Journal of Vaccine Research 2024, Vol.14, No.1, 27-31
http://medscipublisher.com/index.php/jvr

Scientific Review Open Access

New Perspectives on the Impact of BCG Vaccination on Bovine Tuberculosis Transmission: A Comprehensive Study Analysis

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Journal of Vaccine Research, 2024, Vol.14, No.1 doi: 10.5376/jvr.2024.14.0004
Received: 30 Mar, 2024
Accepted: 05 Apr., 2024
Published: 08 Apr., 2024

Preferred citation for this article:
Fang K.Y., 2024, New perspectives on the impact of BCG vaccination on bovine tuberculosis transmission: a comprehensive study analysis, Journal of Vaccine Research, 14(1): 27-31 (doi: 10.5376/jvr.2024.14.0004)

The paper titled "BCG Vaccination Reduces Bovine Tuberculosis Transmission, Improving Prospects for Elimination," authored by Abebe Fromsa, Katriina Willgert, Sreenidhi Srinivasan, and others, was published in the journal Science on March 29, 2024. The research comes from the Aklilu Lemma Institute of Pathobiology at Addis Ababa University, the College of Veterinary Medicine and Agriculture at Addis Ababa University, and other institutions. This study focuses on the potential of the BCG vaccine to reduce the transmission of bovine tuberculosis (bTB) in Ethiopia. By integrating natural transmission experiments with mechanistic transmission models, the research aims to evaluate the effectiveness of the BCG vaccine in controlling bTB transmission under different herd conditions. Experimental results show that vaccinated animals exhibited a 74% reduction in bTB transmission compared to unvaccinated animals. This finding provides strong evidence supporting the BCG vaccine as an effective strategy for controlling bTB, especially in resource-limited settings.

1 Experimental Data Analysis

In this study, scientists explored the impact of the BCG vaccine on reducing the transmission of bovine tuberculosis (bTB), with a particular focus on its direct and indirect protective effects within cattle herds. Conducting natural transmission experiments in Ethiopia, the research team placed both BCG-vaccinated and unvaccinated herds under the same environmental conditions to observe and compare the transmission of bTB between the two groups. The results were encouraging, showing a significant 74% reduction in the transmission of bTB among the vaccinated herds. This finding not only confirms the direct effect of the BCG vaccine in reducing individual animal infections but more importantly, reveals the indirect benefits of the vaccine in reducing the infectiousness of infected animals, thereby decreasing disease transmission across the entire herd. Furthermore, by combining the results of natural transmission experiments with mechanistic transmission model analyses, this study provides new insights into bTB control strategies, particularly highlighting the potential of using the BCG vaccine as an effective control measure in resource-limited settings.

Figure 1 illustrates the study design for research on the impact of the BCG vaccine on the transmission of bovine tuberculosis (bTB). In the first phase, newly recruited sentinel animals (calves) were acclimatized for about two weeks and then randomly assigned to either the control group (unvaccinated, U) or the vaccine group (vaccinated, V) through a double-blind lottery system. Two months post-vaccination, Interferon-gamma Release Assays (IGRA) and skin tests were conducted to confirm vaccine response. After confirming the vaccine response, approximately 34 adult infected animals (i.e., seeders) were co-housed with 17 unvaccinated and 17 BCG-vaccinated sentinel calves per group. Due to the loss of animals from vaccination to exposure, there were actually 16 to 18 animals per group. During the one-year exposure period, blood was drawn every two months for IGRA and skin tests were conducted every four months. Sentinel animals that survived the first phase were then used as seeders for two new experimental groups (groups 3 and 4), with new sentinel calves in these groups subsequently tracked through the same testing schedule during a second 12-month period of natural exposure.

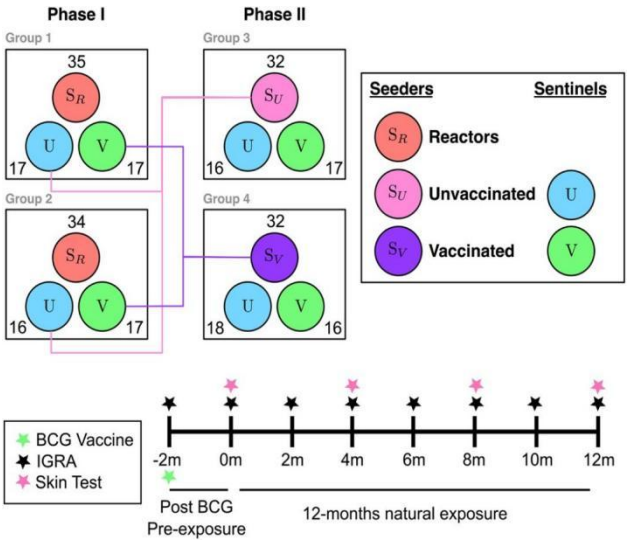

Figure 1 Schematic representation of study design

Figure 2 presents the two modes of action of the BCG vaccine in cattle. Panel A documents the infection history within each experimental group of unvaccinated (purple, orange) and vaccinated (light blue, green) animals, represented by the cumulative number of animals with positive IGRA reactions. All vaccinated seeders in Group 4 exhibited a lower attack rate compared to unvaccinated seeders in other groups, reflecting their reduced infectivity. Panel B shows the transmission rates between sentinel and seeder animals of different vaccination statuses, represented by the experimental reproduction ratio R, with a vertical line at R=1 indicating the threshold. Panel C reflects the posterior estimates for the BCG vaccine's effectiveness in reducing infectivity (VEI, orange), reducing susceptibility (VED, light blue), and overall efficacy (VET, green). This overall efficacy combines the vaccine's direct (reducing susceptibility) and indirect (reducing infectivity) effects.

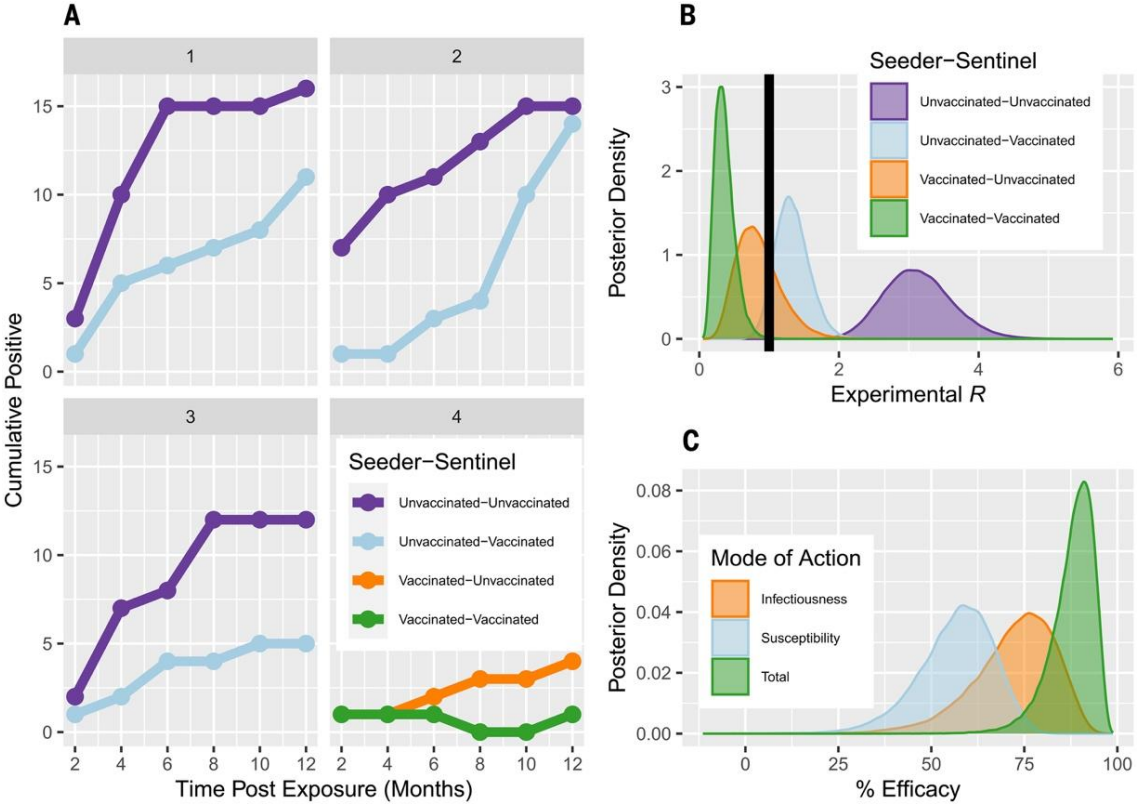

Figure 2 The two modes of action of BCG vaccination in cattle

Table 1 estimated the vaccine efficacy of the BCG vaccine in cattle. Evaluated through different diagnostic tests such as IGRA (DST 1), skin tests (DST 10), and visible lesions, the 95% credible intervals (CrI) for overall efficacy (VET) were 74% to 96%, 55% to 94%, and 1% to 47%, respectively, demonstrating the vaccine's direct (VED) and indirect (VEI) efficacy in reducing the transmission of bTB. The IGRA test showed the highest overall vaccine efficacy at 89%. This indicates that the BCG vaccine not only directly reduces the infection rate among the tested cattle but also indirectly lowers their risk of transmission.

Table 1 Estimated vaccine efficacy for BCG in cattle by mode of action

Diagnostic test	End-point efficacy	Transmission rate efficacy		
-	Total efficacy (95% Cl)	Direct efficacy (VE_D) (95% Crl)	Indirect efficacy (VE_I) (95% Crl)	Total efficacy (VE_T) (95% Crl)
DST 1 (IGRA)	39 (22 to 54)	58 (34 to 73)	74 (46 to 89)	89 (74 to 96)
DST 10 (skin)	40 (19 to 57)	46 (14 to 66)	67 (39 to 87)	82 (55 to 94)
Visible lessions	25 (1 to 57)	-	-	-

Table 2 presents the estimated experimental reproduction ratios (R) for bovine tuberculosis (bTB) within a year and the posterior probabilities of R<1 for different combinations of vaccination statuses (seeder-sentinel pairs). In the unvaccinated control group (unvaccinated-unvaccinated), the R value was 3.1, with no probability of achieving the disease control threshold of R<1. When unvaccinated seeders were paired with vaccinated sentinels (unvaccinated-vaccinated), the R value decreased to 1.3, with a posterior probability of R<1 being 0.075. For combinations of vaccinated seeders with unvaccinated sentinels (vaccinated-unvaccinated), the R value further decreased to 0.8, with the posterior probability of R<1 increasing to 0.72. In pairs of vaccinated seeders with vaccinated sentinels (vaccinated-vaccinated), the R value dropped to the lowest at 0.3, with a posterior probability of R<1 being 1, indicating that vaccination significantly reduces disease transmission and could potentially lead to disease control.

Table 2 Estimated experimental reproduction ratios by vaccination type of sentinel and seeder animals

Seed Sentinel pair	*R* (1-year contact) (95% Crl)	Posterior probability that *R*<1
Unvaccinated-Unvaccinated	3.1 (2.3 to 4.1)	0.0
Unvaccinated-Vaccinated	1.3 (0.9 to 1.8)	0.075
Vaccinated-Unvaccinated	0.8 (0.4 to 1.5)	0.72
Vaccinated-Vaccinated	0.3 (0.1 to 0.7)	1.0

Figure 3 provides scenario analyses for the prospective use of bovine tuberculosis (bTB) vaccines in the Ethiopian dairy sector. Panel A illustrates the transmission rates of bTB within cattle herds around Addis Ababa and in emerging dairy belts in Hawassa, Mekelle, and Kombolcha, calibrated based on herd-level prevalence data collected from these areas. Panel B shows that the estimated prevalence of bTB within herds ranges widely (5.8% to 78%), with the basic reproduction ratio R0 estimates also displaying similar heterogeneity, with no clear correlation to geographical location or herd size. Panel C uses cattle movement data models collected from Gondar, Mekelle, and Hawassa to predict the evolution of bTB prevalence over the next 50 years. These predictions include scenarios without vaccination (pink), with estimated direct vaccine efficacy at 58% (light blue), and with additional indirect effects at 74% (purple). These projections demonstrate the potential impact of different vaccination strategies on controlling the prevalence of bTB.

2 Analysis of Research Findings

This study on the impact of the BCG vaccine against the transmission of bovine tuberculosis (bTB) showcases the significant potential of the BCG vaccine in reducing bTB transmission through field trials conducted in Ethiopia. The research employed an innovative natural transmission experimental design, placing both BCG-vaccinated and unvaccinated cattle herds in the same environment to directly observe the vaccine's effect on bTB transmission. The results indicated a marked reduction in bTB transmission rates among vaccinated herds, not only revealing the direct protective effect of the BCG vaccine on vaccinated animals but also highlighting its potential to reduce

the likelihood of vaccinated animals becoming sources of transmission. Moreover, by constructing mechanistic transmission models, the study further explored the long-term effects and strategies of using the BCG vaccine in different herds and regions, offering new perspectives and approaches for bTB control. The findings of this study are particularly significant for resource-limited areas where traditional test-and-slaughter strategies may be difficult to implement for various reasons. Thus, the use of the BCG vaccine opens a new path, offering hope for the control and eventual eradication of bTB.

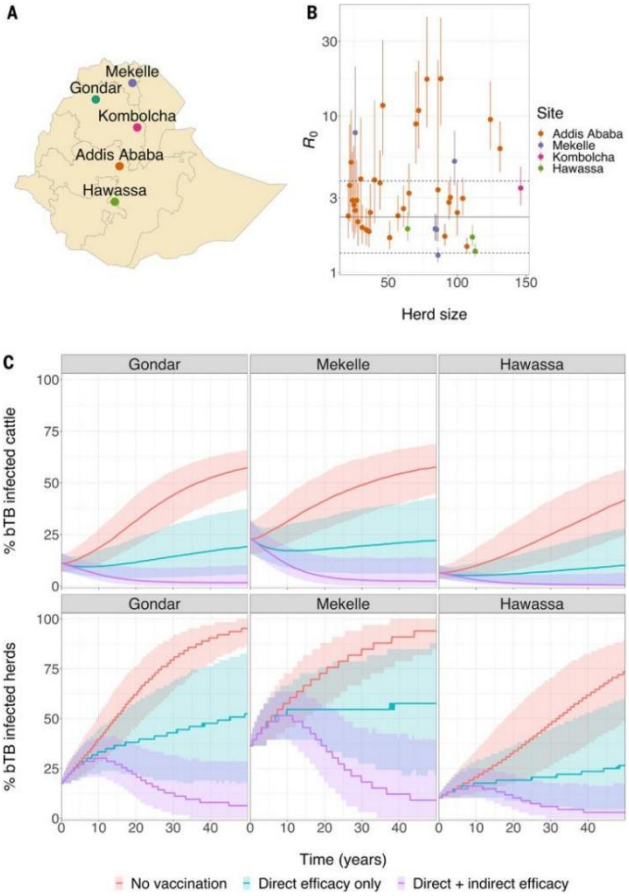

Figure 3 Scenario analyses for the prospective use of cattle vaccination within the Ethiopian dairy sector

3 Evaluation of the Research

This study conducted natural transmission experiments in Ethiopia to thoroughly evaluate the effectiveness of the BCG vaccine in reducing the transmission of bovine tuberculosis (bTB). By employing a crossover design method, the experiment not only measured the direct protective effects of the BCG vaccine on vaccinated individuals but also, for the first time, revealed its significant indirect effects in reducing the capability of vaccinated animals to become sources of transmission. The study found that the transmission rate of bTB in herds vaccinated with the BCG vaccine was reduced by 74% compared to the unvaccinated control groups, highlighting the potential role of the BCG vaccine in bTB control strategies, especially in regions where traditional testing and culling methods are not feasible due to economic or social reasons. Furthermore, through in-depth analysis of experimental data, the study also suggested the potential for widespread use of the BCG vaccine in similar settings and explored its long-term impact on the dynamics of bTB transmission. These findings provide valuable insights for the broader application of the BCG vaccine in the future, while also identifying key areas for further research, such as the long-term effects of the vaccine and its universality across different herd conditions.

4 Conclusions

This study conducted in Ethiopia utilized a combination of natural transmission experiments and mechanistic transmission models to comprehensively assess the potential of the BCG vaccine in reducing the transmission of

bovine tuberculosis (bTB). The results demonstrated a significant 74% reduction in bTB transmission among cattle herds vaccinated with BCG compared to unvaccinated herds. This crucial finding not only confirms the effectiveness of the BCG vaccine in directly protecting vaccinated individuals but, more importantly, reveals its potential in reducing the infectivity of vaccinated animals, thereby indirectly decreasing bTB transmission across entire cattle herds. This research provides strong scientific support for the use of the BCG vaccine as an effective strategy for controlling and potentially eliminating bTB in resource-limited regions.

5 Access the Full Text

Abebe Fromsa et al., BCG vaccination reduces bovine tuberculosis transmission, improving prospects for elimination.Science383,eadl3962(2024).DOI: 10.1126/science.adl3962

Acknowledgments

I sincerely appreciate the open-access policy for papers provided by Science magazine to its wide readership. I am deeply grateful to Nature magazine for giving me this valuable opportunity to write a scientific review and share the latest academic progress with the public. This not only recognizes my contribution but also affirms the importance of scientific communication and knowledge sharing. As a leading figure in the scientific community, Nature magazine's open platform greatly facilitates the dissemination and popularization of scientific knowledge, building a bridge for communication between researchers and those passionate about science. I express my gratitude once again to Science magazine for its contribution and look forward to discovering more exciting content in the scientific world through this platform in the future.