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

Project Theme: Infection and Immunity (/research/themes/infection-and-immunity)

Project Group: Infectious Diseases (/infectiousdiseases)

What is BRACE?

Healthcare workers are at increased risk of contracting COVID-19, caused by SARS-CoV-2. Currently, there are no vaccines or proven preventative interventions available to protect healthcare workers.

The Bacille Calmette-Guérin (BCG) vaccine is designed to protect against tuberculosis (TB). However it also boosts immunity to protect against other infections. The purpose of the BRACE trial is to find out whether BCG vaccination protects against COVID-19 or reduces severity or COVID-19 in Australian healthcare workers.

Why take part:

- We hope that the BCG vaccine will boost your immune system. It may also increase your response to the flu vaccine and provide you with non-specific protection to other illnesses.
- Information we collect in this trial will help to inform how we respond to outbreaks of new viruses in the future.
- We cannot guarantee or promise you will receive any benefits from this trial.

You will need to:

- have initial blood test
- be randomly allocated to receive the BGG vaccine or be in the control group that will not receive this vaccine
- download an app to record respiratory symptoms and a fever
- be tested for SARS-CoV-2 if you have suggestive symptoms
- complete online surveys at 3, 6, 9,12 months
- have a final blood test at 12 months

Potential risks to participants:

- Occasionally some people experience adverse effects of the BCG vaccine. The majority of these are minor and local reactions around the injection site. These are outlined in detail in further information for you to read before taking part in the study.
- Having a blood sample collected may cause some discomfort or bruising. Having a throat swab can sometimes be uncomfortable. Trained members of the research team will collect these samples.

Who can take part?

Due to the urgency of the COVID-19 situation and the recent release of the flu vaccine we are keen to sign on interested participants early.

Click the button below to establish your eligibility, read the Participant Information Sheet (PIS) and sign the consent form. We will also be collecting information about you and your role in the hospital which will remain strictly confidential within the MCRI trial team. As with all clinical trials you may decide later not to participate, up to and including at your vaccination appointment.

CLICK HERE TO REGISTER

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Project Details

Healthcare workers are at greater risk of contracting COVID-19 pandemic. There is currently no vaccine for COVID-19, so protection of health care workers relies on the use of personal protective equipment. When healthcare workers are sick and unable to come to work, this puts extra pressure on the healthcare system.

The results of this trial will help us find out whether, in future novel viral outbreaks, BCG vaccination could be used as an early intervention to protect healthcare workers and other high-risk groups.

In the BRACE trial we aim to recruit 4170 healthcare workers in hospitals in Australia. We will not tell the hospital where you work which of their staff members have consented to participate in this trial. There are no costs associated with participating in this trial, nor will you be paid. All medication, tests and medical care required as part of the trial will be provided to you free of charge.

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What to expect

What to expect following the BCG vaccination

- The BCG vaccination is given just under the skin (into the 'intradermal' layer) of the left upper arm
- The usual expected reaction to BCG vaccination is redness and/or a small 'papule' (a pimple or lump) at the injection site that appears weeks to months after vaccination
- A few weeks later, the papule usually softens and breaks down to a small ulcer (an open sore - usually less than 15 mm in diameter)
- The ulcer may last from weeks to months
- Once the ulcer has healed, this usually (but not always) leaves a small flat scar

Care of the injection site

- Keep the area clean and dry
- Normal bathing is acceptable – pat dry after washing
- A temporary dry dressing with gauze may be used if the area starts to ooze
- A sterile alcohol swab may be used to clean the area if required
- Do not apply ointment, antiseptic creams, sticking plaster or band aids
- Do not attempt to squeeze any pus out of the papule or ulcer that develops

Rare complications following BCG vaccine

- A large abscess (collection of pus) at the injection site
- Infection of the glands in the left armpit ('axillary lymph nodes') causing tenderness and swelling under the arm 'Keloid' scarring (very noticeable scarring on the skin)
- Severe immediate allergic reaction (very rare), please stay on the hospital grounds for the next 20mins

When to seek medical advice

- If you notice any severe or rare reactions, such as a large persistent discharging abscess at the injection site
- If you notice swelling or tenderness of the glands ('lymph nodes') in the left armpit

Whom to contact for advice

- BRACE team
  - Tel: 0409 846 988
  - Email: brace@mcri.edu.au (mailto:brace@mcri.edu.au)
- Your General Practitioner

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FAQs

Will I be able to choose whether or not I receive the BCG vaccination?
No. You will be randomly allocated to receive or not receive BCG vaccination.

If I am allocated to the no BCG vaccination group, do I still have to continue in the trial?
Yes. We need to follow up both the BCG-vaccinated and non-BCG-vaccinated groups, so that we can compare outcomes between the 2 groups.

I have had a BCG vaccination before. Is it safe to have another one?
Yes. There is an increased risk that you may have an earlier, "accelerated" reaction which may begin within 24-48 hours of vaccination with induration followed by pustule formation in 5-7 days and healing within 10-15 days. Local skin lesions (ulceration and discharge) are more frequent in adults who have had a previous BCG vaccine than those who have never had BCG vaccine before. However, the risk of severe armpit lymph gland infection and disseminated BCG or reactivated tuberculosis disease has not been found to be more common in adults who have had previous BCG vaccine or positive tuberculosis screening tests.

Why give me another BCG vaccination if I have had one in the past?
There is evidence that the beneficial off-target effects of BCG vaccine are negated after another live vaccine is given. As most health care workers in Australia receive the annual live influenza vaccine each year it is necessary to give another BCG vaccination to maximise the beneficial off-target effects.

It is safe to receive BCG if I have been exposed to tuberculosis in the past?
Yes. There is an increased risk that you may have an earlier, "accelerated" reaction which may begin within 24-48 hours of vaccination with induration followed by pustule formation in 5-7 days and healing within 10-15 days. Local skin lesions (ulceration and discharge) are more frequent in adults who have had a previous BCG vaccine than those who have never had BCG vaccine before. However, the risk of severe armpit lymph gland infection and disseminated BCG or reactivated tuberculosis disease has not been found to be more common in adults who have had previous BCG vaccine or positive tuberculosis screening tests.

Is it safe to have the BCG vaccination on the same day as influenza vaccine?
Yes.

Will BCG vaccination affect the effectiveness of my influenza vaccine?
BCG vaccination can reduce the effectiveness of the influenza vaccine if the influenza vaccine is given before BCG vaccination. However, in this study, you will be receiving both vaccines on the same day, so the effectiveness of your influenza vaccine will not be affected.

Is it safe to have BCG vaccination if there are people in my home who are immunosuppressed?
Yes.

How soon does BCG vaccination work?
Epidemiologic data shows that the beneficial off-target effects of BCG vaccination are evident within days of vaccination. These effects have been shown to persist out to 12 months in adults.

Can I choose where I receive the BCG vaccine?
BCG vaccination through the BRACE trial will be administered with the influenza vaccine provided by your hospital immunisation program.

Can I participate in the trial if I am pregnant?
No, BCG vaccination is a live vaccine and thus it is not recommended in pregnancy. If there is a chance you may be pregnant, discrete pregnancy testing will be made available for any potential participants on the day of vaccination.

If I get the BCG vaccine is there a period of time I should wait before falling pregnant?
Pregnancy should be avoided for 28 days after receiving a live vaccine such as BCG [1].

1. Kroger AT, Duchin J, Vázquez M. General best practice guidelines for immunization. Best Practices Guidance of the Advisory Committee on Immunization Practices (ACIP). https://www.cdc.gov/vaccines/hcp/acip-recs/general-recs/index.html. Accessed on March 22, 2020.

BCG Revaccination

This section may require you to have some medical or research background.

Current Australian BCG vaccination recommendations

Bacille Calmette-Guérin (BCG) vaccination in Australia is limited to selected high-risk groups and is not routinely recommended for most health care workers (HCW). [1] 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. It is 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.[1]

BCG is contraindicated in immunocompromised individuals due to the risk of disseminated BCG infection. [1] This includes individuals immunocompromised by HIV infection, primary immunodeficiencies, corticosteroids or other immunosuppressive agents, and malignancies involving bone marrow or 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. [2] While BCG has not been shown to cause foetal damage the use of live vaccines is contraindicated in pregnancy. [1]

Global BCG vaccination 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. [3] A number of countries have previously included BCG revaccination as part of their national immunisation policies.[4] 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. At least seven countries revaccinate adults over 18 years of age. [5] In some countries, particularly in Eastern Europe, revaccination with BCG up to five times 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. [4, 6] In countries where BCG revaccination has been part of national immunisation practice, passive surveillance has not reported 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). [7] 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. [7] 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 from previous exposure to mycobacterial antigens [8] A comprehensive review of complications following more than 1.5 billion BCG doses in children and adults did not find that TST predicted serious complications from BCG vaccination. The most serious reactions recorded were disseminated BCG (3 per million) and death (0.02 per million) due to primary immunodeficiency that would not be detected by TST. The development of subcutaneous abscesses and regional lymphadenopathy were not predicted by prior TST, although the rate of necrotic skin reactions was higher in those who had previously received BCG vaccination. [9]

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. [10-12]

Participants in the Malawi study did not undergo any pre-randomisation screening with TST or IGRA. [11] 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, those with a measurable TST (1-14 mm) had increased rates of large local reaction compared to controls (3/6 compared with 18/388). Two months after revaccination, all had healed vaccination scars with no axillary node enlargement, fever or suppurative lymphadenitis.[12] Participants in the South African study all had a negative IGRA at enrolment. [10] 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 one severe and seven serious adverse events in each of the BCG and control groups. The serious adverse events reported in the BCG group 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. [13] 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 (>15 mm) 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. [14] Among the 76% of participants who developed ulceration, the median ulcer size was 5 mm (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. [15] There were 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. [16] There were no cases of suppurative lymphadenitis or disseminated BCG.

Two large randomised controlled trials showed BCG revaccination did not confer any additional protection against tuberculosis, however, it may provide some additional protection against leprosy (cause by Mycobacterium leprae). [11, 15] Cohort studies done in countries where BCG revaccination was routinely performed also showed no additional protection against tuberculosis. [17, 18] 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'.[19]

One aim of the BRACE trial is to document the safety of BCG vaccination (and revaccination) in HCW in Australia. The decision not to perform pre-vaccination TST screening in the study is pragmatic 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. Adverse events will be actively monitored during the trial and medical review available for any participants who have concerns about their BCG vaccination site or scar.

1. The BCG vaccine: information and recommendations for use in Australia, in Communicable Diseases Intelligence. Australian Government Department of Health.
2. Australian Immunisation Handbook. Tuberculosis. 2018: Australian Government Department of Health.
3. WHO News and activities. Bulletin of the World Health Organization, 1995. 73(6): p. 805-817.
4. Paul Fine, I.C., Julie Milstien, C. John Clements, Issues relating to the use of BCG in immunization programmes: a discussion document. 1999, Department of Vaccines and Biologicals, World Health Organization: Geneva.

5. Trnka, L., et al., Survey of BCG vaccination policy in Europe: 1994-96. Bull World Health Organ, 1998. 76(1): p. 85-91.
6. Immunisation schedules in the WHO European Region, in WHO Wkly Epidem Rec. 1995, World Health Organization. p. 221-227.
7. Coulter, C., Tuberculosis testing. Australian Family Physician, 2012. 41(7): p. 489-492.
8. Bothamley, G.H., et al., Tuberculin testing before BCG vaccination. BMJ, 2003. 327(7409): p. 243-4.
9. Lotte, A., et al., BCG complications. Estimates of the risks among vaccinated subjects and statistical analysis of their main characteristics. Adv Tuberc Res, 1984. 21: p. 107-93.
10. Nemes, E., et al., Prevention of M. tuberculosis Infection with H4:IC31 Vaccine or BCG Revaccination. N Engl J Med, 2018. 379(2): p. 138-149.
11. Randomised controlled trial of single BCG, repeated BCG, or combined BCG and killed Mycobacterium leprae vaccine for prevention of leprosy and tuberculosis in Malawi. Karonga Prevention Trial Group. Lancet, 1996. 348(9019): p. 17-24.
12. Roth, A.E., et al., Effect of revaccination with BCG in early childhood on mortality: randomised trial in Guinea-Bissau. BMJ, 2010. 340: p. c671.
13. Rakshit, S., et al., BCG revaccination boosts adaptive polyfunctional Th1/Th17 and innate effectors in IGRA+ and IGRA- Indian adults. JCI Insight, 2019. 4(24).
14. Hatherill, M., et al., Safety and reactogenicity of BCG revaccination with isoniazid pretreatment in TST positive adults. Vaccine, 2014. 32(31): p. 3982-8.
15. Rodrigues, L.C., et al., Effect of BCG revaccination on incidence of tuberculosis in school-aged children in Brazil: the BCG-REVAC cluster-randomised trial. Lancet, 2005. 366(9493): p. 1290-5.
16. Cunha, A.J., et al., Adverse effects of BCG revaccination: a report on 13 cases from Rio de Janeiro, Brazil. Int J Tuberc Lung Dis, 2002. 6(12): p. 1110-3.
17. Tala-Heikkila, M.M., J.E. Tuominen, and E.O. Tala, Bacillus Calmette-Guerin revaccination questionable with low tuberculosis incidence. Am J Respir Crit Care Med, 1998. 157(4 Pt 1): p. 1324-7.
18. Leung, C.C., et al., Efficacy of the BCG revaccination programme in a cohort given BCG vaccination at birth in Hong Kong. Int J Tuberc Lung Dis, 2001. 5(8): p. 717-23.
19. Bulletin of the World Health Organization 1995. World Health Organization. p. 805-810.

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Pregnancy and lactation

This section may require you to have some medical or research background.

BCG vaccination in pregnancy and lactation

BCG vaccination is not recommended for use in pregnancy due to a lack of safety data and theoretical concerns associated with a live vaccine. However, no evidence of adverse effects to the developing foetus have been observed [1-3].

BCG vaccination is not contraindicated in lactating women, although there is limited data on safety and immunogenicity of the vaccine in this group [1].

- Although no harmful effects of the BCG vaccine on the foetus have been observed, BCG vaccination should not be given during pregnancy due to theoretical concerns associated with a live vaccine [2]
- BCG vaccination is not contraindicated in lactating women, although there is limited data on safety and immunogenicity of the vaccine in this group [1].
- In the 1990s, a number of European countries gave repeat BCG vaccinations in adolescence or early adulthood, including Luxembourg (18-25 years), Portugal (18-20 years), Albania (18 years), Greece (21 years), Hungary (16-17 years), Poland (18 years), Slovakia (16 years), Yugoslavia (15 years), Azerbaijan (25 years), Lithuania (17 years) and Russia (21-22 years) [4].
- Bulgaria is the only European country that routinely gives BCG vaccine in adolescence, with a catch-up dose given at 17 years if previous doses were missed [5]. Patients are screened for latent TB infection (LTBI) with a tuberculin skin test (TST) prior to the catch-up doses.

[1] World Health Organization. BCG vaccines: WHO position paper - February 2018. Wkly Epidemiol Rec 2018;93:73-96.
[2] Centers for Disease Control and Prevention. BCG Vaccine Sheet.
[3] National Centre for Immunization and Respiratory Diseases. General recommendations on immunization - recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep 2011;60:1-64.
[4] World Health Organization. Bulletin of the World Health Organization. 1998;76:85-91.
[5] European Centre for Disease Prevention and Control. Vaccine scheduler.

This review was done in accordance with the 'preferred reporting items for systematic reviews and meta-analyses' (PRISMA) statement. A systematic search of MEDLINE was done in March 2020 using the OVID interface using the following search terms: (exp BCG vaccine OR exp tuberculosis vaccines) AND (exp pregnancy OR exp breast feeding OR exp pregnant women OR exp pregnancy complications/ OR exp prenatal care/ OR exp pregnancy complications, infectious). Reference lists of identified relevant publications were also hand-searched.

Studies were included if they: 1) assessed the safety of BCG vaccination antenatally or during lactation, or 2) described case reports of BCG vaccination during pregnancy or lactation. The search identified a total of 253 studies, none of which fulfilled the inclusion criteria.

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