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CADTH RAPID RESPONSE REPORT: REFERENCE LIST

Bacillus Calmette–Guérin Vaccine Dosage Timing for Neonates in the NICU: Safety and Guidelines

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Research Questions

1. What is the comparative safety of differing Bacillus Calmette–Guérin vaccine timing for neonates in or discharged from the neonatal intensive care unit?
2. What are the evidence-based guidelines for Bacillus Calmette–Guérin vaccine timing for neonates in or discharged from the neonatal intensive care unit?

Key Findings

No relevant clinical evidence was identified regarding the comparative safety of differing Bacillus Calmette–Guérin vaccine timing for neonates in or discharged from the neonatal intensive care unit. In addition, no relevant evidence-based guidelines were identified.

Methods

A limited literature search was conducted on key resources including PubMed, The Cochrane Library, University of York Centre for Reviews and Dissemination (CRD), Canadian and major international health technology agencies, as well as a focused Internet search. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2014 and February 12, 2019. Internet links are provided where available.

Selection Criteria

One reviewer screened citations and selected studies based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Neonates in the neonatal intensive care unit (NICU) setting or discharged from the NICU
Intervention	Bacillus Calmette–Guérin (BCG) vaccine administered directly before discharge (*e.g.*, 2 to 3 hours before discharge)
Comparator	Q1: Bacillus Calmette–Guérin (BCG) vaccine administered at an alternative interval or timing Q2: No comparator
Outcomes	Q1: Safety (e.g., risk of cross contamination between vaccinated neonates and non-vaccinated neonates, mortality, adverse events) Q2: Guidelines regarding timing of vaccine administration
Study Designs	Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies, evidence-based guidelines

Results

Rapid Response reports are organized so that the higher quality evidence is presented first. Therefore, health technology assessment reports, systematic reviews, and meta-analyses are presented first. These are followed by randomized controlled trials, non-randomized studies, and evidence-based guidelines.

No relevant health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies, or evidence-based guidelines were identified differing Bacillus Calmette–Guérin vaccine timing for neonates in or discharged from the neonatal intensive care unit.

References of potential interest are provided in the appendix.

Health Technology Assessments

No literature identified.

Systematic Reviews and Meta-analyses

No literature identified.

Randomized Controlled Trials

No literature identified.

Non-Randomized Studies

No literature identified.

Guidelines and Recommendations

No literature identified.

Appendix — Further Information

Systematic Reviews and Meta-Analyses

Alternative Outcome – Not Specific to Cross-Contamination Outcome

1. Badurdeen S, Marshall A, Daish H, Hatherill M, Berkley JA. Safety and immunogenicity of early bacillus Calmette-Guerin vaccination in infants who are preterm and/or have low birth weights: a systematic review and meta-analysis. *JAMA Pediatr*. 2018.
   PubMed: PM30476973

Randomized Controlled Trials

Alternative Comparator – No Vaccination

2. Biering-Sorensen S, Aaby P, Lund N, et al. Early BCG-Denmark and neonatal mortality among infants weighing <2500 g: a randomized controlled trial. *Clin Infect Dis*. 2017;65(7):1183-1190.
   PubMed: PM29579158

3. Stensballe LG, Sorup S, Aaby P, et al. BCG vaccination at birth and early childhood hospitalisation: a randomised clinical multicentre trial. *Arch Dis Child*. 2017;102(3):224-231.
   PubMed: PM27443836

Alternative Comparator – Timing Not Specific to Hospital Discharge

4. Gasper MA, Hesseling AC, Mohar I, et al. BCG vaccination induces HIV target cell activation in HIV-exposed infants in a randomized trial. *JCI Insight*. 2017;2(7):e91963.
   PubMed: PM28405623

5. Nankabirwa V, Tumwine JK, Namugga O, et al. Early versus late BCG vaccination in HIV-1-exposed infants in Uganda: study protocol for a randomized controlled trial. *Trials*. 2017;18(1):152.
   PubMed: PM28359325

6. Biering-Sorensen S, Andersen A, Ravn H, Monterio I, Aaby P, Benn CS. Early BCG vaccine to low-birth-weight infants and the effects on growth in the first year of life: a randomised controlled trial. *BMC Pediatr*. 2015;15:137.
   PubMed: PM26416147

7. Blakney AK, Tchakoute CT, Hesseling AC, et al. Delayed BCG vaccination results in minimal alterations in T cell immunogenicity of acellular pertussis and tetanus immunizations in HIV-exposed infants. *Vaccine*. 2015;33(38):4782-4789.
   PubMed: PM26259542

8. Hesseling AC, Jaspan HB, Black GF, Nene N, Walzl G. Immunogenicity of BCG in HIV-exposed and non-exposed infants following routine birth or delayed vaccination. *Int J Tuberc Lung Dis*. 2015;19(4):454-462.
   PubMed: PM25860002

9. Saroha M, Faridi MM, Batra P, Kaur I, Dewan DK. Immunogenicity and safety of early vs delayed BCG vaccination in moderately preterm (31-33 weeks) infants. *Hum Vaccin Immunother*. 2015;11(12):2864-2871.
PubMed: PM26431252

10. Tchakoute CT, Hesseling AC, Kidzeru EB, et al. Delaying BCG vaccination until 8 weeks of age results in robust BCG-specific T-cell responses in HIV-exposed infants. *J Infect Dis*. 2015;211(3):338-346.
PubMed: PM25108027

Non-Randomized Studies

Alternative Comparator – No Vaccination

11. Schaltz-Buchholzer F, Biering-Sorensen S, Lund N, et al. Early BCG vaccination, hospitalizations, and hospital deaths: analysis of a secondary outcome in 3 randomized trials from Guinea-Bissau. *J Infect Dis*. 2019;219(4):624-632.
PubMed: PM30239767

Alternative Comparator – Timing Not Specific to Hospital Discharge

12. Biering-Sorensen S, Jensen KJ, Monterio I, Ravn H, Aaby P, Benn CS. Rapid protective effects of early BCG on neonatal mortality among low birth weight boys: observations from randomized trials. *J Infect Dis*. 2018;217(5):759-766.
PubMed: PM29216358

13. Oberoi S, Amarjit S, Avneet R, Neha C, Patnaik S. Positive impact of rescheduling bacillus Calmette-Guerin vaccination on vaccinations at birth. *J Family Community Med*. 2017;24(1):13-17.
PubMed: PM28163570

14. O'Leary M, Edmond K, Floyd S, et al. Neonatal vaccination of low birthweight infants in Ghana. *Arch Dis Child*. 2017;102(2):145-151.
PubMed: PM27737837

15. Berendsen MLT, Smits J, Netea MG, van der Ven A. Non-specific effects of vaccines and stunting: timing may be essential. *EBioMedicine*. 2016;8:341-348.
PubMed: PM27428443

16. Lutwama F, Kagina BM, Wajja A, et al. Distinct T-cell responses when BCG vaccination is delayed from birth to 6 weeks of age in Ugandan infants. *J Infect Dis*. 2014;209(6):887-897.
PubMed: PM24179111

Clinical Practice Guidelines

Methods Unspecified

17. Gallagher A, Ashenford Z. WAHT-NEO-007: neonatal BCG vaccination v. 6.1. Worcester (UK): Worcestershire Acute Hospitals NHS Trust; 2013: http://www.treatmentpathways.worcsacute.nhs.uk/neonatal-information-portal/. Accessed 2019 Feb 15.
See: Section 2: Timing of vaccine, page 5

Additional References

Position Statement

18. World Health Organization. BCG vaccine: WHO position paper, February 2018 - recommendations. *Vaccine*. 2018;36(24):3408-3410. PubMed: PM29609965