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Review Article

Effect of Bacilli Calmette-Guerin vaccine on severe combined immunodeficiency patient: a narrative review and proposed workup algorithm

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ABSTRACT

This systematic review critically investigates the administration of the Bacillus Calmette-Guérin (BCG) vaccine in neonates with severe combined immunodeficiency (SCID). The BCG vaccine, derived from *Mycobacterium bovis*, is a live attenuated vaccine recognized for its significant role in mitigating the impacts of tuberculosis (TB) in endemic areas. Despite its beneficial effects in controlling TB, safety and efficacy concerns have been raised when the vaccine is administered to SCID patients, who have a severe dysfunction or absence of the immune system. The potential for the vaccine to lead to severe complications due to the immunocompromised state of SCID patients necessitates a comprehensive investigation. To better understand these issues, a thorough literature review was carried out, integrating data from clinical trials and observational studies available on the PubMed database. An extensive review and analysis of 32 relevant articles revealed substantial evidence of complications from BCG vaccination in SCID patients. These findings emphasize the urgency for a more effective pre-vaccination screening process to circumvent potential adverse effects. Given the crucial role of the BCG vaccine in controlling TB, its potential to induce severe complications in SCID patients warrants careful consideration. Therefore, this review proposes an in-depth screening algorithm for newborns before BCG vaccination administration. The goal is to prevent these adverse events, offering critical insights to health policymakers, researchers, and clinicians in the field.

Keywords: BCG vaccine, Complications, SCID, Screening, Prevention, Newborns, Algorithm

INTRODUCTION

There are more than 190 different species present in mycobacterium genus.[1] TB is one troublesome disease caused by the members of this genus. Under certain circumstances they can be responsible for causing widespread disseminated infection.[2] After years of extensive research and BCG vaccine awareness in TB endemic areas, newborns are now being routinely vaccinated at birth or in the first month following the birth.[3]

BCG vaccine is derived from *Mycobacterium bovis* and is a live attenuated vaccine administered intradermally. It is thought to reduce the severity or prevent complications from TB but has no role in preventing transmission. Several TB endemic countries across Asia, Africa and South America continents have opted for nationwide BCG vaccination policy in which all neonates, irrespective of immune status, are vaccinated within a few hours to the first month of life. Vaccination has reported to provide up to 95% protection against meningeal and miliary type of TB.[4]

However, some countries with low TB prevalence opted for no vaccination policy at all or vaccination restricted to high-risk population.[5]

LITERATURE SEARCH

At the end of the narrative review total 32 papers were used as a reference and they are mentioned below. The primary questioning line of our search was BCG vaccine complications in SCID patients and how we would avoid these complications. To address this, we employed a systematic search strategy on the PubMed database, with the following criteria:

Keywords used were search incorporated a combination of terms such as 'BCG vaccine', 'complications', 'severe combined immunodeficiency', 'SCID', 'screening', 'prevention', 'newborns', and 'algorithm'.

Inclusion criteria

The search was narrowed down to English-language, peer-reviewed, full-text articles from both clinical trials and observational studies, without any restriction on the publication date.

Exclusion criteria

Articles that were not directly relevant to our research question, alongside commentaries, editorials, and those without full text availability, were excluded.

Data extraction

All relevant information was extracted from the selected papers, focusing primarily on SCID diagnostic methods, complications related to the BCG vaccine, and strategies to circumvent them.

All the below mentioned papers were sourced from PubMed or PubMed-indexed journals. Each paper was thoroughly read and the analyzed by the entire author panel.

BCG VACCINE

A vaccine known as the BCG vaccine is primarily used to prevent TB. It bears the names of its creators, Camille Guérin and Albert Calmette. Vaccine is administered on the left upper arm intradermally, and it typically leaves a small scar. A weakened strain of the *Mycobacterium bovis* is used in the vaccine that stimulates the immune system to fight the infection but does not actually cause the TB. BCG vaccine related complications are the rare but may occur in immunocompromised states such as SCID.

BCG vaccine associated complications are as described in Figure 1.

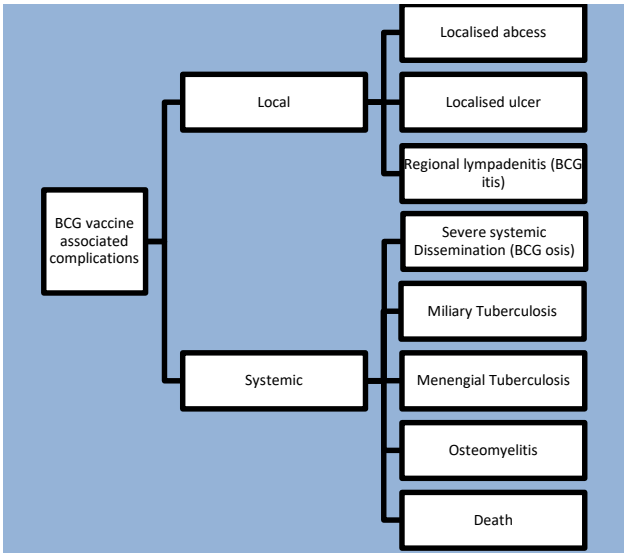

Figure 1: BCG vaccine associated complication: localized and systemic.

PRIMARY IMMUNE DEFICIENCY (PID)[6]

Primary immunodeficiency are the disorders which affect innate and adaptive immunity of our immune system.[7-9] The incidence of primary immunodeficiency disorders is 1:1000-2000 live births with a significant high morbidity and mortality.[7,10]

Primary immunodeficiency is characterized by impaired development of hematopoietic and non-hematopoietic cells leading to increased risk of infection.[2] BCG vaccine related complications have been associated with impaired phagocytic function, interferon-gamma immunity and cellular immunity.[11]

Different types of PID are as mentioned in Table 1.

Table 1: Types of PID.

S. no.	Types
1	Cellular and humoral immunity
2	Combined immunodeficiency with associated or syndromic features
3	Predominantly antibody deficiencies
4	Diseases of immune dysregulation
5	Congenital defects of phagocyte number, function, or both
6	Defects in intrinsic and innate immunity
7	Auto inflammatory disorders
8	Complement deficiencies

SCID

An increased likelihood of infections is the most common clinical symptom of inborn error of immunity (IEI). It is imperative to investigate any patients who have persistent infections, unusual infections, or infections that are challenging to treat.

Clinical manifestations of combined immunodeficiency vary greatly, ranging from diarrhoea and sinopulmonary bacterial infections to opportunistic infections caused by mycobacteria and fungi and vaccine reactions with local to systemic symptoms (by BCG). SCID exhibits more severe clinical manifestations, which are typically fatal in the first few years of life if untreated.[12] A B cell dysfunction due to absent T-cells, SCID affects both cellular and humoral immunity.[6] For diagnosing a patient with SCID, PID treatment consortium (PIDTC) suggested that patient should be negative for Human immunodeficiency virus (HIV) and should be positive for 2/3 criteria mentioned below:[13] 1) Marked lymohocytopenia. 2) T cell proliferation defect and 3) Decrease in thymic function

The above criteria were modified and now for a patient to be classified under SCID should have:[14] Absence or less than 300 cells/mm^3 T cell, maternal origin of T cell.

SCID is responsible for causing many types of bacterial, viral and fungal infections and symptoms like diarrhea, rash and failure to thrive.[15]

ASSOCIATION OF BCG AND SCID

Studies have demonstrated that there is almost twice risk of BCG vaccine complications arising in SCID children who have taken the vaccine in first month of life compared to the SCID children who have taken the BCG vaccine later in life.[16] It can be very harmful when a live vaccine is administered to a child who has been suffering from SCID as individuals with this disease will have a very low levels of antibodies.[17] They can have severe reaction to BCG vaccine such as BCGOsis, BCGitis, and chronic diarrhoea. BCGitis, also known as purulent regional lymphadenitis is the most common reaction.[18-20] Clinically it is seen as localized erythema with ipsilateral lymph node enlargement.[21] BCGOsis is a systematic infection after BCG vaccine and it is fairly less common. It usually involves distant lymph nodes, bone, liver and spleen.[18,20,22]

SCREENING TEST FOR SCID

Nearly all children with SCID are lymphopenic at birth and thus can be primarily screened with complete blood count as it is cost effective and widely available in developing countries.[23] If needed, an additional screening test, known as the TREC test, can be done. The TREC test measures T-cell receptor excision circles (TREC) in a newborn's blood sample, indicating T-cell count, which can help identify SCID, a serious immune system disorder. If cord-blood CBC is examined for absolute lymphocyte counts (ALC) before giving live BCG vaccine, it may prevent vaccine associated complications and also help in early diagnosis of SCID.[6] Low ALC is used by the UK primary immunodeficiency network as a threshold for SCID evaluation.[24] The lower limit of normal is 2000/ul, and the mean normal cord blood lymphocyte count is 5500/ul.[23] While the majority of SCID patients have low ALC at birth (114-2210/ul reported in 25 SCID children), some patients can present with low normal ALC due to the presence of B cells (IL2RG, JAK3, and IL7R gene abnormalities) or maternal lymphocytes.[24] Setting the standard ALC cut-off number to capture all SCID patients would increase the false positive rate. Shereen et al found lymphopenia in 1.6% of 500 babies (ALC 2500/ul). Further analysis revealed that none of these patients had SCID. Despite these limitations, using CBC to determine absolute lymphocyte count as a screening test at birth has some advantages: a) Widespread availability with no considerable increase in infrastructure costs. b) The cost per test is approximately ten times less than that of TREC and c) Technically simple and well-standardized assay to run and interpret. d) Can also provide information on absolute neutrophil counts (ANC). An extremely low ANC indicates severe congenital neutropenia, while a very high ANC indicates leukocyte adhesion deficit (LAD). It also offers information on other haematological parameters such as haemoglobin and platelet count, which may be relevant for disease management. e) It is performed at the point of care, and results are available before the newborn is released, allowing for action before the infant is lost to follow-up.[6]

Given these advantages and disadvantages, a proposed screening algorithm before administering BCG vaccine with a two-tier ALC cut-off is mentioned below (Figure 2).

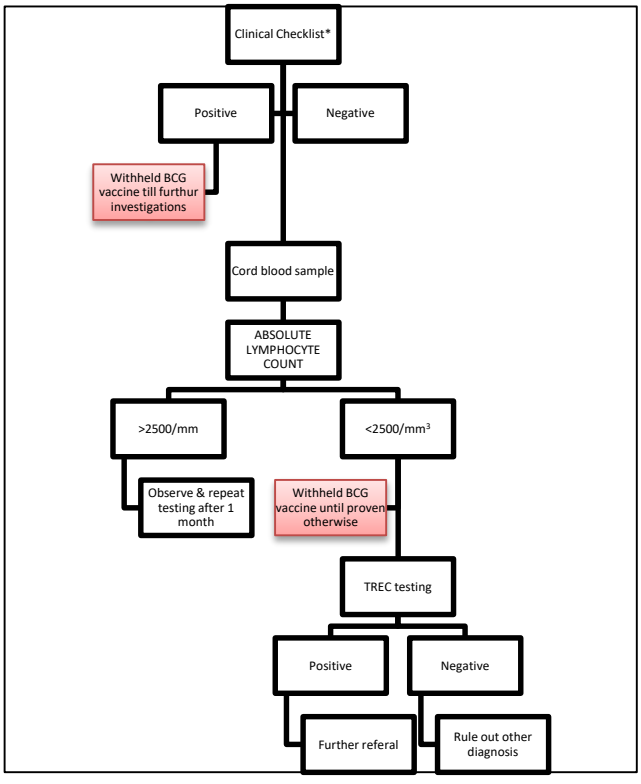

Figure 2: Proposed algorithm for screening of SCID before administering BCG vaccine in newborn.

Lymphopenia seen on a CBC and verified by lymphocyte subset analysis (LSSA) requires clinical evaluation and appropriate treatment/intervention while additional lab investigations are conducted to confirm diagnosis. Until final diagnosis is proven otherwise BCG vaccine should be withheld to prevent vaccine associated complications.[6]

TREC SCREENING TEST

Multiple genetic variants that develop into SCID. Most of defects are associated with abnormal T-cells development and maturation. T-cells regenerate in bone marrow and then undergo process of recombination in secondary lymphoid organ thymus. During recombination T-cell receptors undergo excision of certain fragments. These fragments form by products, called TREC/TRECS which are basically excised circular DNA.[25,26]

TRECS are expressed only in naive T-cells, serving as markers for T-cell development in thymus and useful in screening of SCID. Depending upon age, TREC copy number varies in peripheral blood. Neonates have around 1 TREC per 10 T Cells, older children 1 per 100 and adults 1 per 1000.[27] Infants with SCID will have either undetectable or very low quantity of TRECS.[25] TRECS is widely used as a screening test in many countries for SCID. TREC test is used more commonly for newborn screening of SCID in many countries.

The TREC test offers high sensitivity and specificity for SCID, making it a more suitable choice for this specific purpose compared to the complete blood count (CBC) test. However, this might vary based on the specific health policies and resources of each country or region.

AEFI-ADVERSE EVENT FOLLOWING IMMUNIZATION

Complications of BCG vaccine in SCID patients and it's timeline has been mentioned in the Table 2.

Table 2: Complication of BCG vaccine in SCID patient and their time line.

Age at diagnosis (In years)	Vaccine status	AEFI	Age	Severity	Casuality	Observation
1	Complete	BCGosis	NB	Serious	Probable	
1	Complete	BCGitis (Submandibular abscess)	NB	Serious	Definitive	Death
0	Outdated	BCGitis/ BCGosis	NB	Serious	Definitive	Death

BARRIERS FACED IN SCREENING SCID

Majority of patients have no symptoms at birth so it may go unnoticed. Moreover, the majority of the cases are sporadic and those who do have a family history may go undetected due to lack of awareness and knowledge about disease. Routinely used screening test TREC for SCID in developed countries is not affordable and nor widely available in most developing countries.[6]

ALGORITHM

In view of advantages and disadvantages a screening algorithm before BCG vaccine administration to prevent vaccine related complications in newborns is proposed in Diagram 02. In developing countries, it may help in reducing BCG vaccine related complication in newborns with SCID. It could also potentially help reduce healthcare cost by preventing these complications.

CLINICAL CHECKLIST[6]

SCID-related physical characteristics (e.g., skin rash, mouth ulcers, midline abnormalities, coarse face features), H/o any immunosuppressive medication/immunosuppression in mother, Previous siblings with a positive family background include: Infant mortality, BCGOsis, Severe infections and PIDs diagnosis.

After reviewing the clinical checklist all physicians should measure the absolute lymphocyte count, following which the patient should undergo TREC test which may give us a probable SCID diagnosis. Until then, the BCG vaccine should be withheld.

TREATMENT

Steroids and anti TB therapy are frequently used in the treatment of BCGosis.[28,29] In individuals who have suspected BCGosis, it is critical to have a low threshold for initiating anti- TB therapy.[29]

The majority of children with injection site problems and non-suppurative lymphadenitis responded completely within 6 months when treated conservatively. Few occurrences of suppurative lymphadenitis in children are managed conservatively; instead, the majority of these cases are managed with anti TB treatment and/or a procedure (most commonly aspiration or surgery).[30]

Early diagnosis of BCG osteomyelitis is crucial because treatment is most successful when initiated before the onset of the illness.[31,32] Rare cases of osteomyelitis following BCG vaccination typically affect the epiphysis of long tubular bones.[33,34]

Early surgical debridement in conjunction with suitable anti TB treatment has been demonstrated to produce excellent results.[34]

CONCLUSION

Depending on the reporting nation, the vaccine strain used, and the age at vaccination, there can be significant variations in the prevalence of BCG-associated complications in the general population and specially in cases of SCID. Hence, developing countries may benefit by following the algorithm especially in potentially high-risk newborns to overcome the cases of BCG vaccine related complications. In developing countries, certain guidelines should be proposed for screening of diseases like SCID mandatory. Still detailed studies regarding live vaccine complications in inborn errors of immunity would be helpful.

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