

# Observational study to estimate the changes in the effectiveness of bacillus Calmette–Guérin (BCG) vaccination with time since vaccination for preventing tuberculosis in the UK

Punam Mangtani,<sup>1\*</sup> Patrick Nguipdop-Djomo,<sup>1</sup>  
Ruth H Keogh,<sup>1</sup> Lucy Trinder,<sup>1</sup> Peter G Smith,<sup>1</sup>  
Paul EM Fine,<sup>1</sup> Jonathan Sterne,<sup>2</sup> Ibrahim Abubakar,<sup>3</sup>  
Emilia Vynnycky,<sup>4</sup> John Watson,<sup>1</sup> David Elliman,<sup>5</sup>  
Marc Lipman<sup>6,7</sup> and Laura C Rodrigues<sup>1</sup>

<sup>1</sup>Faculty of Epidemiology and Population Health, London School of Hygiene & Tropical Medicine, London, UK

<sup>2</sup>School of Social and Community Medicine, University of Bristol, Bristol, UK

<sup>3</sup>Institute for Global Health, University College London, London, UK

<sup>4</sup>Public Health England, London, UK

<sup>5</sup>Whittington Health, St Ann's Hospital, London, UK

<sup>6</sup>Royal Free London NHS Foundation Trust, London, UK

<sup>7</sup>University College London Respiratory, Division of Medicine, University College London, London, UK

\*Corresponding author [punam.mangtani@lshtm.ac.uk](mailto:punam.mangtani@lshtm.ac.uk)

**Declared competing interests of authors:** Jonathan Sterne was a member of the National Institute for Health Research (NIHR) Health Technology Assessment Clinical Evaluation and Trials Board while the study was being conducted.

Published July 2017

DOI: 10.3310/hta21390

## Scientific summary

### BCG effectiveness for TB prevention in UK

Health Technology Assessment 2017; Vol. 21: No. 39

DOI: 10.3310/hta21390

NIHR Journals Library [www.journalslibrary.nihr.ac.uk](http://www.journalslibrary.nihr.ac.uk)

# Scientific summary

## Background

Until recently, there was no evidence that protection against tuberculosis (TB) by bacillus Calmette–Guérin (BCG) vaccination lasted for > 10 years. In the past few years, studies in Brazil and the USA (in Native Americans) have suggested that protection from BCG vaccination against TB can last for several decades in some populations. These findings were interesting and we conducted this research to add to this body of evidence and to determine its relevance to the UK.

Establishing the duration of protection from BCG vaccination against TB is of relevance given the higher disease risks in young adults and the increase with age in the proportion of TB cases that are pulmonary, the main source of onward transmission. We carried out two case–control studies of the duration of protection of BCG vaccination: one of infant BCG vaccination and one of school-aged BCG vaccination. The studies took advantage of the UK's long-standing universal school-aged BCG vaccination programme and the changes introduced in 2005, when school-aged vaccination was discontinued and the programme of selective vaccination of high-risk (usually ethnic minority) infants was enhanced.

## Methods

We carried out two case–control studies in England of cases of TB and population-based control subjects (controls), frequency matched for age. One study involved those in minority ethnic groups who were eligible for infant BCG vaccination 1–19 years earlier. The other involved those who were UK born and white, and who were eligible for school-aged BCG vaccination 10–29 years earlier. TB cases included in both studies were drawn from among those notified in the years 2003–12 to the UK national Enhanced Tuberculosis Surveillance system. Controls were recruited from the community in the areas where sampled cases had arisen. BCG vaccination status was established based on BCG records when available, scar reading (inspection of both arms) and BCG history (recall of vaccination). Information on potential confounders (including demographic and social variables) was collected from cases and controls using face-to-face computer-assisted interviews. We studied vaccine effectiveness as a function of time since vaccination, using a case–cohort analysis based on Cox regression.

## Results

In the study of infant BCG vaccination, vaccination status was based on available vaccination records as there was poor concordance between vaccination records and either a history of BCG vaccination or scar reading. For infant vaccination, in the subset with vaccine records, a protective effect was seen for up to 10 years following vaccination [ $< 5$  years since vaccination: vaccine effectiveness (VE) 66%, 95% confidence interval (CI) 12% to 85%; 5–10 years since vaccination: VE 76%, 95% CI 44% to 89%], but there was weak evidence of an effect 10–15 years after vaccination (VE 36%, 95% CI negative to 76%;  $p = 0.361$ ). The analyses of the protective effect of infant BCG vaccination were adjusted for several confounding variables, including birth cohort and ethnicity. Adjusting only for ethnicity, sex and birth cohort, for which there were fewer missing data (on covariates), gave weak evidence of effectiveness (VE 50%, 95% CI negative to 78%;  $p = 0.096$ ) 10–15 years after vaccination. The high infant BCG vaccine uptake in this high-risk ethnic minority study population and the sparsity of vaccine record data in the later periods precluded further assessment. These results may be modified when methods to deal with missing data are further explored.

After school-aged BCG vaccination, a protective effect of 51% (95% CI 21% to 69%) was found 10–15 years after vaccination and a protective effect of 57% (95% CI 33% to 72%) was found 15–20 years after vaccination, beyond which time protection appeared to wane. Ascertainment of vaccination status was based on self-reported history and scar reading.

## Conclusions

Although the findings for infant BCG vaccination in a population at high risk for TB are insufficient to conclude that the protection extends beyond 10 years, the evidence is stronger for a moderate protective effect for up to 20 years after school-aged BCG vaccination in the native white population. The findings are consistent with the limited literature available.

This new evidence may be useful when making decisions on TB vaccine programmes (e.g. the timing of the administration of improved TB vaccines, if they become available) and for cost-effectiveness studies.

Methods to deal with missing record data in the infant study could be explored, including the use of scar reading.

## Funding

Funding for this study was provided by the Health Technology Assessment programme of the National Institute for Health Research. During the conduct of the study, Jonathan Sterne, Ibrahim Abubakar and Laura C Rodrigues received other funding from NIHR; Ibrahim Abubakar and Laura C Rodrigues have also received funding from the Medical Research Council. Punam Mangtani received funding from the Biotechnology and Biological Sciences Research Council.



ISSN 1366-5278 (Print)

ISSN 2046-4924 (Online)

Impact factor: 4.236

*Health Technology Assessment* is indexed in MEDLINE, CINAHL, EMBASE, The Cochrane Library and the Clarivate Analytics Science Citation Index.

This journal is a member of and subscribes to the principles of the Committee on Publication Ethics (COPE) ([www.publicationethics.org/](http://www.publicationethics.org/)).

Editorial contact: [journals.library@nhr.ac.uk](mailto:journals.library@nhr.ac.uk)

The full HTA archive is freely available to view online at [www.journalslibrary.nhr.ac.uk/hta](http://www.journalslibrary.nhr.ac.uk/hta). Print-on-demand copies can be purchased from the report pages of the NIHR Journals Library website: [www.journalslibrary.nhr.ac.uk](http://www.journalslibrary.nhr.ac.uk)

## Criteria for inclusion in the *Health Technology Assessment* journal

Reports are published in *Health Technology Assessment* (HTA) if (1) they have resulted from work for the HTA programme, and (2) they are of a sufficiently high scientific quality as assessed by the reviewers and editors.

Reviews in *Health Technology Assessment* are termed 'systematic' when the account of the search appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

## HTA programme

The HTA programme, part of the National Institute for Health Research (NIHR), was set up in 1993. It produces high-quality research information on the effectiveness, costs and broader impact of health technologies for those who use, manage and provide care in the NHS. 'Health technologies' are broadly defined as all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care.

The journal is indexed in NHS Evidence via its abstracts included in MEDLINE and its Technology Assessment Reports inform National Institute for Health and Care Excellence (NICE) guidance. HTA research is also an important source of evidence for National Screening Committee (NSC) policy decisions.

For more information about the HTA programme please visit the website: <http://www.nets.nhr.ac.uk/programmes/hta>

## This report

The research reported in this issue of the journal was funded by the HTA programme as project number 08/17/01. The contractual start date was in May 2011. The draft report began editorial review in November 2015 and was accepted for publication in November 2016. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the reviewers for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

This report presents independent research funded by the National Institute for Health Research (NIHR). The views and opinions expressed by authors in this publication are those of the authors and do not necessarily reflect those of the NHS, the NIHR, NETSCC, the HTA programme or the Department of Health. If there are verbatim quotations included in this publication the views and opinions expressed by the interviewees are those of the interviewees and do not necessarily reflect those of the authors, those of the NHS, the NIHR, NETSCC, the HTA programme or the Department of Health.

**© Queen's Printer and Controller of HMSO 2017. This work was produced by Mangtani *et al.* under the terms of a commissioning contract issued by the Secretary of State for Health. This issue may be freely reproduced for the purposes of private research and study and extracts (or indeed, the full report) may be included in professional journals provided that suitable acknowledgement is made and the reproduction is not associated with any form of advertising. Applications for commercial reproduction should be addressed to: NIHR Journals Library, National Institute for Health Research, Evaluation, Trials and Studies Coordinating Centre, Alpha House, University of Southampton Science Park, Southampton SO16 7NS, UK.**

Published by the NIHR Journals Library ([www.journalslibrary.nhr.ac.uk](http://www.journalslibrary.nhr.ac.uk)), produced by Prepress Projects Ltd, Perth, Scotland ([www.prepress-projects.co.uk](http://www.prepress-projects.co.uk)).

## **Health Technology Assessment Editor-in-Chief**

**Professor Hywel Williams** Director, HTA Programme, UK and Foundation Professor and Co-Director of the Centre of Evidence-Based Dermatology, University of Nottingham, UK

## **NIHR Journals Library Editor-in-Chief**

**Professor Tom Walley** Director, NIHR Evaluation, Trials and Studies and Director of the EME Programme, UK

## **NIHR Journals Library Editors**

**Professor Ken Stein** Chair of HTA and EME Editorial Board and Professor of Public Health, University of Exeter Medical School, UK

**Professor Andree Le May** Chair of NIHR Journals Library Editorial Group (HS&DR, PGfAR, PHR journals)

**Dr Martin Ashton-Key** Consultant in Public Health Medicine/Consultant Advisor, NETSCC, UK

**Professor Matthias Beck** Chair in Public Sector Management and Subject Leader (Management Group), Queen's University Management School, Queen's University Belfast, UK

**Dr Tessa Crilly** Director, Crystal Blue Consulting Ltd, UK

**Dr Eugenia Cronin** Senior Scientific Advisor, Wessex Institute, UK

**Ms Tara Lamont** Scientific Advisor, NETSCC, UK

**Dr Catriona McDaid** Senior Research Fellow, York Trials Unit, Department of Health Sciences, University of York, UK

**Professor William McGuire** Professor of Child Health, Hull York Medical School, University of York, UK

**Professor Geoffrey Meads** Professor of Health Sciences Research, Health and Wellbeing Research Group, University of Winchester, UK

**Professor John Norrie** Chair in Medical Statistics, University of Edinburgh, UK

**Professor John Powell** Consultant Clinical Adviser, National Institute for Health and Care Excellence (NICE), UK

**Professor James Raftery** Professor of Health Technology Assessment, Wessex Institute, Faculty of Medicine, University of Southampton, UK

**Dr Rob Riemsma** Reviews Manager, Kleijnen Systematic Reviews Ltd, UK

**Professor Helen Roberts** Professor of Child Health Research, UCL Institute of Child Health, UK

**Professor Jonathan Ross** Professor of Sexual Health and HIV, University Hospital Birmingham, UK

**Professor Helen Snooks** Professor of Health Services Research, Institute of Life Science, College of Medicine, Swansea University, UK

**Professor Jim Thornton** Professor of Obstetrics and Gynaecology, Faculty of Medicine and Health Sciences, University of Nottingham, UK

**Professor Martin Underwood** Director, Warwick Clinical Trials Unit, Warwick Medical School, University of Warwick, UK

Please visit the website for a list of members of the NIHR Journals Library Board:  
[www.journalslibrary.nihr.ac.uk/about/editors](http://www.journalslibrary.nihr.ac.uk/about/editors)

**Editorial contact:** [journals.library@nihr.ac.uk](mailto:journals.library@nihr.ac.uk)