune cell subpopulations
d) measurement of immune cell activation and differentiation
e) measurement of immune cell function (e.g. cytokine production and cell division) following *in vitro* stimulation with SARS-CoV-2, COVID-19-specific vaccines, or their components)

Sample size estimation:

As COVID-19-specific vaccines are novel, immune responses following vaccination have yet to be extensively characterised and there is currently no agreed correlate of protection. As such, formal sample size calculations are not possible.

In Australia, based on our previous experience assessing immune responses to other vaccines we estimate that for each region in which this sub-study will take place a sample size of 150 participants per randomisation group and per COVID-19-specific vaccine type (aiming to have 100 participants with blood samples for all three timepoints) will be sufficient to detect a meaningful effect of BCG vaccination on the vaccine responses to COVID-19-specific vaccines. With the expectation that within a region the majority of participants will receive one of two vaccines we will recruit an estimated 600 participants: 150 participants x 2 randomisation groups (BCG or No BCG vaccination) with 2x COVID-19-specific vaccine types.

In Brazil, all BRACE participants will be invited to join the sub-study. This subset of participants provides a unique opportunity to study the influence of natural infection and COVID-19-specific vaccination on both infection and reinfection with SARS-CoV-2, and critically, the impact of variant strains, particularly the P.1 variant. Samples from a large proportion of participants in Brazil will be collected, to optimise capture of participants who may become infected with SARS-CoV-2 different variants.

References

1. Messina NL, Zimmermann P, Curtis N. The impact of vaccines on heterologous adaptive immunity. *Clin Microbiol Infect* 2019; **25**(12): 1484-93.
2. Arts RJW, Moorlag S, Novakovic B, et al. BCG Vaccination Protects against Experimental Viral Infection in Humans through the Induction of Cytokines Associated with Trained Immunity. *Cell Host Microbe* 2018; **23**(1): 89-100 e5.
3. Ramasamy MN, Minassian AM, Ewer KJ, et al. Safety and immunogenicity of ChAdOx1 nCoV-19 vaccine administered in a prime-boost regimen in young and old adults (COV002): a single-blind, randomised, controlled, phase 2/3 trial. *Lancet* 2021; **396**(10267): 1979-93.

17.9 Appendix 9 Optional Sub-study: analysis of swab samples to determine the impact of SARS-COV-2 variants

Sub study locations:

Brazil

Overview:

Eligibility:

Inclusion Criteria

- Participant in the BRACE trial who has previously consented to be contacted for future ethically approved projects.
- Positive SARS-CoV-2 respiratory swab
- Participant recruited to the BRACE trial at a site taking part in this sub-study.

Exclusion Criteria

N/A

Recruitment

BRACE study staff will identify eligible participants for the sub-study. Potential participants will be informed of this sub-study and invited to participate as per their recruitment sites' existing communication approach. Participants will be provided access to the site-specific participant information and consent form (PICF) prior to enrolment in the sub-study.

Consent

An additional PICF will be provided to participants to allow them to optionally consent to this sub-study. If a participant declines to consent for this sub-study it will not affect their participation in the BRACE trial.

Data collection

Participants will be contacted as per their recruitment sites' existing communication approach.

Sample collection process

- **Respiratory swabs**

  During episodes of illness participants agreed to provide a respiratory swab as part of the main BRACE trial. The swabs collected by the BRACE study team are stored at BRACE sites laboratories, following testing in line with government health guidelines and will be accessed for variant testing. If possible, swabs collected through alternative channels will be accessed for further testing or variant results.

What we will do with the sample:

SARS-CoV-2 variant testing/sequencing of respiratory swabs collected as part of the main BRACE trial.

Sample size estimation:

In Brazil, all BRACE participants who have reported a positive COVID-19 test and the respiratory swab is accessible by the BRACE team will be invited to join the sub-study. This subset of participants provides a unique opportunity to study the impact of variant strains.

Objectives of exploratory sub-study

The analysis of available swabs for SARS-CoV-2 variants will contribute to the existing planned subgroup exploratory analyses of BRACE:

BRACE Protocol exploratory analyses 12. To determine and compare changes in the immune system induced by vaccination of adult healthcare workers.

- ⇨ (Example) to measure the impact of COVID-19-specific vaccines +/- BCG vaccine on the different SARS-CoV-2 variants

BRACE Protocol exploratory analyses 13. To identify factors (e.g. age, sex, chronic conditions such as diabetes and cardiovascular disease, smoking, asthma, prior BCG vaccination, genetics, other vaccinations including COVID-19-specific vaccines, latent TB, immunological/molecular factors) that influence adult immune responses, infection and COVID-19 risk.

- ⇨ (Example) to measure and compare the long-term effects of the different SARS-CoV-2 variants on the immune system
- ⇨ (Example) to identify individual and immunological/molecular factors associated with the risk of COVID-19 caused by the different SARS-CoV-2 variants

Population: A sub-group of the BRACE trial participants who have reported a positive COVID-19 test and the respiratory swab is accessible by the BRACE team or variant data available.

Outcomes:

(i) Influence of COVID-19-specific vaccines +/- BCG vaccine on immunity to and protection against SARS-CoV-2 variants

(ii) Association of immunological factors (e.g. immune responses to prior SARS-CoV-2 infection and vaccination) with infection and COVID-19 caused by the different SARS-CoV-2 variants.

(iii) Changes in immune system caused by infection with the different SARS-CoV-2 variants.

Study Duration: As per the BRACE trial protocol – 2 years.

Participant Duration: As per the BRACE trial protocol – 2 years.

Sub-study Principal Investigator: Prof Nigel Curtis

Potential risks and benefits

Known potential risks

This sub-study involves minimal risk to participants as there are no additional samples required.

Known potential benefits

This sub-study is exploratory in nature and is not expected to provide any direct additional benefit to the participants. The findings of the study, may be of significant value for understanding the impact of SARS-CoV-2 variants on individuals, and the efficacy of the vaccines on the different SARS-CoV-2 variants.

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