

LONDON
SCHOOL of
HYGIENE
& TROPICAL
MEDICINE



Abubakar, I; Sridhar, S; Eisenhut, M; Roy, A; Harris, RJ; Rodrigues, LC; Mangtani, P; Adetifa, I; Lalvani, A (2014) Authors' reply to Turner and colleagues. *BMJ (Clinical research ed)*, 349. g5441. ISSN 0959-8138 DOI: 10.1136/bmj.g5441

Downloaded from: <http://researchonline.lshtm.ac.uk/1924960/>

DOI: [10.1136/bmj.g5441](https://doi.org/10.1136/bmj.g5441)

Usage Guidelines

Please refer to usage guidelines at <http://researchonline.lshtm.ac.uk/policies.html> or alternatively contact researchonline@lshtm.ac.uk.

Available under license: Creative Commons Attribution Non-commercial
<http://creativecommons.org/licenses/by-nc/2.5/>

LETTERS

BCG VACCINATION AND TB IN CHILDREN

Authors' reply to Turner and colleagues

I Abubakar professor of infectious disease epidemiology¹, S Sridhar research associate², M Eisenhut consultant paediatrician³, A Roy senior scientist⁴, R J Harris statistician⁴, L C Rodrigues professor of epidemiology⁵, P Mangtani senior lecturer⁵, I Adetifa paediatrician and medical epidemiologist⁶, A Lalvani professor of infectious disease²

¹Centre for Infectious Disease Epidemiology and MRC Clinical Trials Unit, University College London, London, UK; ²Tuberculosis Research Centre, Respiratory Infections Section, National Heart and Lung Institute, Imperial College London, London, UK; ³Luton and Dunstable University Hospital, NHS Foundation Trust, Luton, UK; ⁴Centre for Infectious Disease Surveillance and Control, Public Health England, London, UK; ⁵London School of Hygiene and Tropical Medicine, London, UK; ⁶Medical Research Council, Fajara, Gambia

Turner and colleagues do not accept our conclusion that BCG prevents *Mycobacterium tuberculosis* infection without a valid mechanism and propose an alternative hypothesis for an apparent effect.^{1 2} We presented the consistent epidemiological finding of a protective effect of BCG against tuberculosis infection rather than speculating on a mechanism of action for this effect, which was not one of the stated objectives of our meta-analysis. Absence of a valid mechanism is not usually a basis for rejecting conclusions from consistently observed findings.³ Indeed, the protective effect of BCG against tuberculosis is not in doubt, even though a mechanism (and a correlate) of protection remain elusive after decades of investigation.⁴ Nonetheless, we believe that new vaccines for tuberculosis will be found only if we undertake more research to disentangle the mechanism of action of BCG vaccines, including their effects on innate and adaptive immune responses.⁵

Turner and colleagues' explanation, based on the fact that antigens used in the interferon γ release assay (IGRA) are absent from BCG, is undermined by the protective effect of BCG against tuberculosis infection when the tuberculin skin test (TST) is used instead of IGRA as a marker of infection.^{6 7} Purified protein derivative comprises hundreds of *M tuberculosis* antigens shared by BCG, so that TST results in these studies could not be subject to "original antigenic sin." The observation in our review of BCG and active tuberculosis that people

sensitised to tuberculin are less protected further argues for the vaccine's role in protecting against infection.^{8 9}

Competing interests: None declared.

Full response at: www.bmj.com/content/349/bmj.g4643/rr/763154.

- Roy A, Eisenhut M, Harris RJ, Rodrigues LC, Sridhar S, Habermann S, et al. Effect of BCG vaccination against *Mycobacterium tuberculosis* infection in children: systematic review and meta-analysis. *BMJ* 2014;349:g4643.
- Turner R, Tweed C, Bothamley G. No proof that BCG protects against infection with *Mycobacterium tuberculosis*. *BMJ* 2014;349:g5436.
- Parascandola M, Weed DL. Causation in epidemiology. *J Epidemiol Community Health* 2001;55:905-12.
- Kagina BMN, Abel B, Scriba TJ, Hughes EJ, Keyser A, Soares A, et al. Specific T cell frequency and cytokine expression profile do not correlate with protection against tuberculosis after bacillus Calmette-Guérin vaccination of newborns. *Am J Respir Crit Care Med* 2010;182:1073-9.
- Lalvani A, Sridhar S, von Reyn CF. Tuberculosis vaccines: time to reset the paradigm? *Thorax* 2013;68:1092-4.
- Soysal A, Millington KA, Bakir M, Dosanjh D, Aslan Y, Deeks JJ, et al. Effect of BCG vaccination on risk of *Mycobacterium tuberculosis* infection in children with household tuberculosis contact: a prospective community-based study. *Lancet* 2005;366:1443-51.
- Pulickal AS, Fernandez GVJ. Comparison of the prevalence of tuberculosis infection in BCG vaccinated versus non-vaccinated school age children. *Indian Pediatr* 2007;44:344-7.
- Abubakar I, Pimpin L, Ariti C, Beynon R, Mangtani P, Sterne J, et al. Systematic review and meta-analysis of the current evidence on the duration of protection by bacillus Calmette-Guérin vaccination against tuberculosis. *Health Technol Assess* 2013;17:1-372, v-vi.
- Mangtani P, Abubakar I, Ariti C, Beynon R, Pimpin L, Fine PEM, et al. Protection by BCG vaccine against tuberculosis: a systematic review of randomized controlled trials. *Clin Infect Dis Off Publ Infect Dis Soc Am* 2014;58:470-80.

Cite this as: *BMJ* 2014;349:g5441

© BMJ Publishing Group Ltd 2014