Exposure to Mycobacterium tuberculosis (Mtb) results in heterogeneous clinical outcomes including active tuberculosis (TB) and latent Mtb infection (LTBI). Mtb infection is identified using the tuberculin skin test (TST) and IFN-γ release assay (IGRA), and a positive result may prompt chemoprophylaxis to prevent progression to TB. As part of a large collaborative study, we identified a cohort of Ugandan household contacts that were highly exposed to Mtb but remained IGRA and TST negative, apparently “resisting” LTBI. We show that “resisters” possess non IFN-γ T-cell responses and class-switched IgG antibody responses to Mtb-specific proteins ESAT6 and CFP10, providing immunologic evidence of exposure to Mtb. Our data reveal a distinct adaptive immune profile among Mtb exposed subjects who are otherwise not part of the current clinical spectrum of Mtb infection. I will discuss the implications of our work for public health as well as the design of interventional clinical trials.