Effect of BCG vaccination against *Mycobacterium tuberculosis* infection in children: systematic review and meta-analysis

A Roy,[1] M Eisenhut,[2] R J Harris,[1] L C Rodrigues,[3] S Sridhar,[4] S Habermann,[2] L Snell,[2] P Mangtani,[3] I Adetifa,[5] A Lalvani,[4] I Abubakar[1 6]

[1]Centre for Infectious Disease Surveillance and Control, Public Health England, London NW9 5EQ, UK
[2]Luton and Dunstable University Hospital, NHS Foundation Trust, Luton, UK
[3]London School of Hygiene and Tropical Medicine, London, UK
[4]Tuberculosis Research Unit, National Heart and Lung Institute, Imperial College London, London, UK
[5]Medical Research Council, Fajara, Gambia
[6]Centre for Infectious Disease Epidemiology and MRC Clinical Trials Unit, University College London, London, UK
Correspondence to: I Abubakar
i.abubakar@ucl.ac.uk

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Research: Efficacy of percutaneous versus intradermal BCG in the prevention of tuberculosis in South African infants: randomised trial (*BMJ* 2008;337:a2052)

STUDY QUESTION

Does BCG vaccination protect against *Mycobacterium tuberculosis* infection as assessed by interferon γ release assays in children?

SUMMARY ANSWER

BCG protects against *M tuberculosis* infection as well as against progression from infection to disease.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Numerous efficacy trials indicate that BCG has 60-80% protective efficacy against severe forms of tuberculosis in children, particularly meningitis, and its efficacy against pulmonary diseases varies geographically. Use of interferon γ release assays shows that BCG also protects against infection with tuberculosis as well as clinical disease, with implications for the development of new vaccines and policy.

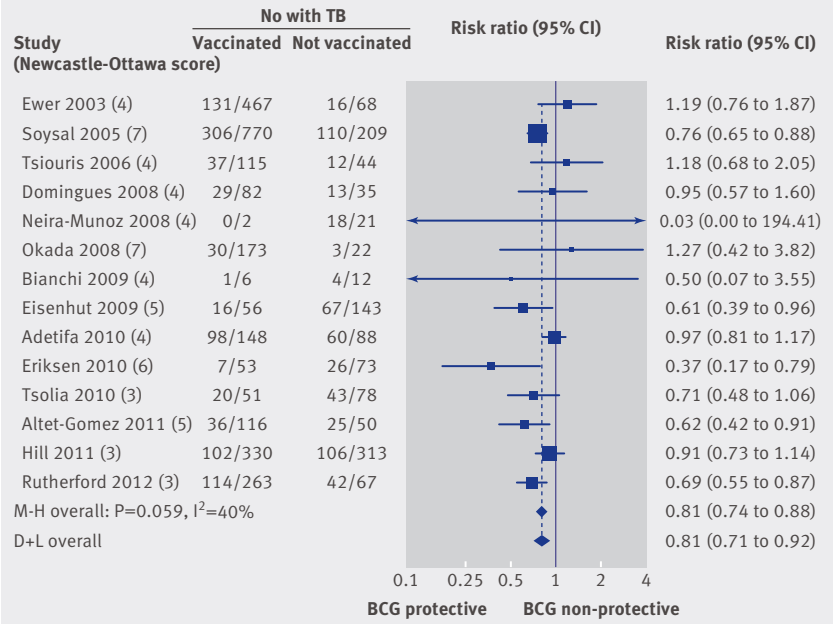
Selection criteria for studies

We searched electronic databases from 1950 until November 2013. Eligible studies included BCG vaccinated and unvaccinated children aged under 16 who were screened for *M tuberculosis* infection with interferon γ release assays after recent exposure to pulmonary tuberculosis.

Primary outcome

Tuberculosis infection as measured by interferon γ release assays (as proxy for TB infection).

Protection against *Mycobacterium tuberculosis* infection (TB) with BCG vaccination in children as determined by interferon γ release assay



Main results and role of chance

We included 14 cohort studies with 3855 participants. BCG vaccination protected against *M tuberculosis* infection with a protective efficacy of 19% (95% confidence interval 0.71 to 0.92). There was moderate heterogeneity (I^2=40 %, P<0.06) between the studies. Subgroup analysis of the observed protection against *M tuberculosis* infection was independent of the assay method used. The risk ratio was similar for the two types of assay: 0.83 (95% confidence interval 0.68 to 1.02; four studies) for ELISpot and 0.78 (0.64 to 0.96; 10 studies) for QuantiFERON. Studies conducted above 40° latitude showed a protective efficacy of BCG vaccination of 26% (0.74, 0.60 to 0.91), which was not seen at lower latitudes of 20-40° (0.88, 0.54 to 1.45) and 20-0° (0.87, 0.72 to 1.04). Quality rating of studies with a score of ≥5 showed protection of 32% (0.68, 0.55 to 0.84) compared with 12% (0.88, 0.77 to 1.01) for studies with a score of 3 or 4, suggesting that study design factors in smaller low quality studies led to the inability to detect a protective effect.

About half (48%) of the children (n=1862) from five studies included were exposed to a single well defined source simultaneously or it was known that there was no difference in exposure. A subgroup analysis of these studies found a higher vaccine efficacy of 28% (risk ratio of 0.73, 95% confidence interval 0.52 to 1.00).

Restriction of the analysis to the six studies (n=1745) with information on progression to active tuberculosis showed protection against infection of 27% (0.73, 0.61 to 0.87) compared with 71% (0.29, 0.15 to 0.58) against active tuberculosis. Among those infected, protection against progression to disease was 58% (0.42, 0.23 to 0.77).

Bias, confounding, and other reasons for caution

We assumed that there was no infection before the documented exposure, which might not always be the case. We could not determine the probability of prior exposure or quantify the degree of exposure as in most included studies the data were extracted from reports that were not designed to compare presence of latent TB after exposure among children vaccinated against BCG or unvaccinated. We attempted to lower the probability of previous exposure by restricting the analysis to children aged under 16. The small number of studies limited the power to explore whether the variation in protection by BCG against tuberculosis is mostly through variation in protection against infection.

Study funding/potential competing interests

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors. IA is supported by the National Institute for Health Research.

Predicting risk of upper gastrointestinal bleed and intracranial bleed with anticoagulants: cohort study to derive and validate the QBleed scores

Julia Hippisley-Cox, Carol Coupland

EDITORIAL by Steinberg

Division of Primary Care, University Park, Nottingham NG2 7RD, UK
Correspondence to: J Hippisley-Cox
Julia.hippisley-cox@nottingham.ac.uk

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Research: Refined bleeding estimates in adults starting anticoagulants (*BMJ* 2014;349:g4800)

STUDY QUESTION

How good is the performance of newly developed risk algorithms (QBleed) for estimating the absolute risks of upper gastrointestinal and intracranial bleed in patients with and without anticoagulation aged 21-99 years in primary care?

SUMMARY ANSWER

The QBleed algorithms provided valid measures of absolute risk of both types of bleed as shown by the performance of both algorithms in a separate validation cohort. Further research is needed to evaluate the clinical outcomes and cost effectiveness of using these algorithms in primary care.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Current scoring methods to identify patients at increased risk of intracranial and gastrointestinal bleed do not take account of some established risk factors or are difficult to implement. The new QBleed algorithms include established risk factors, are designed to work in primary care, and provide valid measures of absolute risk of bleed in the general population of patients.

Participants and setting

4.4 million patients (16.4 million person years of follow-up) were included in the derivation cohort. During follow-up, 21 641 patients had an upper gastrointestinal bleed and 9040 an intracranial bleed. For the validation cohort we identified 1.4 million patients (>4.9 million person years of follow-up). During follow-up, 6600 patients had an upper gastrointestinal bleed and 2820 an intracranial bleed. We excluded patients without a valid Townsend score and those prescribed anticoagulants in the 180 days before study entry.

Performance of each algorithm in validation cohort using incident events included in hospital or mortality data

	Mean (95% CI)	
Incident events	Women	Men
Upper gastrointestinal bleed:		
ROC statistic*	0.766 (0.758 to 0.775)	0.747 (0.738 to 0.756)
R^2 (%)†	40.7 (38.9 to 42.6)	36.9 (35.1 to 38.7)
D statistic‡	1.70 (1.63 to 1.76)	1.57 (1.51 to 1.63)
Intracranial bleed:		
ROC statistic*	0.847 (0.838 to 0.856)	0.812 (0.80 to 0.824)
R^2 (%)†	58.0 (56.0 to 60.0)	53.3 (51.1 to 55.4)
D statistic‡	2.40 (2.30 to 2.50)	2.19 (2.09 to 2.28)

Discrimination is ability of risk prediction model to differentiate between patients who do and do not experience an admission event during the study.
*Receiver operating characteristic (ROC) curve statistic; higher values indicate better discrimination.
†Measures explained variation, with higher values indicating more variation explained.
‡Measure of discrimination specific to censored survival data. As with ROC, higher values indicate better discrimination.

Design, size, and duration

Prospective open cohort study using routinely recorded data from general practices in England providing data to QResearch. We used 565 practices to develop the scores and a separate set of 188 practices to validate the scores. We used Cox proportional hazards models in the derivation cohort to derive risk equations that could be evaluated from one up to five years. Candidate variables for inclusion in the risk equations were personal characteristics (age, sex, Townsend deprivation score, ethnicity), lifestyle (smoking, alcohol intake), chronic diseases, prescribed drugs, clinical values (body mass index, systolic blood pressure), and laboratory test results (haemoglobin, platelets). We also included previous bleed recorded before entry to the study.

Main results and the role of chance

The final QBleed algorithms incorporated 21 variables. When applied to the validation cohort, the algorithms in women explained 40% of the variation for upper gastrointestinal bleed and 58% for intracranial bleed. The corresponding D statistics were 1.67 and 2.42. The receiver operating curve statistic values were 0.77 and 0.86. The sensitivity values for the top 10th of men and women at highest risk were 38% and 51%, respectively. The model was well calibrated. The algorithms are based on simple clinical variables that patients are likely to know or that are routinely recorded in general practice computer systems.

Bias, confounding, and other reasons for caution

Limitations include lack of formally adjudicated outcomes, information bias, missing data, and residual confounding.

Generalisability to other populations

A strength of our study is that we developed the algorithms in one cohort and validated them in a separate cohort representative of patients likely to be considered for preventive measures.

Study funding/potential competing interests

JHC is co-director of QResearch, a not for profit organisation that is a joint partnership between the University of Nottingham and EMIS (leading commercial supplier of information technology for 60% of UK general practices), and director of ClinRisk, which produces software to ensure reliable and updatable implementation of clinical risk algorithms to help improve patient care. CC is an associate professor and a consultant statistician for ClinRisk.

Prison tobacco control policies and deaths from smoking in United States prisons: population based retrospective analysis

Ingrid A Binswanger,[1] E Ann Carson,[2] Patrick M Krueger,[3] Shane R Mueller,[1] John F Steiner,[4] William J Sabol[2]

EDITORIAL by Ritter

[1]Division of General Internal Medicine, Department of Medicine, University of Colorado School of Medicine, Mail Stop B180, 12631 E 17th Avenue, Aurora, CO 80045, USA
[2]Bureau of Justice Statistics, Department of Justice, 810 Seventh Street, NW, Washington, DC 20531, USA
[3]Department of Health and Behavioral Sciences, University of Colorado Denver, Campus Box 188, PO Box 173364, Denver, CO 80217, USA
[4]Institute for Health Research, Kaiser Permanente Colorado, PO Box 378066, Denver, CO 80237, USA
Correspondence to: I A Binswanger
ingrid.binswanger@ucdenver.edu
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- Letters: New Zealand leads the way in banning smoking in prisons (*BMJ* 2013;346:f3923)
- Analysis: Promoting health in prison (*BMJ* 2013;346:f2216)
- Editor's choice: The inside story on Prison Health (*BMJ* 2013;346:f3471)
- Editorial: Managing the health of Prisoners (*BMJ* 2013;346:f3463)

STUDY QUESTION

What is the smoking attributable mortality and years of potential life lost from smoking among prisoners in the United States and are prison smoking bans associated with reductions in smoking related deaths?

SUMMARY ANSWER

Smoking attributable mortality and years of potential life lost from smoking were higher in people in prisons than in the general population, and there was a reduction in smoking related deaths in prisons that implemented smoking bans.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

People in prison have a high prevalence of both direct and secondhand exposure to tobacco smoke in prisons that allow smoking. Smoking contributes to substantial mortality in prison, and prison tobacco control policies are associated with reduced mortality. Smoking bans have health benefits for people in prison, despite the limits they impose on individual autonomy and the risks of relapse after release.

Participants and setting

Smoking prevalence was obtained from a nationally representative survey of individuals in state prisons in 2004 (n=14 499). Deaths among individuals in state prisons in the United States in 2001-11 were reported to the Bureau of Justice Statistics. We searched public websites, legislation, and reports to determine the tobacco control policies in the 50 states from 2001 to 2011.

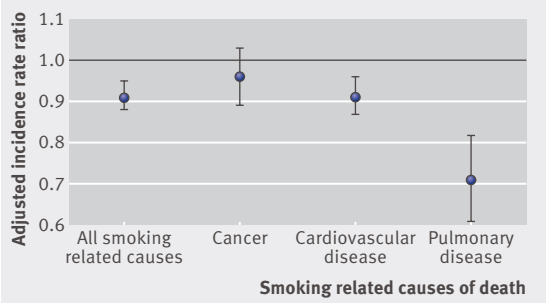
Design, size, and duration

We used the smoking attributable mortality, morbidity, and economic costs system from the Centers for Disease Control and Prevention to calculate smoking attributable mortality and years of potential life lost. We classified deaths in prisons into smoking related disease categories and conducted a population based time series analysis to determine the association between smoking bans and mortality.

Main results and the role of chance

The most common causes of deaths from smoking in prisons were lung cancer, ischemic heart disease, other heart disease, cerebrovascular disease, and chronic airways obstruction. Age adjusted smoking attributable mortality and years of potential life lost were 360 and 5149 per 100 000, respectively, compared with 248 and 3501, respectively, in the general US population. The number of states with any smoking ban increased from 25 in 2001 to 48 by 2011. The mortality rate from smoking related causes was lower during years with a ban than during years without a ban (110.4/100 000 v 128.9/100 000). Prisons that implemented smoking bans had a 9% reduction (adjusted incidence rate ratio, 0.91, 95% confidence interval 0.88 to 0.95) in smoking related deaths. Bans in place for longer than nine years were associated with reductions in cancer mortality (0.81, 0.74 to 0.90). Estimates of the association between smoking bans and smoking related mortality were adjusted for calendar year to account for secular trends and prevalence of current smoking in the general population in each state to account for the potential confounding effect of state variation in smoking prevalence and sex.

Effect of prison smoking bans on deaths in prisons related to smoking



Bias, confounding, and other reasons for caution

Smoking attributable mortality could be underestimated because effects of secondhand smoke were not included in calculations of smoking attributable mortality. We estimated smoking attributable mortality and years of potential life lost using several different assumptions.

Generalisability to other populations

The generalisability of our results to prison systems in other countries is unknown.

Study funding/potential competing interests

This study was supported by the Bureau of Justice Statistics Visiting Fellows Program, US Department of Justice (grant No 2011-BJ-CX-K073). The views, opinions, or conclusions presented here are those of the authors and should not be attributed to the Bureau of Justice Statistics or the US Department of Justice.