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Neonatal BCG: a time for change

Thillagavathie Pillay ^{1,2}, Gergely Toldi,³ Abid Hussain,⁴
Mercy Murinye Magwenzi,⁵ Prakash Satodia,^{6,7} Ruth Radcliffe⁸

¹Neonatology, University Hospitals of Leicester NHS Trust, Leicester, UK

²Faculty of Science and Engineering, University of Wolverhampton, Wolverhampton, UK

³Starship Children's Health Neonatal Intensive Care Unit, The University of Auckland Liggins Institute, Auckland, New Zealand

⁴Department of Microbiology, University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK

⁵Birmingham Community Healthcare Trust, Birmingham Heartlands Hospital, Birmingham, UK

⁶Neonatal Intensive Care Unit, University of Warwick Warwick Medical School, Coventry, UK

⁷Warwick Medical School, University Hospitals Coventry and Warwickshire NHS Trust, Coventry, UK

⁸Department of Paediatrics, University Hospitals of Leicester NHS Trust, Leicester, UK

Correspondence to

Professor Thillagavathie Pillay, Neonatology, University Hospitals of Leicester NHS Trust, Leicester, Leicester, UK; tilly.pillay@uhl-tr.nhs.uk

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ABSTRACT

The BCG vaccination programme in the UK is risk based and has usually been given to eligible babies soon after birth. On advice from the Joint Committee on Vaccination and Immunisation, NHS England and Improvement recently revised the timing of this vaccination to 28 days after birth or soon thereafter. In this article, we highlight the change in timing of vaccination, the rationale and barriers to BCG uptake that this change may pose.

INTRODUCTION

The BCG vaccination programme focuses on providing optimal protection for babies and children most at risk from tuberculosis (TB), and especially from the more serious forms of the disease in childhood.¹ The vaccine is live, attenuated and derived from *Mycobacterium bovis*. Only one vaccination per lifetime is generally recommended. There are 13 vaccine strains globally, and while there is some evidence that protection against TB differs between strains, there are insufficient data to recommend one particular strain.² The only licensed version in the UK is the BCG vaccine AJV, which contains the Danish strain 1331.

In the UK, the BCG vaccination strategy is risk based (table 1). For these babies, it has, until recently, been recommended for administration soon after birth, up to the first year of life.

WHAT'S CHANGING WITH BCG VACCINATION SCHEDULE AND WHY?

Current evaluation of T cell receptor excision circles (TREC) bloodspot screening for severe combined immunodeficiency (SCID) (a pilot addition to the routine UK newborn blood spot screening, in selected regions) at 5 days of age has led to a policy to delay administering BCG to all eligible neonates at birth (figure 1). This is to ensure that babies who have been tested for SCID are not inadvertently given the BCG vaccine, as they may

develop disseminated BCG disease as a consequence of immunisation.³

As a result, BCG is now recommended by the Joint Committee on Vaccination and Immunisation (JCVI), to be given at 28 days of life or soon thereafter at the earliest opportunity. For regions participating in the pilot, this is once the results of this TREC screening are available. SCID screening notification should be effected to the newborn failsafe system by 21 days of life, facilitating delivery of BCG at 28 days of age, or as soon after TREC bloodspot screening results are available.

CAN BCG BE GIVEN TO BABIES WHO HAVE SPECIFIC IMMUNODEFICIENCY?

In babies who have a specific immunodeficiency relating to T lymphocytes, innate immunity and phagocytic function, or specific cytokine receptor deficiencies, the potential for the live attenuated vaccine to develop into disseminated BCG disease exists. This may happen weeks or months after being given BCG vaccination.

For example, in babies with severe combined immunodeficiency syndrome (SCID), disseminated BCG can have a devastating clinical impact (table 2). A large multicentre pilot, undertaken by NHS England and Improvement, is evaluating TREC levels via the newborn blood spot screening programme to identify babies with SCID before they present with infectious complications.⁴ This service covers approximately two-thirds of all births in England and is detailed in figure 1. The implications for this service includes a change in the timing of BCG for these participating units to after results of SCID screening are available, which is usually within 28 days after birth. To standardise care delivery across the country, all services are required to delay administration of BCG vaccine to after a month of age. The algorithm of administration can be seen in figure 1.

As a live vaccine, BCG, while previously not being recommended in children who

Table 1 Indications and contraindications to BCG vaccination in the UK (adapted from¹)

Population group	Indication
For all infants (aged 0 to 12 months)	<ul style="list-style-type: none"> ▶ With a parent or grandparent who was born in a country where the annual incidence of TB is $\geq 40/100\ 000$ ▶ Living in areas of the UK where the annual incidence of TB is $\geq 40/100\ 000$ ▶ Living with/close contact with someone with infectious TB, once TB has been excluded
For older children (1–16 years)	<ul style="list-style-type: none"> ▶ Previously unvaccinated, with a parent or grandparent born in a country where the annual incidence of TB is $\geq 40/100\ 000$* ▶ Previously unvaccinated tuberculin-negative household or close contacts of cases of sputum smear-positive pulmonary or laryngeal TB ▶ Previously unvaccinated, tuberculin-negative, born in or have lived for at least 3 months in a country with an annual TB incidence of $\geq 40/100\ 000$

*<https://www.gov.uk/government/publications/tuberculosis-tb-by-country-rates-per-100000-people> (no tuberculin testing prior to vaccination is required for those 1–5 years old; for those 6–16, do tuberculin test and vaccinate if test is negative).
TB, tuberculosis.

are confirmed HIV infected, may now be considered under specific circumstances, outlined in the WHO position paper published in November 2021, on recommendations for routine immunisation.⁵ HIV-infected children <5 years receiving antiretroviral therapy who are clinically well and immunologically stable (CD4 >25%) should be vaccinated with BCG. Babies born to mothers of unknown HIV status should

be vaccinated if indicated, and where HIV status of the baby is indeterminate (awaiting diagnosis) and mother is HIV infected, clinically well babies may also be offered BCG vaccination, regardless of mother’s treatment status. For babies where HIV infection is confirmed by early virological testing, BCG vaccination should be delayed until antiretroviral treatment has commenced and the baby is immunologically stable

Risk-determined BCG eligibility identified at birth

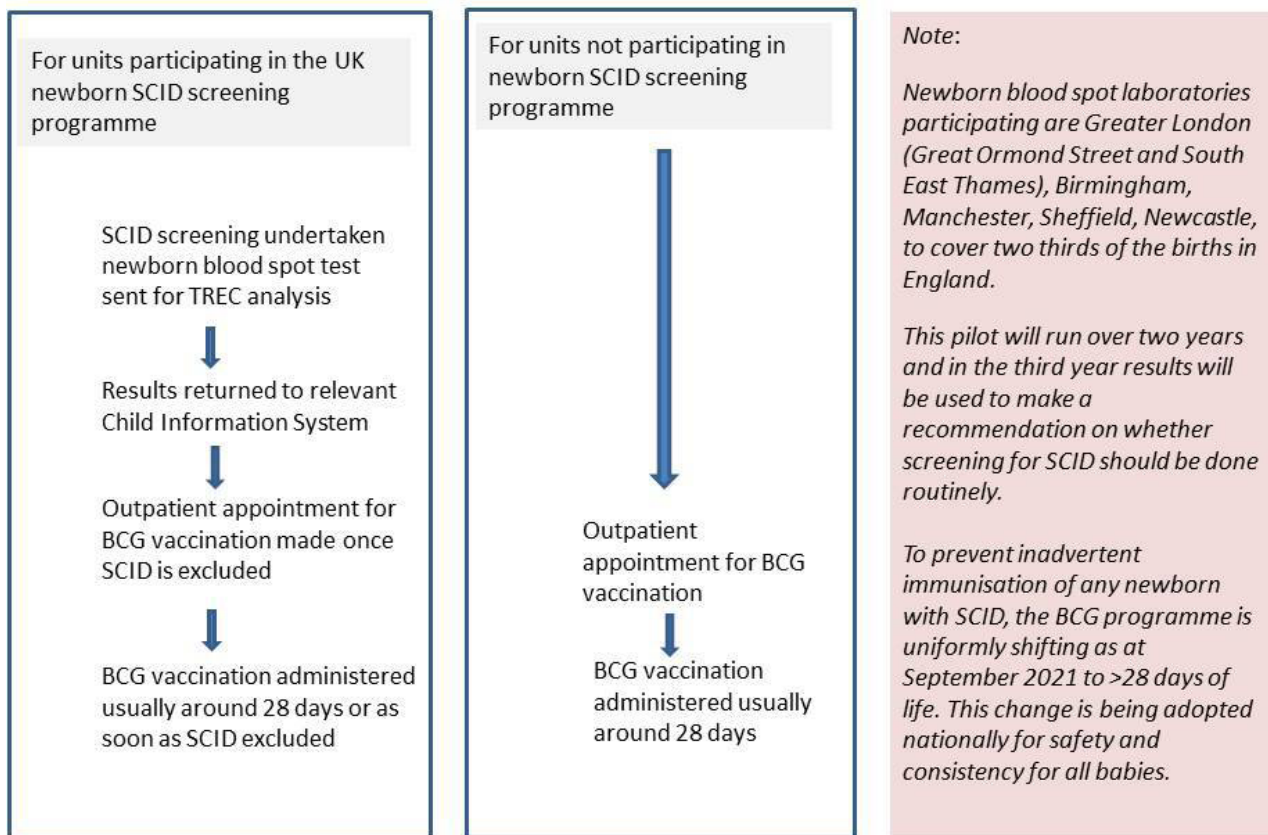


Figure 1 SCID screening and BCG administration flowchart for England. SCID, severe combined immunodeficiency; TREC, T cell receptor excision circles.

Table 2 Side effects of BCG vaccination

Side effects of BCG vaccination	Notes
None	A correctly given intradermal injection should produce a tense, blanched, raised bleb which generally results in a local reaction of a small pustule followed by a small scar. Local complications below occur in about 1:1000 given BCG vaccine
Injection site reaction/ abscess	Local abscess can develop around 1 month post-vaccination. This is more common when vaccination is given at less than 6 months of age or when the vaccine is administered by an untrained vaccinator. These can usually be managed conservatively with no additional intervention. The efficacy of anti-tuberculous therapy for local abscess is unclear and limited by poor penetration of drugs into the abscess cavity
BCG lymphadenitis	Adenitis in the regional lymph nodes is common and may be suppurative or non-suppurative. Non-suppurative nodes can be managed conservatively There is a lack of consensus on suppurative node management. ¹⁷ Options include conservative management, needle aspiration and surgical excision if there is sinus formation. Incision and drainage should be avoided
Disseminated BCG disease	Also called BCG-osis, occurs in the context of T cell immunodeficiencies, innate immunity, natural killer cells phagocytic or specific cytokine-mediated immune deficiencies (such as chronic granulomatous disease and Mendelian susceptibility to mycobacterial diseases). These should prompt investigation. It is defined by the presence of BCG in more than one anatomical site distant from the region of inoculation. Common sites include bones, skin, liver, spleen and lung. Mortality is high, in part reflecting the underlying immune deficiency. This condition should be managed by experts in paediatric immunology and infectious disease
Immune reconstitution inflammatory syndrome	This can occur following the initiation of antiretroviral therapy in HIV-infected BCG-vaccinated children or following successful haematopoietic stem cell transplant for SCID. This can manifest as local reaction, adenitis or systemic inflammatory response. This condition should be managed by experts in paediatric immunology and infectious disease
SCID, severe combined immunodeficiency.	

(CD4 >25%). These apply as the benefits of BCG vaccination far outweigh its risks in these scenarios.⁶ Examples of clinical conditions and circumstances where BCG vaccination is contraindicated are shown in table 3.

DOES IMMUNISATION IN NEONATES/EARLY INFANCY OFFER THE BEST OVERALL PROTECTION AGAINST TB?

BCG vaccination in the neonate or young child protects against *Mycobacterium tuberculosis* infection and progression from infection to disease.⁷ The greatest risk of progression from infection to disease, including miliary TB, TB meningitis, pulmonary TB and mediastinal lymphatic disease, is during infancy.⁸

BCG provides protection against disseminated and pulmonary TB disease.⁹ This efficacy, while significant if given early in life, is variable against pulmonary TB in adults, when given later in life. In a meta-analysis of randomised controlled trials, the summary protective effect of early immunisation against miliary or meningeal TB was 86% (95% CI 65 to 95).¹⁰ This protective effect is consistent, reliable and cost-effective.^{11 12}

When given in early life, administration at around 3 months as opposed to the first 3 days of life is associated with a higher degree of induration response to PPD (purified protein derivative), bigger BCG scars and fewer lymphadenopathies.¹³ Whether this relates to a relative immune immaturity at birth compared with 3 months is speculative, but this improved response at

Table 3 Specific immunodeficiencies in which BCG vaccination is contraindicated in infants and children

Category	Specific immunodeficiencies in which is BCG contraindicated
Immunosuppression in mother	▶ Mother on immunosuppressive biological agents in pregnancy, eg, TNF alpha inhibitors (delay BCG in infant for 6 months) ¹
Immunosuppression in baby	▶ Corticosteroid use >2 mg/kg/day for more than 1 week or >1 mg/kg/day for more than 2 weeks (delay BCG in infant for 3 months) ▶ Severe combined immunodeficiency (through its impact on affecting T cell immunodeficiency) ▶ Disorders of phagocytosis, eg, chronic granulomatous disease ▶ Mendelian susceptibility to mycobacterial diseases (MSMD) (eg, gamma interferon receptor deficiency, natural killer lymphocyte deficiency) ▶ Infection-related conditions that can cause immunosuppression associated with T cell function, eg, HIV with severe immunosuppression ▶ Other T cell disorders, eg, 22q deletion (Di George's syndrome, with severe immunosuppression)
Host immune response	▶ Confirmed anaphylaxis to vaccine component
Evidence for previous exposure to pathogen/ antigen	▶ Previous BCG vaccination ▶ History of TB ▶ An induration of 5 mm or more following Mantoux tuberculin skin testing
BCG is contraindicated in immune deficiencies associated with T cell function, phagocytosis and cytokine-mediated disorders such as chronic granulomatosis and MSMD. BCG is not contraindicated in pure B cell or antibody deficiencies. HIV infection and Di George's syndrome are relative contraindications based on degree of immunosuppression.	

3 months is reassuring in the context of the change in vaccination schedule.

WHAT ARE THE POTENTIAL CHALLENGES FOR UPTAKE OF BCG IMMUNISATION WITH THE NEW BCG VACCINE SCHEDULE?

Will the rate of TB increase?

The JCVI noted that benefits from SCID screening and delay in BCG administration currently outweigh the risks for any increase in TB disease.¹⁴ The potential for babies at risk of acquiring TB, to acquire TB while waiting for BCG vaccination or inadvertently missed, may be small, but exists. This could be limited if there is effective, sustained, cohesive working between the different relevant sectors within the NHS.

Will it impact on other infections and mortality in babies?

Although the non-specific effects of BCG are well described, we have no data in the UK reporting a beneficial effect of BCG on reducing neonatal and infant mortality, nor of it offering a pathogen-agnostic protective effect.

Will TREC screening pose additional barriers to BCG vaccine uptake?

Suspected SCID

Only a small proportion of babies (1:10) who are flagged up in the screening by TRECs are likely to have significant lymphopaenia or SCID. Therefore, most of those who screen 'SCID suspected' on TREC results will be eligible for BCG. Effective pathways are essential to communicate between immunology departments, general practitioners and BCG providers to ensure timely vaccination of these babies, who may be delayed due to secondary testing to confirm or exclude SCID.

Preterm babies and TREC screening

Premature babies are also more likely to have low TRECs (but not more likely to have SCID); therefore, a proportion of premature babies will require a repeat TREC screen at 37/40 weeks post-menstrual age or discharge. Waiting for further results will further delay vaccination in those at risk for TB. Some of these babies may be additionally compromised by having chronic lung disease of prematurity. Healthcare workers managing this cohort will need to be vigilant in ensuring that such vulnerable babies are not inadvertently missed due to further testing to rule out SCID.

Logistical challenges

Barriers common to vaccine uptake in general will be applicable. In the UK, invitation to BCG vaccination happens by post and is generally written in English. Families who move regularly and/or do not speak English as their first language will need to be prioritised to reduce the health inequalities. This could include using measures such as multilingual audio-visual social

media to promote vaccine uptake, highly focused, targeted, health service support similar to the NHS programme delivering midwifery continuity of care for vulnerable pregnant women,¹⁵ multi-agency, peer and voluntary support group engagement, all of which are coupled with every effort to communicate in the language familiar to families.

Health beliefs about co-administration of BCG with other vaccines from the routine schedule, and mild inter-current illness may also influence timely uptake. It is important to note that BCG can be given at the same time as other vaccines administered as part of the routine immunisation programme, but these should not be given into the same arm as the BCG vaccine, for at least 3 months after BCG vaccination.³

In pilot areas, all babies whose parents have consented to screening need to have a TREC result available before BCG can be given. The majority of term and preterm babies whose screening results are abnormal but who turn out not to have SCID will still require laboratory evaluation and clinical assessment by an immunologist for clearance prior to receipt of BCG. This will add an increased workload for NHS service delivery, and will need to be carefully evaluated and strategies modified over time.

A further logistical challenge will come from babies who move from a pilot area to a non-pilot area between the test being taken at 5 days and BCG being offered at 28 days. Here, a screening result is available, but these babies may be offered BCG in a system where reviewing screening results is not routine. Conversely, babies who move into a pilot area will be attending for BCG without a screening result. Both of these scenarios will require that the screening programme be fine-tuned to accommodate algorithms for careful follow-up of babies screened

Learning points

- ▶ The NHS vaccination programme no longer offers a BCG vaccination at birth, but one that begins at 28 days or soon thereafter. This is to allow results of newborn screening for severe combined immunodeficiency (SCID) to be available before BCG immunisation.
- ▶ BCG vaccination is contraindicated in individuals with severe immunocompromise such as SCID. It can progress to BCG disease (BCG-osis) if administered.
- ▶ BCG is a safe vaccine, with its greatest impact in infancy, where the risk of progression from infection to disseminated disease is greatest. When given in infancy, immunisation at 3 months is associated with a greater response to PPD, bigger scar and fewer side effects than when given within 3 days of birth.
- ▶ Potential challenges for the uptake of the new BCG immunisation schedule in infancy include maintaining and optimising vaccine uptake, and avoiding an increase in rate of TB disease due to change in timing of vaccination.

Test your knowledge

1. The BCG vaccine
 - A. Is a live, attenuated vaccine
 - B. Contains *Mycobacterium tuberculosis*
 - C. Is only available as one strain worldwide
 - D. Does not induce an innate immune response
 - E. Requires booster doses through childhood
2. The following are contraindications of BCG vaccination:
 - A. An infant with severe combined immunodeficiency
 - B. Infants born to a mother who received infliximab in the third trimester of pregnancy
 - C. A positive tuberculin skin test (Mantoux test)
 - D. An infant with severe HIV infection (CD4 count <25%)
 - E. An infant being treated with penicillin
3. As of September 2021, the NHS vaccination programme
 - A. No longer administers BCG vaccination at birth
 - B. No longer offers BCG vaccination to infants at increased risk of exposure to TB infection
 - C. Offers BCG immunisation to 28 days or later to all babies in the UK, regardless of risk
 - D. Requires all infants to have a tuberculin skin test (Mantoux test) prior to BCG vaccination
 - E. Offers a booster dose of BCG within the first year of life
4. The following are side effects of BCG vaccination:
 - A. A correctly administered BCG should never produce a local reaction
 - B. A local abscess necessitates rifampicin therapy
 - C. Non-suppurative BCG lymphadenitis can be managed conservatively
 - D. BCG scars often remain visible well into adulthood
 - E. BCG lymphadenitis must always be referred to surgeons for incision and drainage
5. Which of the following are true about BCG-osis?
 - A. BCG-osis refers to disseminated BCG disease
 - B. It is defined by the presence of BCG in more than one anatomical site distant from the region of inoculation
 - C. BCG-osis should be managed by experts experienced in paediatric immunology and infectious disease
 - D. If BCG-osis is confirmed, investigations for immunodeficiency should be initiated
 - E. BCG-osis is always a benign condition with minimal mortality.

Answers to the quiz are at the end of the references.

regardless of where they relocate to, as well as uptake of new babies not screened into pilot areas.

For areas in England deferring BCG without the benefit of early SCID diagnosis, this still carries the

potential for infants with undiagnosed SCID in non-screening areas to continue to receive BCG. TREC screening does exist in developed economies around the world, such as in New Zealand, Switzerland, Germany, Iceland, Israel, Norway, parts of Italy, Canada and Australia, with multiple pilot studies in further nations contemplating universal screening.¹⁶ For the UK, the pilot of delaying BCG immunisation in the interest of SCID screening needs to be carefully studied from an overall health economic perspective taking into account both SCID and TB morbidity and mortality in the communities before universal roll-out. This is to ensure that any gains in the SCID programme do not outweigh the losses of an effective BCG immunisation programme, both to the individual and to society, especially from the perspective of TB as a communicable disease.

Limiting disseminated BCG disease through delay of BCG immunisation where indicated and TREC screening

Disseminated BCG disease may be the consequence of failure in T cell function, which may be picked up by TREC screening. However, deficiencies in other immunologically mediated pathways such as innate immunity and phagocytic function (eg, chronic granulomatous disease), or specific cytokine receptor deficiencies (eg, MSMD) which can also lead to disseminated BCG disease in infancy if vaccinated, will not be detected through TREC screening. TREC screening will therefore not completely eliminate disseminated BCG disease in the UK.

CONCLUSION

In babies and young children at risk for TB disease and infection, BCG vaccination remains a safe, effective and targeted programme in the UK. New developments in newborn screening for SCID have shifted the timing of the current BCG vaccination to beyond the neonatal period. This will require coordinated multi-disciplinary community and hospital engagement to capture all those at risk, for timely immunisation. All healthcare personnel should be aware of this change in timing, noting the potential risks for missed or delayed immunisation, while the new schedule is established. An appropriate index of suspicion for TB as a differential diagnosis in young children, as well as ensuring that at-risk babies are triaged appropriately for BCG vaccination is important.

Twitter Thillagavathie Pillay @_tpillay

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ORCID iD

Thillagavathie Pillay <http://orcid.org/0000-0002-4159-3282>

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Answers to the multiple choice questions

- (A) True; (B) False; (C) False; (D) False; (E) False.
- (A) True; (B) True; (C) True; (D) True; (E) False.
- (A) True; (B) False; (C) False; (D) False; (E) False.
- (A) False; (B) False; (C) True; (D) True; (E) False.
- (A) True; (B) True; (C) True; (D) True; (E) False.