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Effectiveness of primary Bacillus Calmette-Guérin against the risk *Mycobacterium tuberculosis* infection and tuberculosis disease: an individual-participant meta-analysis of trials and observational studies

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Background: Tuberculosis (TB) vaccine trials using disease as the primary endpoint are large, time consuming and expensive. An earlier immunologic measure against TB disease would accelerate TB vaccine development. We aimed to assess if the effectiveness of BCG for prevention of Mycobacterium tuberculosis (Mtb) infection was consistent with that for prevention of TB disease.

Methods: We conducted an individual participant data meta-analysis on longitudinal studies identified through systematic reviews conducted between 2014 and 2019 reporting on BCG status, Mtb infection test and TB incidence. We compared the protective efficacy of BCG against Mtb infection (PoI) with that against tuberculosis disease (PoD) using mixed-effects, multivariable proportional hazards modeling, by study type, Mtb infection test (QuantiFERON interferon-gamma release assay and tuberculin skin test (TST)), cutoff applied for defining test positivity, age, sex, and latitude.

Results: We included one of ten BCG vaccine trials, two of three cohort studies of adolescents in high TB incidence settings, and 11 of 27 household contact studies. Among 29,592 participants we found no protection by BCG against TST conversion regardless of cut-off in any type of study. Among 1,491 household contacts, but not among 5,644 adolescents, BCG protected against QuantiFERON conversion at the primary cut-off ≥ 0·7 IU/ml with the adjusted hazard ratio (aHR, 0·65, 95% CI, 0·51-0·81) being consistent with that for protection against disease (aHR 0.68, 95% CI, 0·18-2.59). Protection against QuantiFERON conversion at cut-off ≥ 0·35 IU/ml (aHR 0·64, 95% CI, 0·51-0·81) was similar.

Discussion: BCG protection against infection measured as QuantiFERON conversion exhibits inconsistent results across different groups. Among groups with recent household exposure, QuantiFERON conversion consistent with protection against disease and could be considered as a proxy for disease in TB vaccine trials. We found that

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Conflicts of Interest
None