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Prior *Mycobacterium tuberculosis* exposure enhances the efficacy of subunit vaccination

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Despite widespread vaccination, BCG has failed to curb tuberculosis (TB) transmission. Because it is not feasible for all new vaccine candidates to enter clinical trials, animal models must be used for prioritization. However, current models use mice that are naïve to prior infection, limiting their relevance to individuals in endemic areas and to prevention of disease vaccine clinical trials that exclusively enroll QFT+ individuals. Here, we use a mouse model of prior Mycobacterium tuberculosis (Mtb) exposure, termed concomitant Mtb (coMtb), to test the post-exposure efficacy of two protein subunit vaccines, H56/CAF01 and H107/CAF01. coMtb itself protected against Mtb challenge, and both subunit vaccines further durably reduced lung burdens. This protection was associated with a reduction in KLRG1+ lung vascular CD4+ T cells and increased polyfunctional parenchymal CD4+ T cells, features that have been associated with protection. While there was no change in the overall level of IL-2-producing T cells between prophylactic (i.e., Mtb-naïve) and post-exposure (i.e., coMtb) H107-vaccinated mice, coMtb mice had an expansion of IL-2+ CD4+ T cells that co-express IFNg, suggesting that these cells represent a hybrid of natural Mtb infection and vaccination. These T cell populations were expanded in the spleen by coMtb plus subunit vaccination, but not BCG, even prior to aerosol challenge, suggesting that protective CD4+ T cell priming is enhanced by these vaccines in the setting of prior Mtb exposure. Our findings were corroborated in an analysis of Quantiferon (QFT)-negative and QFT+ humans vaccinated with H56/IC31, wherein vaccinated QFT+ individuals had significantly enhanced IFNg+TNFa+IL-2+ Mtb-specific CD4+ T cells compared to QFT- individuals. These data support the use of coMtb as a platform to test vaccine efficacy in Mtb-exposed animals and can enable the prioritization of prospective vaccine candidates, particularly those intended for use in TB endemic regions.

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Conflicts of Interest
None.