

# Delaying Bacillus Calmette-Guerin (BCG) Vaccine in HIV-Exposed Infants: A Systematic Review and Meta-Analysis

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**Abstract:** Background: Infants who have been exposed to the human immunodeficiency virus (HIV) are at a higher risk of contracting *Mycobacterium tuberculosis*, have a higher chance of developing tuberculosis (TB), and are more likely to experience bacillus Calmette-Guerin (BCG)-related side effects. The only antituberculosis (TB) vaccine now available is Bacillus Calmette Guérin (BCG). We assessed when BCG may be given to an HIV-exposed uninfected (HEU) infant without exposing the child to HIV or tuberculosis. Objective: To establish the best time for administering BCG vaccination to HIV-exposed infants and to evaluate the impact of administering BCG vaccine at birth vs delaying BCG vaccine at delivery. Methods: We searched in studies related to the subject in different databases: Web of Science, LILACS, CENTRAL (Cochrane Central Register of Controlled Trials), PubMed and CINAHL, Scopus, as well as conference abstracts from the HIV/AIDS website, then we conducted a systematic review and Meta-analysis. Results: CD4<sup>+</sup> T cells activation after 14 weeks comparing BCG delayed to BCG given at birth in HIV-exposed infants, the random-effects meta-analysis of CD4<sup>+</sup> T cells activation (14 weeks) yielded a pooled MD estimate of -3.58 (95% CI -6.73 to -0.43, P=0.03) with I<sup>2</sup>= 97%. Conclusion: In HIV-exposed uninfected (HEU) infant, BCG vaccination causes immunological alterations, and the intensification in the percentage of activated CCR5+CD4<sup>+</sup> HIV target cells. Therefore, delaying BCG vaccine would be advantageous to HEU rather than giving it shortly after the delivery, but more evidence is still needed to explore this new paradigm.

## 1. Background

Tuberculosis (TB) continues to be the global health concerns, with at least 1 million children getting the disease each year [WHO 2018]. According to the World Health Organization, 233 000 children die from tuberculosis (TB) per year (including children with HIV-related TB) [1]. Importantly, children account for around 10% of all TB cases and Sub-Saharan Africa accounts for one-quarter of all new cases [2]. In addition, the combined pandemic of HIV and TB is a primary cause of morbidity and mortality among children in Sub-Saharan Africa. Unfortunately, there is insufficient information on the association between TB and perinatal HIV exposure in HIV-exposed infants. Despite being born HIV-free, numerous studies have found that HIV-exposed newborns had higher rates of morbidity and mortality compared to those who are not exposed to HIV in utero [3,4,5,6], including high TB rates in their early life [7,8,9].

In reality, a reduced levels of particular maternal transferred antibodies to the infants from HIV-infected mothers are the most unequivocal immunological difference between HIV-exposed and unexposed infants [10, 11, 12, 13]. A delay in immune system development has been proven among HIV-exposed infants and variety of factors might play a role in this, most notably immunological consideration, which have been linked to several pathways in HIV-exposed infant [14, 15, 16, 17].

These immune changes could be mediated by fetal HIV exposure, as they are not present in mothers who are on antiretroviral therapy (ART) at the time of conception

[18,19]. Infants accumulate maternal IgG antibodies during the third trimester, which actively cross the placenta via Fc-receptor-mediated transport and normally survive for many months, giving protection from infection based on the mother's immunological experiences [20,21]. Cell-mediated immunity is altered in HIV-exposed infant, with impaired T-cell maturation, hypo- and hyperresponsive T-cell activation [15, 22]. Importantly, many of these abnormalities appear to be temporary, with many of them fading as infant grow older [14]. Impaired immunity, increased household or maternal TB, and ART exposure are possible contributing factors that raise the risk of infectious in HIV-exposed infants, including TB.

In addition to altering immunogenicity in HIV-exposed uninfected (HEU) infants, immunological activation generated by bacillus Calmette-Guerin (BCG) immunization has the potential to make these neonates more vulnerable to HIV infection in the post-partum period [23,24]. HIV preferentially infects and replicates in CD4<sup>+</sup>T cells that have been activated [24,25]. Furthermore, peripheral blood mononuclear cells (PBMCs) from people who have persistent CD4<sup>+</sup> T cell activation are also more vulnerable to in vitro HIV infection [24,26] however, in both in vivo and in vitro, a lower level of CD4 T cell immunological activation is associated with protection from HIV infection [24].

BCG protects young children from disseminated tuberculosis (TB); it also has various "non-specific" protective benefits and reduces non-TB-related child morbidity and death in environments with high infectious

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morbidity [27]. It is the only approved live-attenuated (BCG) vaccine which is normally given immediately after delivery to protect children against TB [24, 28, 29].

The coverage and success of local prevention of maternal-to-child transmission programs, the possibility of deferring BCG vaccination based on the timely availability of appropriate HIV diagnostic tests, and the provision of early antiretroviral therapy are all factors that influence the risk-benefit ratio of BCG vaccination in HIV-exposed infants, according to current WHO tuberculosis treatment guidelines [27, 30].

On the one hand, if immunizing HIV-1-exposed infants with BCG at birth protects them from severe infection other than TB [26, 31, 32], delaying immunization might result in higher morbidity and even mortality [14]. Infants who have been exposed to HIV are at a higher risk of contracting TB early in life and delaying BCG immunization to them until later a confirmed diagnosis might result in lower coverage and serious consequences [14, 34].

Research examining BCG immunogenicity in HIV- (HEU) infants show that cellular responses to BCG are changed [35,36], implying that HEU children may not benefit as much from BCG immunization as those who are not HIV exposed [24]. However, BCG vaccine remains efficient, safe, and cost-effective against TB in HIV-unexposed infants, especially in cases of disseminated infection [24,37]. Vaccine effectiveness and safety in the setting of HIV infection is a debatable issue that has been the subject of extensive recent and continuing research and the precise nature of protection against tuberculosis illness following BCG immunization has yet to be determined [38]. Even at birth, BCG triggers strong T-helper type 1 (Th-1) cellular immune responses but the immune factors of vaccine-induced protection against TB are yet unknown. The Th-1 cytokine response, which is characterized by the production of IFN- $\gamma$ , TNF- $\alpha$ , and IL-2, is commonly considered to be crucial. Research have demonstrated that BCG generate CD4 and CD8 populations in HIV-exposed infants that produce a combination of IL-2, IFN- $\gamma$ , and TNF- $\alpha$  [39,40].

Mazzola and Nankabirwa observed that younger HIV-1-exposed uninfected children's cellular immune responses to BCG were compromised compared to their unexposed peers and IFN- $\gamma$  concentrations as well as BCG-specific proliferation T-cell were found to be higher in the older than younger HIV-1-exposed uninfected infants compare to their unexposed counterparts [14,41]. These BCG-specific immunological aberrations are consistent with a broader variety of other abnormalities documented in HIV-1-exposed uninfected infants and are considered to be the consequence of in-utero HIV-1 infection and/or antiretroviral medications [14]. These comprise a modified cell mediated immunity and T-cell maturation [42], decrease in IL-12 production that lasts until 6 months of age [43], decreased CD4/CD8 ratio, decreased CD4+ and CD8+ naive T-cell percentages, and an elevation percentage of activated CD8+ T-cells [42,44].

These criteria are geared at reducing the risk of mistakenly administering BCG vaccine to HIV-positive infants;

nonetheless, the unknowns surrounding the vaccine's immunogenicity and clinical effectiveness in HIV-exposed newborns are just as important [27]. BCG vaccine at the optimal period would allow ample time to establish HIV infection status in HIV-exposed newborns while still maintaining the vaccine's protective benefits [45]. As a result, HIV transmission from mother to child has decreased dramatically; nonetheless, giving BCG vaccine to HIV high-risk infants may be a vital concern. Furthermore, in nations with limited resources, receiving findings for PCR or NAT tests may be difficult. Therefore, serious concerns about the risk and benefits of BCG vaccine in HIV-positive infants at birth become now questionable. The literature is still not evident about the impact of delaying the BCG vaccination on HIV-exposed infants' responses to other standard immunizations [45]. Reason why this study has been conducted to emphasize the impact of delaying BCG vaccine in HIV-exposed infant, as well as to determine the best timing to administrate BCG vaccine without dramatically altering immunological response or vaccination coverage.

### Objectives

- To assess the effect of administrating BCG vaccine compared to delaying BCG vaccine at birth in HIV-exposed infants
- To determine the optimal time of administrating BCG vaccine to HIV-exposed infants

## 2. Methods

The review protocol was registered on PROSPERO with ID: Jacques Lukenze Tamuzi, Jonathan Lukusa Tshimwanga BCG vaccine and HIV-exposed infants: a review. PROSPERO 2017 CRD42017058730 Available from: [https://www.crd.york.ac.uk/prospéro/display\\_record.php?ID=CRD42017058730](https://www.crd.york.ac.uk/prospéro/display_record.php?ID=CRD42017058730)

We undertook an electronic search in different databases among which the Cochrane Central Register of Controlled Trials (CENTRAL), the Cochrane Library, MEDLINE, CINAHL, Scopus, LILACS, the WHO International Clinical Trials Registry Platform (ICTRP; <http://www.who.int/ictrp/en/>), ClinicalTrials.gov and the ISRCTN registry (<http://www.isrctn.com/>).

Authors screened 377 studies after excluding duplicates. 364 studies were eliminated, and 13 full texts were assessed for eligibility. At that point, 5 studies had been rejected for various reasons, and 8 RCTs had been included in the qualitative analysis. After all, the meta-analysis comprised 6 RCTs (Figure 1).

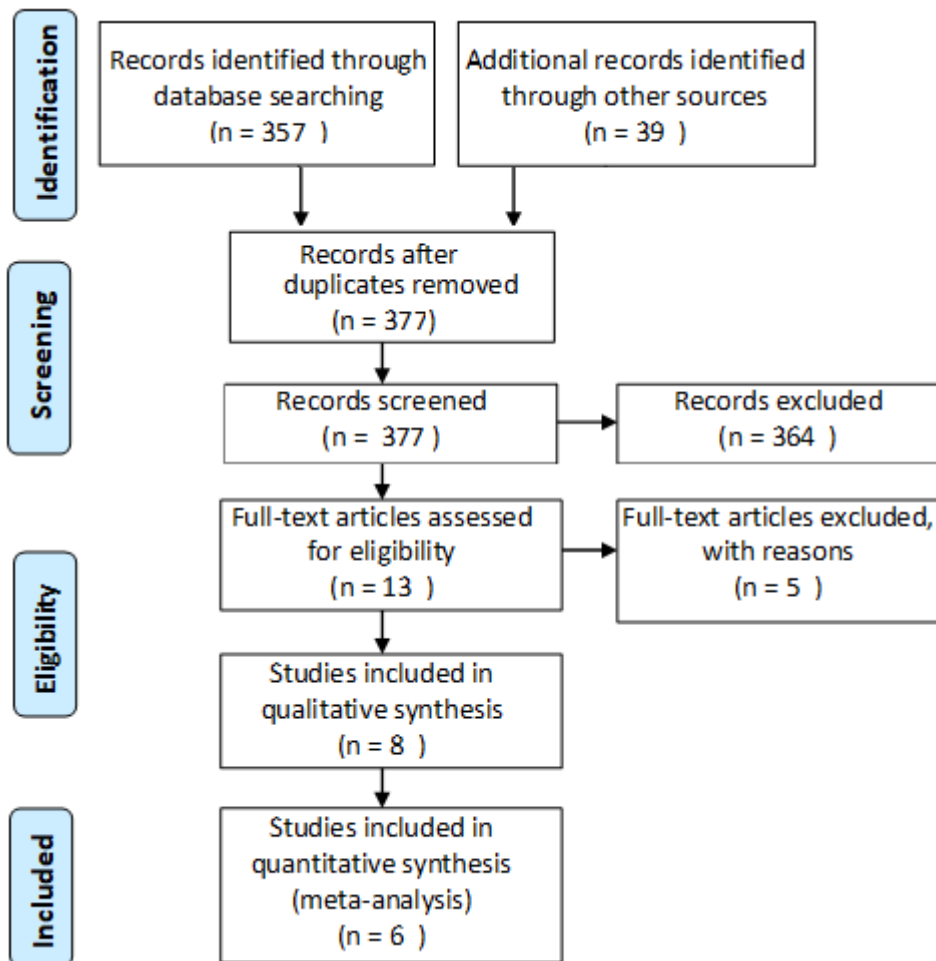
Data from the included studies table was gathered by the two authors (Table 1). The critical appraisal was carried out by J.L.T and J.L.T, who assessed the risk of bias in the studies that were included. Six standard domains of RCT were used to assess the quality of trials among which sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and other biases. For each of these domains, a 'yes', 'no,' or 'unclear' assessment was assigned to the possibility of bias. Authors entered the findings into Review Manager (RevMan) 5.1. standard tables and used figures to describe

the risk of bias assessment. The included studies were evaluated by two reviewers (J.L.T and J.L.T) using Cochrane Collaboration methods. A judgement of high risk was made for domains with insufficient information for assessing risk of bias (such as undescribed randomization processes) and where this domain was likely to impact the outcome of interest.

Using review manager (RevMan), meta-analyses were conducted. When the heterogeneity ( $I^2$ ) statistic value was less than or equal to 50%, a fixed-effect model was chosen, in contrast a random-effects when the heterogeneity ( $I^2$ ) was

more than 50%. Inverse variance analysis was used for continuous data including CD4<sup>+</sup> T cell activity, CD8<sup>+</sup> T cell activity, and plasma inflammatory cytokine concentrations (IL-13 and INF- $\alpha$ ). The results were presented in the mean difference with 95% confidence interval (CI). Sensitivity analyses were planned and performed for assessing the effects of heterogeneous studies and studies with high risk of bias by sequential exclusion.

### 3. Results

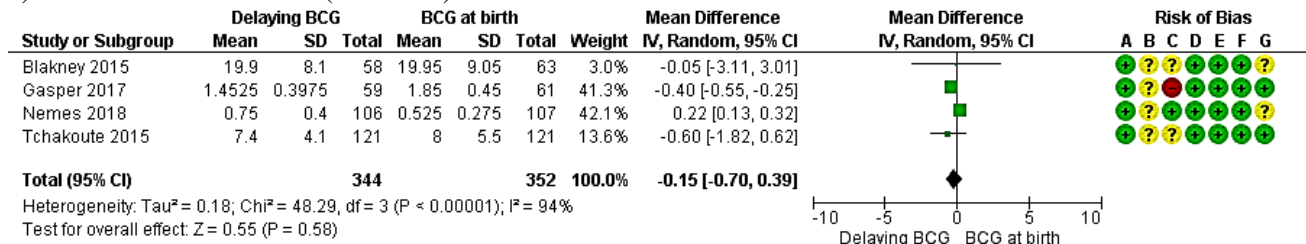


**Table 1:** Characteristics of included studies

Study ID	Methods	Participants	Interventions	Outcomes/status
Blakney 2015	Randomized control trial	149 HIV-exposed uninfected infants were recruited. Setting: community health center in Khayelitsha, Western Cape Province, South Africa.	routine BCG vaccination versus delayed vaccination until 8weeks	At 8 and 14 weeks CD4+ T cell activation CD8+ T cell activation Plasma inflammatory cytokine concentrations
Gasper 2017	Randomized, open-label trial	149 HIV-exposed uninfected infants were recruited. Setting: Western Cape Province, South Africa	routine BCG vaccination versus delayed vaccination until 8weeks	At 8 and 14 weeks CD4+ T cell activation CD8+ T cell activation Plasma inflammatory cytokine concentrations
Hesseling 2015	Open-label, exploratory randomized Phase 2 clinical trial		routine BCG vaccination versus delayed vaccination until 14 weeks	Plasma inflammatory cytokine concentrations
Kagina 2009	Randomized control trial		routine BCG vaccination versus delayed vaccination	Plasma inflammatory cytokine concentrations
Nemes 2018	A Phase 2 Randomized,	A total of 248 HIV-exposed infants were enrolled	BCG at birth versus delayed vaccination until 8 weeks	At 8 and 16 weeks CD4+ T cell activation

	Controlled Trial			Plasma inflammatory cytokine concentrations
Tchakoute 2015	Randomized control trial		To receive BCG vaccination at birth (the early vaccination arm) or 8 weeks of age (the delayed vaccination arm)	At 8 and 14 weeks CD4+ T cell activation CD8+ T cell activation Plasma inflammatory cytokine concentrations
Jaspan 2012	Randomized controlled trial	HIV-exposed infants	Delayed BCG vs BCG at birth; standard of care	Ongoing trial: NCT02062580
Nankabirwa 2017	Randomized controlled trial	HIV-1-exposed infants/ The study is being conducted in three health centers in Uganda.	The intervention is BCG vaccination within 24 h of birth while the comparator is BCG given at 14 weeks of age	Ongoing trial

1) CD4<sup>+</sup> T cells activation (6-8 weeks)



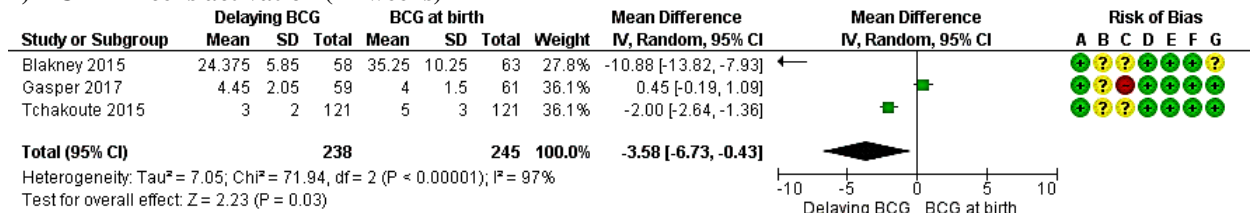
Risk of bias legend

- (A) Random sequence generation (selection bias)
- (B) Allocation concealment (selection bias)
- (C) Blinding of participants and personnel (performance bias)
- (D) Blinding of outcome assessment (detection bias)
- (E) Incomplete outcome data (attrition bias)
- (F) Selective reporting (reporting bias)
- (G) Other bias

Figure 2

Interpretation: In HIV exposed infants, the mean difference of CD4<sup>+</sup> T cells activation percentage after 6 to 8 weeks was decreased in delaying BCG compared to BCG administered at birth -0.15 (-0.70 to 0.39) with P=0.58, showing that the results were not statistically significant. The results were highly heterogeneous (I<sup>2</sup> = 94%).

2) CD4<sup>+</sup> T cells activation (14 weeks)



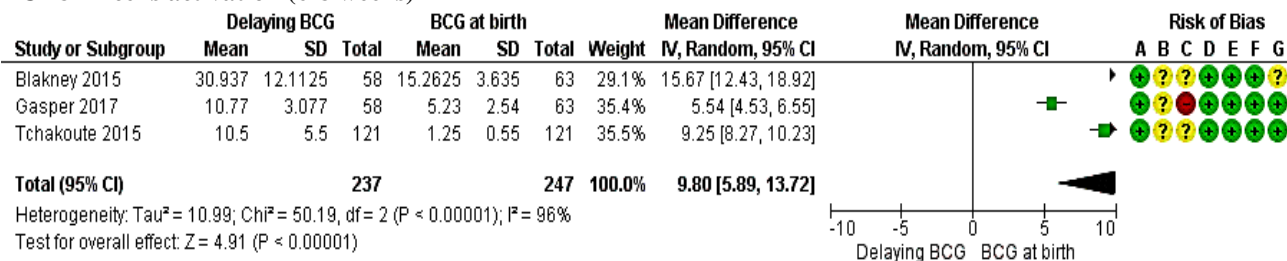
Risk of bias legend

- (A) Random sequence generation (selection bias)
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- (D) Blinding of outcome assessment (detection bias)
- (E) Incomplete outcome data (attrition bias)
- (F) Selective reporting (reporting bias)
- (G) Other bias

Figure 3:

Interpretation: For 3 RCTs included in CD4<sup>+</sup> T cells activation after 14 weeks comparing BCG delayed to BCG given at birth in HIV-exposed infants, the random-effects meta-analysis of CD4<sup>+</sup> T cells activation (14 weeks) yielded a pooled MD estimate of -3.58(95% CI -6.73 to -0.43, P=0.03) with I<sup>2</sup>=97%

3) CD8<sup>+</sup> T cells activation (6-8 weeks)



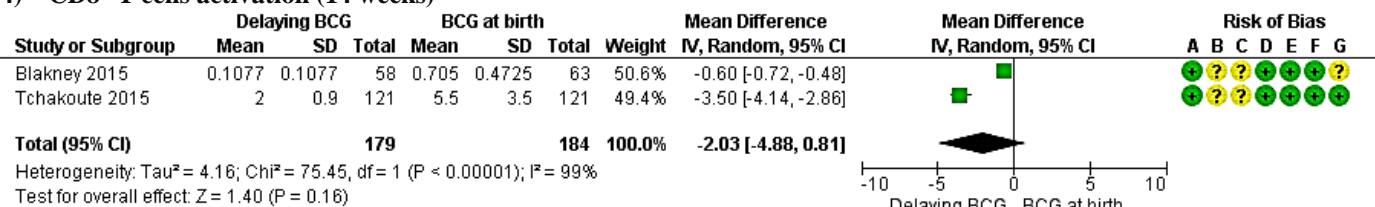
Risk of bias legend

- (A) Random sequence generation (selection bias)
- (B) Allocation concealment (selection bias)
- (C) Blinding of participants and personnel (performance bias)
- (D) Blinding of outcome assessment (detection bias)
- (E) Incomplete outcome data (attrition bias)
- (F) Selective reporting (reporting bias)
- (G) Other bias

Figure 4:

Interpretation: HIV-exposed infants had high MD of CD8<sup>+</sup>T cells activation at birth than delaying from 6 to 8 weeks (MD 9.80, 95%CI 5.89, 13.72, P<00001). Among three included studies, the results were consistent, with higher point estimates.

4) CD8<sup>+</sup> T cells activation (14 weeks)



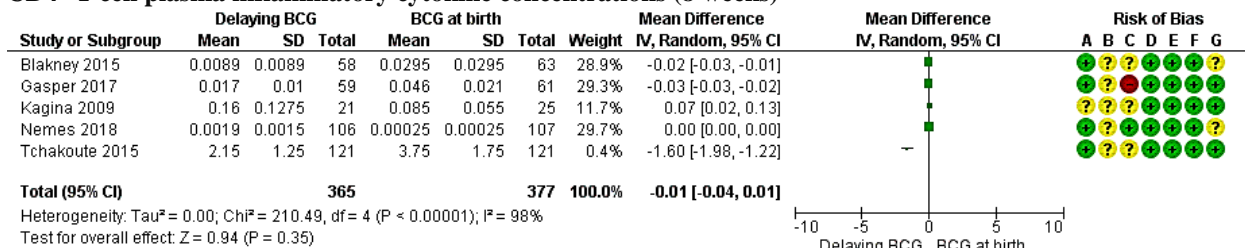
Risk of bias legend

- (A) Random sequence generation (selection bias)
- (B) Allocation concealment (selection bias)
- (C) Blinding of participants and personnel (performance bias)
- (D) Blinding of outcome assessment (detection bias)
- (E) Incomplete outcome data (attrition bias)
- (F) Selective reporting (reporting bias)
- (G) Other bias

Figure 5:

Interpretation: After 14 weeks, HIV-exposed infants had low MD of CD8<sup>+</sup>T cells activation indelayingBCG administration compared to giving BCG at birth (MD -2.03, 95%CI -4.88, 0.81, P<0.16).

5) CD4<sup>+</sup> T cell plasma inflammatory cytokine concentrations (8 weeks)



Risk of bias legend

- (A) Random sequence generation (selection bias)
- (B) Allocation concealment (selection bias)
- (C) Blinding of participants and personnel (performance bias)
- (D) Blinding of outcome assessment (detection bias)
- (E) Incomplete outcome data (attrition bias)
- (F) Selective reporting (reporting bias)
- (G) Other bias

Figure 6

Interpretation: Plasma inflammatory cytokine concentrations (IL-13 & INF-α) did not shown statistically significant MD between delaying and administrating BCG vaccine at birth in HIV- exposed infants with MD -0.01 (95%CI -0.04, 0.01), P=0.35.

#### 4. Discussion

The risk of HIV infection by administering the BCG vaccination to an infant born to HIV positive mother with undetectable viral load despite a high CD4 + T cell count has been determined to be insignificant. The administration of BCG vaccine at birth induces cytokines which protect infant born to HIV mother from getting TB; however, it intensifies the activation of CD4+ CCR5+ HIV target cells, exposing the new-born to HIV infection (Card et al., 2012). Furthermore, the risk of tuberculosis (TB) among HIV-exposed uninfected infants in South Africa was substantial, with incidence of 41 per 1,000 child years (95 percent CI 31–52 per 1,000 child years) as studies by Madhi et al. [8].

Gaspar et al. observed that the expression of CCR5, which is the HIV coreceptor, after the administration of BCG vaccine at birth might be susceptible to HIV infection and the persistent T cell activation observed in the systemic circulation of BCG-vaccinated newborns implies that BCG may generate a longer opening period of enhanced HIV susceptibility which activation is 3-fold increase in HIV-exposed infants who received BCG at birth compared to HIV-exposed uninfected infant who delayed the BCG vaccine [24]. Nevertheless, BCG vaccine administered to HEU infants at 8 weeks of age boost cytokines functionality and in CD4 and CD8 T cells and increase IFN- $\gamma$  responses [46,47] and infants administered at 14 weeks of age had the same response to BCG and TB which was raised considerably [48,49]

Delaying giving BCG vaccine to infants born to mothers who tested HIV positive during labor or early postpartum and those who have inadequate adherence to antiretroviral treatment with unsuppressed viral load during delivery might reduce the HIV susceptibility opening period while also giving the mother more time to attain the virological suppression [24,50,51]. Our findings from the meta-analysis show that postponing BGG vaccination in HIV-exposed, uninfected infants until they are 8 weeks old has no detrimental impact on vaccine immunogenicity and may even improve Th1 responses in HIV-exposed, uninfected infant as also found by Tchakoute et al. [46]. BCG vaccination should only be given when HIV status has been confirmed as negative and HIV infection has been ruled out for maximum safety.

#### 5. Conclusion

Despite the fact that antiretroviral therapy has decreased HIV transmission from mother to child, the BCG vaccination has also helped to protect against fulminant TB [38], However, the risk and the benefit of BCG administration to HEU infant should be established with regard to the appropriate timing. On the other hand, delaying BCG vaccine slows humoral immune development, placing the child at danger of contracting tuberculosis. According to our research, delayed BCG to HEU infants at 8 and 14 weeks of age from birth have a lower risk of HIV by producing a marked IFN- $\gamma$  responses and protect the infants from TB infection as shown. Administering BCG vaccine as an option for HIV-exposed infants in tuberculosis-endemic areas should be investigated further research is still needed

for more evidence especially about delaying the administration timing.

#### 6. Acknowledgements

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#### 7. Declarations of interest

The authors have declared not having any conflict of interests

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