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Assessing vaccine-mediated protection in an ultra-low dose *Mycobacterium tuberculosis* murine model

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Despite numerous tuberculosis (TB) vaccines in the developmental pipeline, the lack of a robust animal model to assess vaccine efficacy has hindered our ability to measure correlates or mechanisms of protection to prioritize candidate vaccines. Here we used a murine ultra-low dose (ULD) Mycobacterium tuberculosis (Mtb) challenge model (~1 CFU/mouse) to assess mechanisms of protection of BCG, the only currently licensed TB vaccine. We show that BCG reduced lung bacterial burdens more durably in ULD-infected mice than in conventional dose (CD)-infected mice (~100 CFU/mouse), curbed Mtb dissemination to the contralateral lung, and prevented detectable infection in a small percentage of mice. These observations are consistent with the ability of BCG to mediate protection in humans in some settings. We also dissected the relative roles of different T cell subsets to each aspect of vaccine-mediated immunity using CD4 and CD8 depleting antibodies. CD4 T cells contributed to the control of lung burden regardless of vaccination and restricted Mtb dissemination after vaccination. While CD8 T cells played minor roles in controlling bacterial burdens and dissemination in BCG-vaccinated mice, in preliminary experiments they seemed to be more important than CD4 T cells in preventing Mtb infection after ULD Mtb challenge. In contrast, CD8 T cells played no detectable role in protection after CD challenge, demonstrating how the ULD model can reveal novel mechanisms of protection. These data suggest that BCG induces CD4 and CD8 T cells that play complementary roles in protection against TB. Overall, the ULD Mtb infection model can measure distinct parameters of immunity that cannot be assessed with CD infection, and each parameter could be controlled by different aspects of immunity. Current efforts are geared towards testing vaccine candidates for which human efficacy data are available to validate the translational value of the ULD model.

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Conflicts of Interest
None