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Abstract

Systematic review and meta-analysis of the current evidence on the duration of protection by bacillus Calmette–Guérin vaccination against tuberculosis

I Abubakar,[1,2*] L Pimpin,[1] C Ariti,[3] R Beynon,[4] P Mangtani,[3] JAC Sterne,[4] PEM Fine,[3] PG Smith,[3] M Lipman,[5] D Elliman,[6] JM Watson,[1] LN Drumright,[1] PF Whiting,[4] E Vynnycky[1] and LC Rodrigues[3]

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Background: Recent evidence suggests that the duration of protection by bacillus Calmette–Guérin (BCG) may exceed previous estimates with potential implications for estimating clinical and cost-efficacy.

Objectives: To estimate the protection and duration of protection provided by BCG vaccination against tuberculosis, explore how this protection changes with time since vaccination, and examine the reasons behind the variation in protection and the rate of waning of protection.

Data sources: Electronic databases including MEDLINE, Excerpta Medica Database (EMBASE), Cochrane Databases, NHS Economic Evaluation Database (NHS EED), Database of Abstracts of Reviews of Effects (DARE), Web of Knowledge, Biosciences Information Service (BIOSIS), Latin American and Caribbean Health Sciences Literature (LILACs), MEDCARIB Database, Cumulative Index to Nursing and Allied Health Literature (CINAHL) were searched from inception to May 2009. Index to Theses, System for Information on Grey Literature in Europe (SIGLE), Centre for Agricultural Bioscience International (CABI) Abstracts, Scopus, Article First, Academic Complete, Africa-Wide Information, Google Scholar, Global Health, British National Bibliography for Report Literature, and clinical trial registration websites were searched from inception to October 2009.

Review methods: Electronic databases searches, screening of identified studies, data extraction and analysis were undertaken. Meta-analysis was used to present numerical and graphical summaries of clinical efficacy and efficacy by time since vaccination. Evidence of heterogeneity was assessed using the tau-squared statistic. Meta-regression allowed the investigation of observed heterogeneity. Factors investigated included BCG strain, latitude, stringency of pre-BCG vaccination tuberculin testing, age at vaccination, site of disease, study design and vulnerability to biases. Rate of waning of protection was estimated using the ratio of the measure of efficacy after 10 years compared with the efficacy in the first 10 years of a study.

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Results: *Study selection* A total of 21,030 references were identified, providing data on 132 studies after abstract and full-text review. *Efficacy* Protection against pulmonary tuberculosis in adults is variable, ranging from substantial protection in the UK MRC trial {rate ratio 0.22 [95% confidence interval (CI) 0.16 to 0.31]}, to absence of clinically important benefit, as in the large Chingleput trial [rate ratio 1.05 (95% CI 0.88 to 1.25)] and greater in latitudes further away from the equator. BCG vaccination efficacy was usually high, and varied little by form of disease (with higher protection against meningeal and miliary tuberculosis) or study design when BCG vaccination was given only to infants or to children after strict screening for tuberculin sensitivity. High levels of protection against death were observed from both trials and observational studies. The observed protective effect of BCG vaccination did not differ by the strain of BCG vaccine used in trials.
Duration: Reviewed studies showed that BCG vaccination protects against pulmonary and extrapulmonary tuberculosis for up to 10 years. Most studies either did not follow up participants for long enough or had very few cases after 15 years. This should not be taken to indicate an absence of effect: five studies (one trial and four observational studies) provided evidence of measurable protection at least 15 years after vaccination. Efficacy declined with time. The rate of decline was variable, with faster decline in latitudes further from the equator and in situations where BCG vaccination was given to tuberculin-sensitive participants after stringent tuberculin testing.
Limitations: The main limitation of this review relates to quality of included trials, most of which were conducted before current standards for reporting were formulated. In addition, data were lacking in some areas and the review had to rely on evidence from observational studies.
Conclusions: BCG vaccination protection against tuberculosis varies between populations, to an extent that cannot be attributed to chance alone. Failure to exclude those already sensitised to mycobacteria and study latitude closer to the equator were associated with lower efficacy. These factors explained most of the observed variation. There is good evidence that BCG vaccination protection declines with time and that protection can last for up to 10 years. Data on protection beyond 15 years are limited; however, a small number of trials and observational studies suggest that BCG vaccination may protect for longer. Further studies are required to investigate the duration of protection by BCG vaccination.
Funding: The National Institute for Health Research Health Technology Assessment programme.

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List of abbreviations

BCG	bacillus Calmette–Guérin
BIOSIS	Biosciences Information Service
CABI	Centre for Agricultural Bioscience International Abstracts
CCH	Cook County Hospital
CDSR	Cochrane Database of Systematic Reviews
CENTRAL	Cochrane Central Register of Controlled Trials
CI	confidence interval
CINAHL	Cumulative Index to Nursing and Allied Health Literature
D+L	DerSimonian and Laird method
DARE	Database of Abstracts of Reviews of Effects
DNA	deoxyribonucleic acid
DU1	tandem duplication 1
DU2	tandem duplication 2
EMBASE	Excerpta Medica Database
HIV	human immunodeficiency virus
HLA	human leucocyte antigen
HTA	Health Technology Assessment
I-V	inverse variance method
IGRA	interferon-gamma release assay
ISI	Institute for Scientific Information
IUATLD	International Union Against Tuberculosis and Lung Disease
KC50	Korner Code 50
LILACS	Literatura Latino-Americana e do Caribe em Ciências da Saúde (Latin American and Caribbean Health Sciences Literature)
M–H	Mantel–Haenszel method
MRC	Medical Research Council
NHS EED	NHS Economic Evaluation Database
NICE	National Institute for Health and Care Excellence
NIHR	National Institute of Health Research
NRAMP	natural resistance-associated macrophage protein
OR	odds ratio
PCT	primary care trust
PPD	purified protein derivative
PY	person-years
RCT	randomised controlled trial
RD1	region of difference 1
RD2	region of difference 2
ref.	reference category
REVAC	Brazilian revaccination study
RR	risk ratio
RRR	ratio of risk ratios
SES	socioeconomic status

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SIGLE	System for Information on Grey Literature in Europe
TBPT	Tuberculosis Prevention Trial
VE	vaccine efficacy
WHO	World Health Organization

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices, in which case the abbreviation is defined in the figure legend or in the notes at the end of the table.

Scientific summary

Background

Recent evidence suggests that the duration of protection by bacillus Calmette–Guérin (BCG) vaccination may exceed previous estimates. Such information is essential for estimating both the impact of BCG vaccination programmes and their cost-efficacy. This systematic review was commissioned by the National Institute for Health Research (NIHR) Health Technology Assessment programme in order to assess the duration of protection by BCG vaccine.

Objectives

To assess and quantify changes in protection by BCG vaccination against tuberculosis over time, against all tuberculosis, tuberculosis mortality, pulmonary tuberculosis and extrapulmonary tuberculosis (meningeal/miliary and other extrapulmonary sites separately and together), based on controlled trials and observational studies. To estimate, if data are available, overall clinical efficacy for the above tuberculosis disease categories and variations in clinical efficacy according to location (latitude/geographic region), time since vaccination and age at vaccination (neonatal, school age, occupational), stringency of tuberculin testing before vaccination, risk of bias in the different study designs, vaccine strain, gender and human immunodeficiency virus (HIV) status.

Methods

Search strategy

Electronic databases were searched from inception to October 2009, including MEDLINE, Excerpta Medica Database (EMBASE), Cochrane Databases, Database of Abstracts of Reviews of Effects (DARE), Health Technology Assessment database and NHS Economic Evaluation Database (NHS EED), Web of Knowledge, Bioscience Information Service (BIOSIS), Latin American and Caribbean Health Sciences Literature (LILACs), MEDCARIB, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Index to Theses, System for Information on Grey Literature in Europe (SIGLE), Centre for Agricultural Bioscience International (CABI) Abstracts, Scopus, Article First, Academic Complete, Africa-Wide Information, Google Scholar, Global Health, British National Bibliography for Report Literature, and clinical trials and controlled trials websites.

Inclusion/exclusion criteria

All studies, observational or trial, which assessed the efficacy of BCG vaccines in any human population compared with another vaccine or a placebo that provided sufficient outcome on tuberculosis disease or mortality were included. Case series and ecological studies, those assessing efficacy of oral BCG vaccination or clinical efficacy of BCG vaccination against infection rather than disease, and cohort studies that did not use stringent tuberculin testing before vaccination were all excluded. For each study design, further criteria were developed to determine which studies had all necessary data and were therefore suitable for data extraction.

Data extraction

Data extraction of English-language papers was carried out by one reviewer and checked by a second reviewer. Any disagreements were resolved by consensus. A baseline data extraction

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form was used to collect information on study design, participants' characteristics, years of recruitment and follow-up, characteristics of BCG vaccination, including strain and whether preceded by tuberculin testing, characteristics of tuberculin testing, *Mycobacterium tuberculosis* Koch infection, regional vaccination policies, BCG vaccination procedures and properties, and tuberculosis outcomes. The Cochrane Risk of Bias tool was used to assess bias in randomised controlled trials (RCTs). Bias assessment forms were developed in order to assess the observational study designs.

Analysis

Estimates of BCG vaccination efficacy were derived for each study and displayed in forest plots together with both fixed- and random-effects summary effect estimates categorised by site of disease and study design. Variation in efficacy according to latitude of study location, age at vaccination (and tuberculin testing stringency for trials), BCG strain (for trials), and diagnostic detection bias whether prospective or retrospective design for cohort studies were examined. Meta-regression analyses were conducted, when sufficient studies were available, for each outcome and heterogeneity was quantified by estimating the between-study variance, tau-squared, using restricted maximum likelihood, using the metareg command in Stata 11 (StataCorp LP, College Station, TX, USA). The analyses of the duration of protection by BCG vaccination focused on changes in efficacy with time since vaccination (or age as proxy for time since vaccination, for infant vaccination) and was estimated within studies.

Results

Study selection

A total of 21,030 references were identified through the literature search. The titles, and abstracts if available, were screened for eligibility. Full-text copies of 800 articles selected for potential inclusions were retrieved. In total, 211 articles met the inclusion criteria for this review (of which 60 were published in non-English languages), providing data on 132 studies.

Efficacy

The results of trials and observational studies are consistent with previous observations that protection against pulmonary tuberculosis in adults is variable and greater away from the equator. One finding is that BCG vaccination efficacy was usually high, and varied little by form of disease (although magnitude of protection appeared to still be higher against meningeal and miliary tuberculosis) or study design when BCG vaccination was given only to infants or to children after strict screening for tuberculin sensitivity. There were not enough studies to determine the individual impact of prior tuberculin sensitivity, age at vaccination and latitude. High levels of protection against death were observed from both trials and observational studies. Our analysis found that the protective effect of BCG vaccination did not differ by the strain of BCG vaccine used in trials.

Duration

We found good evidence from trials and observational studies that BCG vaccination protects against pulmonary and extrapulmonary tuberculosis for up to 10 years. Most studies either did not follow up participants for long enough or had very few cases after 15 years. The meagre evidence from the majority of trials should not be taken to indicate an absence of effect: five studies (one trial and four observational studies) provided evidence of measurable protection at least 15 years after vaccination. Clinical efficacy declined with time. The rate of decline differed between studies and, although the number of studies was limited, the pattern of decline was consistent with faster decline in latitudes further from the equator and in situations where BCG vaccination was given only to either infants or to children after strict screening for tuberculin sensitivity.

Conclusions

This review of clinical trials and observational studies confirmed that BCG vaccination provides protection against tuberculosis, and that effectiveness of BCG vaccines in protecting against tuberculosis varies considerably between populations, to an extent that cannot be attributed to chance alone. BCG vaccination provided good protection when given to naive individuals. Age at which the vaccine was given, pre-vaccination tuberculin sensitivity status and latitude were the factors that explained most of the observed variation. There was no evidence that other factors such as BCG vaccine strain explain the observed variation.

The strength of protection appeared to decline with time. There was evidence of protection beyond 15 years; however, data were limited. Most studies either did not follow up participants for long enough or had very few cases after 10 years. The absence of evidence from the majority of trials should, therefore, not be taken as an absence of effect.

Recommendations for research

For bacillus Calmette–Guérin research

1. Further research into the duration of protection conferred by BCG vaccination would be useful to inform future vaccination policy. We would recommend a case–control study taking into account the purified protein derivative status of participants at vaccination, as this approach is likely to be cheaper and provide results in the shortest amount of time.
2. Replication of the REVAC study (Brazilian revaccination study) (Rodrigues LC, Pereira SM, Cunha SS, Genser B, Ichihara MY, de Brito SC, *et al.* Effect of BCG revaccination on incidence of tuberculosis in school-aged children in Brazil: the BCG–REVAC cluster-randomised trial. *Lancet* 2005;**366**:1290–5) in other settings to see whether similar or different results would be obtained in different environments may also be beneficial.
3. Further research into the efficacy of BCG vaccination in those > 35 years should be carried out.
4. Studies should investigate the role of stringent tuberculin skin testing in the protective effect of BCG vaccination.

For new vaccines

1. Given the limited protection conferred by BCG vaccination against post-primary adult pulmonary disease, new tuberculosis vaccines against these forms of the disease are of high priority.
2. BCG vaccination appears to offer little or no protection to those previously infected with *M. tuberculosis*. Vaccines that are effective in this group ('post-exposure vaccines') should be a priority for research. This will require better animal models of tuberculosis that allow the assessment of the efficacy of BCG vaccination against reactivation disease.
3. Future studies need to take into account the observation from this review that prior tuberculin sensitivity is a key determinant of whether or not a trial shows significant evidence of protection by BCG vaccination. This is particularly pertinent, as most trials of new vaccines will be undertaken in high tuberculosis incidence countries that also have a high burden of non-tuberculous mycobacterial infection.
4. Investigating the mechanism behind the failure of BCG vaccination to protect previously sensitised individuals will provide useful information for the development of new vaccines against tuberculosis. This should be assessed for different non-tuberculous mycobacteria, prior BCG vaccination and tuberculosis exposure.
5. Future research should also investigate whether the clinical efficacy of new vaccines differs depending on the predominant strain of *M. tuberculosis* circulating in the population, as well as the interaction between the predominant circulating strains of *M. tuberculosis* and human

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genetic polymorphisms that affect susceptibility to tuberculosis. There is also a need for studies in HIV-infected individuals.

Implications for practice

1. The economic analysis to inform the tuberculosis incidence threshold at which universal BCG vaccination becomes cost-effective should be re-examined if further evidence emerges that BCG vaccination protects for longer than 15 years.
2. There is a need to consider whether or not all individuals should be tested to identify those likely to benefit from BCG vaccination, especially with the increased used of interferon-gamma release assays for contact investigation.

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The National Institute for Health Research Health Technology Assessment programme.

Chapter 1

Aim of the review

Tuberculosis is a UK public health priority. Rates have increased > 0% over the last two decades.[1] Immunisation with bacillus Calmette–Guérin (BCG) vaccine has been an important component of the national control programme since 1953. In 2005, the policy on BCG vaccination was moved from the universal vaccination of all tuberculin skin test-negative schoolchildren to an approach that targets high-risk groups. This decision was informed by the changing epidemiology of tuberculosis and criteria laid down by the International Union Against Tuberculosis and Lung Disease (IUATLD).[2]

Data on the clinical effectiveness of BCG vaccination have been summarised in several reviews, and show reasonable yet variable levels of protective efficacy.[3,4] One key element of the application of this information to national tuberculosis control programmes is the duration of protection provided by the BCG vaccination. In common with many other vaccines, information on duration of protection (and diminution of effect over time since vaccination) by the BCG vaccination is scarce. Evidence has emerged over recent years[5,6] to suggest that the measurable duration of protection by BCG vaccination may exceed previous estimates.[7] Such information is essential both to estimate the impact of BCG vaccination programmes (including cost efficacy) and for rational decisions on the utility of repeat vaccination and introduction of new booster vaccines. This systematic review was commissioned by the National Institute of Health Research (NIHR) Health Technology Assessment programme to assess the available evidence on duration of protection by BCG vaccine.

Key research objectives

Primary objective

To assess and quantify changes in protection by BCG vaccination over time, against all tuberculosis, tuberculosis mortality, pulmonary tuberculosis and extrapulmonary tuberculosis (meningeal, miliary and other extrapulmonary sites separately and together), based on controlled trials and observational studies.

Secondary objectives

To estimate, where the data are available:

1. overall efficacy for the above tuberculosis disease categories
2. variations in efficacy according to:
   i. latitude/geographic region
   ii. whether prior tuberculin sensitivity was an exclusion criterion for BCG vaccination and, if so, the stringency of the test criterion
   iii. time since vaccination and age at vaccination (neonatal, school age, adult/occupational), if possible separating the effect of time since vaccination from that of age
   iv. risk of bias in the different study designs
   v. vaccine strain
   vi. gender
   vii. human immunodeficiency virus (HIV) status.

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Chapter 2

Background

Tuberculosis epidemiology

Tuberculosis remains a significant and preventable cause of morbidity and mortality globally. The World Health Organization (WHO) estimates that there are about 9 million new cases of, and 1.6 million deaths from, tuberculosis annually.[8] Globally, tuberculosis continues to disproportionately affect low- to middle-income countries, with the highest burden of disease in South-East Asia, Africa and Eastern Europe.[8] The incidence of tuberculosis is currently declining; however, there is considerable variation in the rates at which this is happening in different regions of the world.[8]

The incidence of tuberculosis has increased steadily over the last two decades in the UK, with over 9000 cases reported annually (*Table 1*).[9,10] There is significant variation in the incidence of tuberculosis by region and within regions. The highest burden of disease is in urban areas (*Figure 1*), with London accounting for about 40% of cases. The incidence of childhood tuberculosis, including miliary disease and meningitis, has remained stable in the UK.[11] The proportion of cases with anti-*Mycobacterium tuberculosis* Koch drug resistance is also increasing in the UK.[9] One of the advantages of an effective vaccine is that it should protect against drug-resistant strains.

Bacillus Calmette–Guérin vaccine and its history

The BCG vaccine, derived from an isolate of *Mycobacterium bovis* at the Institut Pasteur in Lille, France, was first given to a human, orally, in 1921 to prevent tuberculosis. Following this, its use increased across Europe. It was not until the 1930s, however, that the first formal trial of BCG vaccination was undertaken, in Native Americans.[5] By the 1940s, BCG vaccination, administered percutaneously or intradermally, had been shown to be efficacious in several studies.[5,12,13] In the 1950s, two major trials were initiated in the UK and the USA, by the Medical Research Council (MRC) and the United States Public Health Service, respectively.[14,15] The results of the two trials were conflicting: the study in the UK found that BCG vaccination was highly efficacious against tuberculosis, whereas the US study concluded that it provided very little protection. Based on this, the UK implemented a policy of universal vaccination of all school-age children who were tuberculin skin test negative, and the USA opted not to use BCG vaccination routinely other than for select high-risk situations. Globally, the use of BCG vaccination increased, supported by recommendations from the WHO.

Bacillus Calmette–Guérin vaccine efficacy

The efficacy of a vaccine is defined as the per cent reduction in risk of disease in vaccines when compared with similar and similarly exposed unvaccinated individuals. There has been a trend in recent years to restrict the word 'efficacy' to refer to measures derived in randomly controlled trials, and to use the word 'effectiveness' in observational studies. It is important to note that this is not always accurate, as some trials will, strictly speaking, be assessing effectiveness and not efficacy. Nevertheless, as this review covers both trials and observational studies, we will use the

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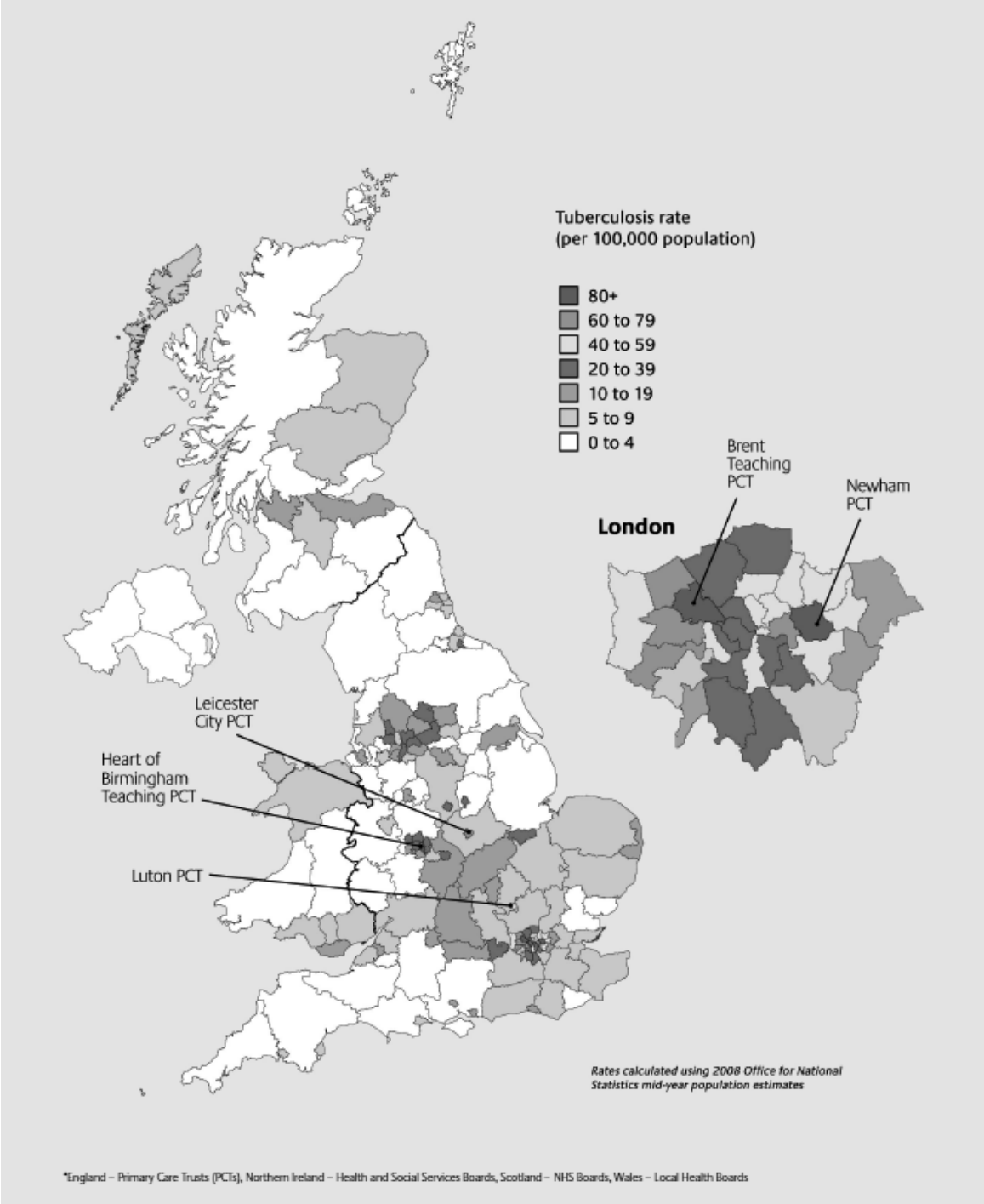

FIGURE 1 Map of tuberculosis rates per 100,000 population by primary care trust in the UK 2007–9.[10] Reproduced with permission from Public Health England. Contains public sector information licensed under the Open Government Licence v1.0.

term 'efficacy' when referring to trials and effectiveness for the results of observational studies to simplify the presentation of data.

Despite considerable debate regarding its role in tuberculosis control globally, BCG vaccination is widely used, with over 100 million doses given annually. Randomised controlled trials (RCTs) and case–control studies have shown consistently high efficacy of infant vaccination in

TABLE 1 Tuberculosis rates per 100,000 population in England by region 2000–9[10]

	Region									
Year	East Midlands	East of England	London	North-east	North-west	South-east	South-west	West Midlands	Yorkshire and the Humber	Total
2000	10.1	5.3	36.5	6.2	9.2	5.8	4.7	13.4	11.1	12.4
2001	13.2	6.0	35.9	7.0	9.5	5.8	4.3	13.4	11.1	12.7
2002	11.4	6.4	40.6	6.0	9.4	6.0	4.6	15.1	10.1	13.4
2003	10.9	5.8	41.5	5.6	8.5	6.9	4.2	14.7	10.9	13.4
2004	10.2	7.1	42.1	5.7	8.4	7.2	5.4	17.3	10.7	14.0
2005	12.5	8.1	46.2	5.2	10.9	6.9	5.2	17.3	11.0	15.1
2006	13.0	7.8	44.2	5.5	10.3	8.0	5.4	17.5	13.0	15.4
2007	12.5	6.7	42.7	7.7	10.7	8.2	5.3	17.4	12.4	15.1
2008	12.3	8.2	44.4	6.9	10.8	8.2	5.5	18.7	12.2	15.4
2009	12.3	8.4	44.4	6.5	11.8	9.3	6.1	18.7	13.4	16.0

preventing severe forms of primary tuberculosis, which usually present as meningitis and miliary disease, but also as pulmonary disease in childhood. Its effectiveness against pulmonary disease in adults is more complex.[3] More recently, Trunz *et al.*,[4] using the data from the same trials included in previous reviews, estimated the efficacy of BCG vaccination against meningitis and miliary tuberculosis to be 73% and 77%, respectively. There is evidence that neonatal vaccination is very cost-effective in medium- and high-incidence settings on the basis of prevention of meningeal and miliary tuberculosis alone.[4] Several systematic reviews[3,4,16–18] have shown that efficacy is variable and have controversially produced pooled estimates of the efficacy of BCG vaccination from overall protective efficacy estimates of 50[16]–74% against mainly pulmonary disease if vaccinated in infancy and 86% for miliary disease or meningitis.[3] However, there is substantial heterogeneity in protection against mostly pulmonary disease between studies,[18] with estimated efficacy ranging from 0% in the South India trial to 84% in the MRC trial conducted in the UK during the 1950s and 1960s.[19–21] There is evidence that BCG vaccination does protect individuals who are already infected with *M. tuberculosis*.[22] Furthermore, there appears to be a strong association between vaccine efficacy (VE) and the latitude at which the study was conducted.[23] BCG vaccination has also been shown to be protective against other infections such as leprosy.[24] Only limited evidence on the efficacy of repeat BCG vaccination is available, largely consistent with the absence of additional benefit from further doses.[25,26]

Several hypotheses have been proposed to explain the different estimates of efficacy obtained in various BCG vaccination trials. These include the potential for different BCG strains to induce different levels of protection, and environmental factors, in particular variation between populations in their exposure to environmental mycobacteria. There appears to be a strong association between VE and the latitude at which the study was conducted,[23] and this has been interpreted as resulting from variations in prevalence of mycobacteria. A previous review concluded that the strain of BCG vaccine does not explain the differences in efficacy.[17] In addition, BCG vaccination may be better at protecting against certain forms of tuberculosis disease (such as primary disease) than other forms (such as reactivating disease).[3]

The idea of genetic differences in strains of *M. tuberculosis* explaining observed differences was initially suggested by Mitchinson *et al.*[27] as an explanation for the lack of effect observed in the Chingleput study,[28] but this was subsequently abandoned following further experiments in guinea pigs.[29] Although there is no new evidence that genetic difference between strains of *M. tuberculosis* is an important factor in explaining the observed heterogeneity, interest in this

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subject may re-emerge with more widespread deoxyribonucleic acid (DNA) fingerprinting of *M. tuberculosis*, as well as the advent of whole-genome sequencing as a tool for investigating outbreaks of tuberculosis.[30]

Recent data suggest that human genes influence susceptibility to tuberculosis. The exact mechanisms for genetic susceptibility still remain unclear. Several genes have been implicated, including those that control the immune response to *M. tuberculosis* [such as 5-hydroxycholecalciferol receptor polymorphisms, natural resistance-associated macrophage protein (NRAMP) and human leucocyte antigen (HLA) types]. This has led to the suggestion that genetic differences may explain some of the variation observed in the effect of BCG vaccination. Some observed non-significant racial differences in susceptibility also point to a genetic cause for the observed variation.[31] By contrast, UK data show that BCG vaccination provides protection among Asians in the UK,[32,33] despite the negative results from India.[19]

Several candidate vaccines are in various stages of clinical trials. The vaccines range from those that improve the current vaccine BCG to recombinant vaccines which can replace the BCG vaccination. The most promising appear to be booster vaccines to top up the immunity of existing BCG vaccination.[34] The process of developing a new tuberculosis vaccine is extremely complex, as the immune response produced by an effective vaccine needs to go beyond the level of the initial natural immune reaction of the body, which failed to prevent infection in the first place. An understanding of the mechanism by which BCG vaccination protects when it does, and what explains variation in protection, will allow further work to investigate why immunity appears to wane over time and for how long it remains at an appreciable level, and also inform the development of future vaccines.

It is recognised that various BCG vaccines result in different reactogenicity and tuberculin skin sensitivity. Some of this is thought to arise from differences in the numbers of viable and dead organisms as a result of processing techniques, as well as possible differences in vaccine strain. However, tuberculin sensitivity is not a correlate for protection.

A well-recognised limitation affecting studies of BCG vaccination efficacy, and future vaccines against tuberculosis, is the lack of a good marker of an effective immune protection.[35] This has implications for the development of new vaccines against tuberculosis. Current approaches include the use of assays to measure T-cell responses. There is little evidence that these measures are correlated with protective effects of vaccination. Ongoing research to better understand responding T-cell populations and the inclusion of functional bactericidal assays into clinical trials may improve this situation.[35] A further limitation of studies investigating VE is the lack of good animal models; most current available models allow the investigation of primary progressive disease rather that subsequent reactivation disease. The latter is the main cause of morbidity and mortality globally.

Evidence relating to the duration of protection by bacillus Calmette–Guérin vaccination

Until recently there was little evidence of protection lasting beyond 10 years.[7] This raises a concern in the UK given the move to neonatal BCG vaccination in at-risk populations in which risk is greatest in early adulthood. Although infant vaccination prevents serious childhood forms of tuberculosis, the incidence of tuberculosis is greatest in early adulthood. Recent additional follow-up of BCG vaccine studies, however, have reported protection (at a lower but measurable levels) lasting for decades.[5,6] An updated systematic assessment of duration of protection is required for evidence-based policy. The only published review[7] investigating the

duration of protection by BCG vaccination was unable to identify convincing evidence of a consistent pattern of protection over time, or of any evidence of protection against pulmonary disease lasting > 10 years. In that review, the pooled estimate of protection after 10 years was 14% [95% confidence interval (CI) –9% to 32%]. Considerable heterogeneity was observed between studies in the annual change in BCG VE with time since vaccination. There was also no relation between average annual change in efficacy and overall efficacy.

The heterogeneity observed in changes in BCG vaccine protection over time may result from a variety of factors (including those proposed as an explanation for differences in overall efficacy) or from differences in the rate of decline between studies with higher and lower initial protection. As with most vaccines, immunological memory may wane with time, leading to lower protection among the vaccinated. In addition, the inclusion in the study population of a large proportion of infected individuals at the outset (whom BCG vaccination would not be expected to protect) may lead to apparently lower protection in the initial period. Other explanations proposed include decreasing susceptibility among the unvaccinated as a result of continued exposure to environmental mycobacteria and an increase in the proportion of cases caused by reactivation or reinfection, against which BCG vaccination may not protect.

It is important to note, however, that the absence of evidence of an effect is not evidence of absence of an effect. Evidence on duration of the effect of BCG vaccination is needed to improve the reliability of estimates of the impact of BCG vaccination on disease. Furthermore, it would be important for cost-effectiveness analysis and would inform the rationale for booster doses of vaccine.

Current local and international policy

UK policy on bacillus Calmette–Guérin vaccination

Along with targeting risk groups from high tuberculosis burden countries, routine BCG vaccination of schoolchildren of aged 10–13 years has been part of the vaccination programme in the UK since 1953. In 2005, the Department of Health restricted the BCG vaccination policy to a risk-based approach, according to which children are eligible for vaccination in infancy if they have a parent/grandparent originating from a high-incidence country. Infants are also eligible if living in a part of the UK with a high incidence of tuberculosis (> 40 per 100,000). Some occupational groups, and uninfected contacts of tuberculosis cases, are also recommended to receive BCG vaccination.[36]

International policy comparison

The current global recommendation is to administer BCG vaccination at birth (or first contact with health services), in particular in developing countries. This advice is based, to a large extent, on consistent evidence that BCG vaccination protects against serious childhood forms of tuberculosis, whereas it does not consistently protect to a high degree against adult pulmonary tuberculosis. A limited number of countries have used repeated/booster BCG vaccinations in the past, for example Switzerland and Portugal (BCG vaccination in infancy and then at school entry or leaving), and in some Eastern Europe countries BCG vaccination has been given up to five times using a variety of criteria. The USA and the Netherlands have never recommended routine BCG vaccination in their tuberculosis control programmes.[37]

International Union Against Tuberculosis and Lung Disease criteria

The IUATLD has suggested criteria under which it may be reasonable for a country to move from routine BCG vaccination to selective vaccination of high-risk groups.[2] The IUATLD recommends that BCG vaccination be discontinued where:

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- an efficient notification system is in place *and*
- the average annual notification rate of smear-positive pulmonary tuberculosis is < 5 per 100,000, *or*
- the average annual notification rate of tuberculous meningitis in children of < 5 years of age is < 1 per 10 million population over the previous 5 years, *or*
- the average annual risk of tuberculous infection is < 0.1%.

Several low-incidence countries including the UK have met these criteria and have discontinued universal BCG vaccination and moved to a selective policy based on these criteria.

Bacillus Calmette–Guérin coverage

At the moment it is not possible to calculate BCG vaccination uptake for the UK overall, or by primary care trust (PCT) or local authority. This is because one cannot ascertain the number of vaccinated infants [only aggregate data on the doses of BCG vaccine given are collected nationally through Korner Code 50 (KC50) returns] or the number of eligible children. Furthermore, there is no estimate of children at risk based either on national guidelines in England or on specific PCT policies. The very limited, and imperfect, estimates carried out suggest variable coverage.

In addition to the KC50 returns, the national tuberculosis surveillance system started collecting data on the BCG vaccination status of tuberculosis cases in 2009. Data on previous BCG vaccination were available for 52% of cases in England, Wales and Northern Ireland (4473/8555) in 2009; 71% (3166) were reported to have previously received BCG vaccination.

Chapter 3

Systematic review methods

Introduction

There were four stages of literature retrieval and appraisal:

1. search of medical literature databases and hand-searching reference lists of relevant reviews
2. screening search hits for potential eligibility based on title and abstract
3. inclusion assessment of full papers
4. data extraction and bias assessment.

Search strategy

Search engines

Studies were systematically identified by searching electronic medical literature databases, trial registers, grey literature sources and relevant websites. The following databases were searched from inception/1920 to May 2009: MEDLINE (1950 to May 2009), MEDLINE In-Process & Other Non-Indexed Citations (1950 to May 2009), Old MEDLINE (1946–65), Excerpta Medica Database (EMBASE) (1980 to May 2009), Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Database of Systematic Reviews (CDSR), Database of Abstracts of Reviews of Effects (DARE), Health Technology Assessment (HTA) database and NHS Economic Evaluation Database (NHS EED) databases on The Cochrane Library Issue 2 2009, Science Citation Index (ISI) Web of Knowledge (1900 to May 2009), Bioscience Information Service BIOSIS (1985 to May 2009), Latin American and Caribbean Health Sciences Literature (LILACs) (1980 to May 2009), MEDCARIB (1920 to May 2009) and Cumulative Index to Nursing and Allied Health Literature (CINAHL) (1982 to May 2009). Between April 2009 and October 2009, additional databases were searched, including Index to Theses, System for Information on Grey Literature in Europe (SIGLE), Centre for Agricultural Bioscience International (CABI) Abstracts, Scopus, Article First, Academic Complete, Africa-Wide Information, Google Scholar, Global Health, British National Bibliography for Report Literature, http://clinicaltrials.gov and www.controlled-trials.com. Full details of the search engines used and websites consulted are documented in *Appendix 1*.

Search terms

Medical subject headings and text-word terms for the disease and the intervention were combined in a search strategy that was developed by an experienced information specialist (MB) and in discussion with tuberculosis specialists (IA, PF, DE, PS and ML). Disease terms included TB, tuberculosis, tubercle bacill*, *M. tuberculosis* complex, *M. bovis*, *M. africanum*, *M. canetti*, *M. microti* and *M. tuberculosis*. Terms for the intervention included BCG Vaccine, BCG, BCG Vacc*, BCG Imm*, bacillus calmette. The search strategy was modified as appropriate for use in the various databases. In order to maximise sensitivity we did not add any additional terms for study design and did not restrict on language. Details of the databases searched and search strategies used are described in *Appendix 1*. All references were downloaded into Reference Manager, version 11 (Thomson ResearchSoft, San Francisco, CA, USA), and de-duplicated.

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Hand-searching

Reference lists of included studies and previous reviews of BCG vaccine were screened and experts in the area of tuberculosis and BCG were contacted to identify additional studies. All studies previously included in Sterne and Rodrigues[7] were searched for and included.

Selection of papers

All stages of the review process were managed using a Microsoft Access 2007 (Microsoft Corporation, Redmond, WA, USA) database developed specifically for the review.

Abstract appraisal

Titles and abstracts of publications identified by the searches were independently assessed for potential inclusion by two members of the review team (LND and RB). Discrepancies were discussed and disagreements resolved through consensus or referral to a third reviewer (IA, PM, PW or JACS). Primary studies reporting on the efficacy of BCG vaccination in preventing tuberculosis diseases were considered potentially eligible. Full, peer-reviewed articles and non-peer reviewed articles (e.g. conference abstracts and dissertations) reporting primary data on the efficacy of protection by BCG vaccination in preventing tuberculosis disease were included. Studies available only as abstracts were included only if sufficient data were available from the abstract. Any reference nominated for inclusion by one or both assessors was retrieved for full paper inclusion assessment. When it was not possible to determine study eligibility from the title and/or abstract, the full manuscript was retrieved.

Inclusion criteria

Full-text papers were independently assessed for inclusion in the systematic review by three members of the review team (LND, RB and LP).

Studies that met the following criteria were included in the review:

- primary study of any design except case series and ecological studies
- appropriate study design: trial or observational, not ecological or case series
- study including both vaccinated and unvaccinated participants
- study reporting on protection against tuberculosis disease not infection
- study not including revaccination
- study reporting sufficient data to construct a 2×2 table or relevant outcome data.

Appendix 5 contains details of all papers that were excluded after initial review, with justifications.

Data extraction strategy

Data extraction methods

Data extraction of English-language papers was carried out by one reviewer (RB, LND or LP) and checked by a second reviewer (RB, LND or LP); any disagreements were resolved by consensus. If an agreement could not be reached, a third reviewer was consulted (IA, PM, PW or JACS). Foreign-language papers were reviewed by trained and supervised extractors (LND and LP) for final inclusion. Further cleaning during the data analysis phase was conducted (CA and LP). A baseline data extraction form was used to collect information on study design, participants' characteristics, dates of recruitment, tuberculosis infection, regional vaccination policies, and BCG vaccination procedures and properties (see *Appendix 2*).

Duplicate publications reporting results from the same study, or reporting additional data on the same study, were identified. Studies that were similar in terms of one or more of the following variables were identified: region of study, calendar-years of participant recruitment and authors. These were reviewed to determine whether or not they related to the same study. If two or more studies related to exactly the same population with no additional information, only one publication was included in the review, with the publication selected being the one that reported the most detail or was most recently published. If multiple publications related to the same study and provided additional details, all were included in the review but they were included as a single study to ensure that the same patients did not contribute more than one set of data to the meta-analysis. Publications were identified using their Reference Manager ID, and an additional 'study ID' was assigned to all publications; multiple publications relating to the same study had a single study ID.

Data on study results were extracted into a separate form to allow for multiple results to be extracted on a single study linked by study ID. Tuberculosis case definition, reported outcome, 2×2 data on BCG vaccination efficacy, summary results and any adjustments were also extracted.

Reviewers were not blinded to the names of study authors, institutions or publications. When case definition or background details were not present in the paper from which the results were extracted, but in another paper, this additional information was extracted with a note stating that it came from another publication. The decision was made not to contact authors of publications if 2×2 data of BCG vaccination efficacy or summary estimates because the majority of papers were published before 1973.

For studies assessing BCG vaccination status through scar reading, it was assumed that BCG vaccination was intradermal, and this assumption was recorded in the extraction form. Tuberculin sensitivity tests were recorded if they had been conducted, along with the strength of purified protein derivative (PPD) used and the size of the reaction and whether or not two-stage testing was used, which was used as the definition of stringent tuberculin testing.

Only studies of injectable BCG vaccination were extracted. All studies using oral BCG or non-BCG tuberculosis vaccines (e.g. vole bacillus, Savioli anti-tuberculosis vaccine or other heat-killed bacillus vaccines) were excluded. Only studies with a comparator group that had received no vaccination, placebo or other control were extracted.

Studies with outcome measures of tuberculosis disease and/or tuberculosis mortality reported in sufficient detail to construct a 2×2 table or relevant outcome data that were sufficient to calculate efficacy measures were extracted.

Studies were not extracted if they met any of the following criteria:

- Studies reporting on the efficacy of BCG vaccination in preventing *M. tuberculosis* infection, as measured by a positive interferon-gamma release assay (IGRA) or tuberculin skin test.
- Any study in which the outcome was only *M. tuberculosis* infection and not tuberculosis disease or mortality.
- Studies evaluating the effect of revaccination only. However, if a study reported on revaccination but it was possible to extract data on those that were vaccinated only once, it was included in the review.
- Studies examining the site or severity of tuberculosis disease among cases only in BCG vaccine recipients and non-recipients.

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Randomised controlled trials

Studies that attempted to allocate participants (even those in which the mode of allocation was not clearly described) were classified as clinical trials. This decision was based on the fact that all reviewed trials were conducted several decades ago, prior to the development of modern standards for the reporting of trials. A few studies allocated a proportion of participants and not another. When data could be separated, the allocated section was considered as a clinical trial and the non-allocated section extracted as a cohort. If data could not be separated, the whole study was recorded as a cohort.

Case–control studies

In assessing case–control study eligibility for extraction, we assessed whether the control subjects were likely to have come from the same population as cases (scope for selection bias was reduced). For hospital-based studies, selection bias was judged to be minimal (1) if there was no detail on the disease status of control subjects but there was no mention of the hospital being a specialist reference centre for a particular disease or (2) if < 30% of control subjects were admitted for diseases that might indicate a different health-seeking behaviour than cases and other control subjects.

If either of the above criteria was not fulfilled for hospital control subjects, the study was not classed as having control subjects from the 'same population', and publications were excluded. To avoid exclusion of infected subjects from vaccinated but not from unvaccinated groups, we excluded case–control studies conducted in populations vaccinated outside the neonatal period, if tuberculin testing was undertaken to exclude positive reactors before vaccination. This was unless all unvaccinated subjects (cases or control subjects) were also tuberculin tested at the age of recommended vaccination. This is because studies that were not able to restrict the study population to those not already infected at the age when they would have received vaccination may be biased because the number of tuberculosis cases in the unvaccinated group would be higher than normal, because those infected with tuberculosis would be over-represented among those unvaccinated, and thus would lead to an overestimate of the effect of the BCG vaccination.[38] Case–control studies with a matched design but no matched analysis were included to avoid losing useful information; this was addressed in the analysis.

Cohort studies

Cohorts were extracted only of children, vaccinated and unvaccinated, who were tuberculin tested before vaccination and were tuberculin negative.

Case population studies

A case population study is undertaken on the total population of a geographical area. Data on all cases emerging during the study period in the population of interest are ascertained through surveillance and all other persons in the population are regarded as 'control subjects'. The characteristics of cases occurring in the population (notably, their possible previous exposure to a given risk factor) are compared with those of the entire set of subjects in the population (supposing that demographic, health or drug use statistics for the whole population are available). The validity of this approach assumes the existence of a surveillance system capable of identifying all of the cases of an event within the population. The null hypothesis is that, in the absence of an association between risk factors and event, the odds of exposure are identical among cases and the rest of the population, barring sampling variations.[39]

Cross-sectional and outbreak studies

Cross-sectional studies are those in which data on BCG vaccination and tuberculosis outcome are collected at the same point in time, whereas outbreak studies refer to investigation of BCG

vaccination effectiveness that were undertaken using an observation study design following the occurrence of an outbreak of tuberculosis.

To be included case population studies, cross-sectional contact and outbreak studies had to account for tuberculin positivity in the design or analysis, or BCG vaccine must have been administered neonatally.

The detailed data extraction forms are included in *Appendix 2*.

Bias assessment criteria

As part of the extraction procedure, one reviewer (RB, LND or LP) independently assessed the risk of bias of each study. This was checked by a second reviewer (RB, LND or LP) and consensus reached in cases of disagreement. The risk of bias assessment of foreign-language publications was discussed and agreed on between the foreign-language extractor and supervising reviewer. Risk of bias assessments were extracted once per study (i.e. if a study was reported in multiple papers, a single bias assessment was completed). A risk of bias assessment form was developed for each study type. The results of this are listed in *Appendix 2*.

Clinical trials

The Cochrane Risk of Bias tool was used to assess bias in RCTs and quasi-randomised trials. Studies in which the mode of allocation was alternation or birth date were considered 'quasi-randomised' and the method of sequence generation was extracted as 'alternation', 'birth date', 'employee number' or any other quasi-method used.

If a placebo vaccination was given, the study was considered blinded only at the point of vaccination, and the patient and vaccinator were considered adequately blinded. The nature of the participants was not taken into account while assessing blinding, i.e. no account was taken of whether subjects were adults, such as nurses, or infants.

Specific quality assessment criteria 'Diagnostic Detection bias' were used for tuberculosis trials based on a paper by Clemens *et al.*[40] This was assessed a priori from a combination of two fields: the method of follow-up (active, i.e. regular chest radiography or active forms of follow-up, or passive, i.e. obtaining cases from routine surveillance) and whether or not the outcome assessors were blinded to the BCG vaccination status of the patient. Studies with passive case finding and no blinding of outcome assessors with regards to the vaccination status of participants were considered to have a higher risk of detection bias. Other studies were considered to have a lower risk of diagnostic bias.

Observational studies

Observational studies were assessed for bias using criteria that we developed, with risks of bias qualified as high, low or unclear.

Case–control studies

Following discussion within the BCG systematic review group, rules were agreed and case–control studies were assessed for risk of bias using the following criteria:

- Were BCG vaccination definitions the same for cases and control subjects?
- Was disease status blinded to BCG assessors?
- Were cases diagnosed assessed independently of vaccination status?

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For case–control studies with a matched design, a criterion was developed based on whether or not matching was performed in the analysis, as an unmatched analysis may have introduced some bias.

Cohort studies

Cohort studies were assessed with regard to risk of loss to follow-up bias, treatment allocation concealment, case ascertainment bias and incomplete case ascertainment bias.

Case population studies

Case population studies were evaluated based on whether or not cases and the populations were consistent in terms of geography, time and age, as well as according to whether case ascertainment was blind to vaccination status, disease status was blind to BCG assessors and methods of case ascertainment were the same for vaccinated and unvaccinated.

Cross-sectional studies

Cross-sectional studies were assessed on whether BCG vaccination definitions were the same for cases and control subjects, whether disease status was blinded to BCG assessors and whether cases and control subjects were assessed independently of vaccination status.

Statistical analysis

Types of study

Study design affects the robustness of findings owing to differing ability to control for confounding or to minimise bias. All analyses were therefore stratified according to study design, as follows:

1. clinical trials
2. observational studies:
    i. case–control studies
    ii. cohort studies
    iii. case population studies (studies in which cases were compared with the general population rather than with individual control subjects)
    iv. cross-sectional studies in the general population
    v. cross-sectional studies in contacts.

Analysis of single studies

Data for each study were checked to identify possible data entry problems. For each study, the rate ratio for vaccinated compared with unvaccinated individuals was derived for the longest duration of follow-up (see *Table 3*), with 95% CI. For case–control and cross-sectional studies, odds ratios (ORs) (which were assumed to approximate rate ratios in the general population) were derived. If sufficient data were available, published estimates were compared with those directly calculated from summary data (e.g. 2×2 tables) and if data existed for two or more time periods then estimates of effect [ORs, rate ratios or risk ratios (RRs)] and 95% CIs were plotted over time. If published results from cohort studies were shown as rate ratios or VE, these were used directly. If person-years (PYs) were provided, calculations of the rate ratios and CIs were based on these. If data were in the form of a 2×2 table, the calculated rate ratios and CIs made no adjustments for losses to follow-up, and so assumed a fixed follow-up period. If some of the randomised groups had no cases, 0.5 was added to calculate RRs. Poisson regression was used to quantify changes in rate ratios with time, by estimating the increase in log-rate ratios per unit time. We also compared rate ratios between fixed time periods (e.g. efficacy in the first 10 years

since vaccination compared with efficacy beyond 10 years). If data permitted, rates of change were examined for non-linearity. RCTs were assessed according to a variable combining age at vaccination and stringency of tuberculin testing protocols prior to vaccination. This variable contained studies of neonatal vaccination, in which participants are considered to be tuberculin negative prior to vaccination, regardless of prior tuberculin testing. Other vaccination ages were classified according to whether or not tuberculin testing was stringent. A stringent tuberculin testing protocol was defined as a two-stage testing, with retesting of initially tuberculin-negative participants using a higher dose of tuberculin to confirm negativity before vaccination.

A non-stringent tuberculin testing study was defined as one that did not exclude participants based on tuberculin testing prior to vaccination or excluded subjects based on a single round of tuberculin testing. Although the strength and type of PPD used differed between studies, our criteria of 'Stringent' testing, which includes a two-stage testing with retesting of initial non-reactors with a stronger dose of tuberculin, allowed exclusion of participants previously sensitised with *M. tuberculosis*. (The strength and type of PPD ranged from 1 TU of RT23 and Tween 80 in 0.1 ml on the volar surface of the left forearm, with no information on the time of reading to a two-stage testing protocol with intracutaneous injection of 0.00002 mg PPD-S from Phipps Institute into the forearm, followed by 0.005 mg PPD-S for non-reactors to the first dose, both read at 48 hours.)

Bacillus Calmette–Guérin strain

Randomised controlled trials were analysed according to strain of BCG used. Studies that provided information on the strain of BCG used were classified using information from Brewer *et al.*[17] to place within a phylogenetic group defined by Brosch *et al.*[41] When the BCG strain was not provided, efforts were made to identify the strain lineage from Brewer *et al.*[42] and other literature sources.[43] As the greatest number of trials reporting which BCG strain was used reported on efficacy for all types of tuberculosis not separately by site, this analysis was performed only for all tuberculosis morbidity outcomes, and not for pulmonary tuberculosis alone.

Meta-analyses

Overall efficacy by categories of tuberculosis outcomes

Results from each study, together with both fixed- and random-effects summary effect estimates, were displayed in forest plots. Meta-analyses were carried out using (log-) rate ratios, and results were displayed both as rate ratios and as VE (= 1 – rate ratios) if this was appropriate. Differences between fixed- and random-effects estimates suggest that there are differences between RRs estimated from smaller and larger studies.

In some studies, vaccination was restricted to individuals who were screened for *M. tuberculosis* infection and confirmed uninfected, whereas the control group may have included individuals who were not eligible for vaccination. Studies in which an attempt was made to adjust estimated efficacy for the tuberculin-positive population were included in meta-analyses. Studies that did not account for the tuberculin-positive population were reported separately, and excluded from meta-analyses.

Variation in efficacy according to characteristics of individuals and studies

Whenever possible, differences in efficacy according to characteristics of individuals (e.g. gender or age) were estimated by comparing efficacy [using ratios of RRs (RRRs)] between subgroups of individuals within studies. Investigation of the reason behind variation in efficacy in different studies used meta-regression, and quantified how much of the heterogeneity in estimates of efficacy was explained by selected factors.

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Differences in efficacy between subgroups of studies (e.g. those classified as at low or high risk of bias, or those conducted at different latitudes) were quantified using random-effects meta-regression to estimate RRRs. Heterogeneity (differences between the true vaccine effects in the different studies) was quantified by estimating the between-study variance tau-squared (τ^2). This is based on the assumption that the distribution of the true vaccine effects is normal: τ^2 corresponds with the variance of this distribution. To illustrate the meaning of this quantity, *Table 2* shows the ratio of the effect (e.g. RR or rate ratio) at the 90th centile of the distribution to the effect in a study at the 10th centile.

In forest plots and meta-analyses, τ^2 was estimated using the method-of-moments estimator proposed by DerSimonian and Laird. Within meta-regression analyses, τ^2 was estimated by restricted maximum likelihood, using the metareg command in Stata. We conducted both univariable and multivariable meta-regression analyses: results from multivariable analyses were interpreted with caution because the number of studies was typically small compared with the number of study characteristics of interest.

We examined variation in efficacy according to the following characteristics.

Latitude of study location

Latitude of study location was stratified into groups of 10° latitude either side of the equator. Meta-regression analyses collapsed these into 20° latitude groups. Forest plots stratified by 20° latitude, for reference, are found in *Appendix 6*.

Age at vaccination and stringency of tuberculin testing

Bacillus Calmette–Guérin VE is known to vary widely with age at which vaccination is given. Studies were classified depending on whether vaccination was given in infancy, at school age or at any other age. The latter category includes studies in which vaccination was given to participants of all ages.

Tuberculin sensitivity testing used for exclusion of participants prior to enrolment into a randomised clinical trial was classified into two categories as 'more stringent' and 'less stringent'. Studies with more stringent testing included those in which vaccination was neonatal, assuming that neonates were not infected with *M. tuberculosis* before randomisation to vaccination or control groups. Studies qualified as 'less stringent tuberculin testing' and 'no tuberculin testing' were combined into one category for the purposes of presenting the forest plots and meta-regression.

Vaccine strain

Bacillus Calmette–Guérin strain variation in VE was examined in terms of phylogeny and attenuation lineage, both in a forest plot and as a scatterplot of the vaccine efficacy estimates for study by year or study start, grouped by BCG strain lineage. Using the review by Brewer *et al.*,[17]

TABLE 2 Ratio of the effect at the 90th centile of the distribution to the effect in a study at the 10th centile at each level of between-study variance τ^2

Variance τ^2	Standard deviation τ	Ratio of effect in study at 90th centile to study at 10th centile
0.02	0.141	1.44
0.05	0.224	1.77
0.10	0.316	2.25
0.20	0.447	3.15
0.40	0.632	5.06

all studies were classified into a lineage group, the molecular basis of which was classified by Brosch *et al.*[41] Studies with strains not falling into any strain lineage family were each analysed as a separate group. Studies in which the strain used was not reported were classified into a separate 'not reported' group.

Risk of bias in the different study designs

The study-specific risk of bias criteria were analysed in the meta-analysis. Criteria for which there were very few details (e.g. all low risk of bias but for one study) were not included in the meta-analyses but presented in the appendices.

Time since vaccination

To account for the stringency of tuberculin testing at baseline, we compared VE during the first 5 years with efficacy after 5 years since vaccination, within two strata of tuberculin testing stringency.

Gender

Data presented on efficacy according to gender were presented if these were available.

Human immunodeficiency virus status

Data on efficacy according to HIV infection status were presented if these were available.

Duration of protection

Analyses of the duration of protection by BCG vaccination included only studies in which efficacy can be estimated separately according to time since vaccination, age at vaccination, or both. Changes in efficacy with time since vaccination (or age for infant vaccination) were estimated within studies and these estimates were then combined in meta-analyses. Random-effects Poisson regression was used to estimate rates of change in the duration of protection with time, allowing for between-study heterogeneity. If data permitted, we examined evidence for non-linearity in the rate of waning protection, for example by including a quadratic term for time. These models were also used to examine associations of study characteristics with the extent and duration of protection. We also derived indirect estimates of changes in efficacy, for instance by comparing estimates from case–control studies in adults and children who were vaccinated at birth. However, such estimates should be interpreted with caution because of the potential for confounding by other study characteristics (ecological fallacy). Decisions were made not to plot studies in the duration plots for which there was no specified age at vaccination and/or age at outcome assessment. Time since vaccination was broken down into four categories: 0–5 years after vaccination, 5–10 years, 10–15 years, ≥ 15 years after vaccination. However, some studies present data only for 0–5 years and are therefore missing from these plots.

Design-specific issues: controlled trials

For each outcome in each controlled trial, we classified results as at low, unclear or high risk of bias, based on domain-specific assessments of risk of bias conducted using the Cochrane Collaboration's Risk of Bias tool. We compared estimates of extent and duration of protection according with risk of bias. We reported sensitivity analyses restricted to studies assessed as at low, and low or unclear, risk of bias if this was feasible.

Tuberculin sensitivity testing was assessed only in trials; cohort studies were included only if all participants were tested before vaccination.

Only trials reports contained sufficient data on BCG strain to allow analyses on the variation of efficacy by strain lineage.

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Design-specific issues: observational studies

Meta-analyses of crude and adjusted rate ratios were derived separately for each observational study design. An a priori minimum set of confounders to designate a rate ratio as adjusted was agreed based on consideration (blind to study results) of a tabulation of all the confounders used in each study, stratified by study design. At minimum, results were not considered adjusted unless they were controlled at least for age and sex.

We reported sensitivity analyses restricted to studies that adjusted for socioeconomic status (SES) in their analyses.

Case–control studies

Further analyses were made of case–control studies that account for SES in adjustment or matching. Factors that may bias estimates from case–control studies were examined by displaying the results in forest plots stratified by these factors and their effects were estimated in meta-regression analyses. These factors include whether a matched design had been ignored in the analysis (giving 'crude' estimates from studies that have a matched design), and whether the control subjects were sampled from the same population as the cases.

Cohort studies

Analyses were made of cohort studies that account for SES in adjustment.

Case population studies

The analyses were broken down only by latitude and age at vaccination for case population studies.

Cross-sectional studies

Cross-sectional contact studies were not combined with cohort contact studies.

Issues of interpretation

We investigated whether it is possible to classify regions or settings according to categories of VE (e.g. low, medium, high), based on whether it is possible to identify subgroups of settings and studies within which the effect of BCG vaccination appears relatively consistent.

All meta-analyses were carried out using the metan and metareg commands for Stata version 11.0 (StataCorp LP, College Station, TX, USA).

Chapter 4

Results

Studies included in the review

A total of 21,030 titles and abstracts were identified, through database searches and reference screening, and screened. A total of 847 articles were considered potentially relevant, based on title and abstract; attempts were made to retrieve all the full papers. Full-text copies of 800 articles selected from potential inclusions were retrieved (*Figure 2*). It was not possible to retrieve or obtain further information on 48 articles. This was mainly due to incorrect referencing in the databases searched, which made the references impossible to identify and retrieve. A few references were requested from specific libraries but were not identified or retrieved and were classified as unobtainable owing to time limits on the project.

In total, 211 articles met the inclusion criteria for this review, of which 60 were not published in English. The included articles reported data on 132 individual studies: several papers were published in relation to the same groups of patients. These were grouped together and data were

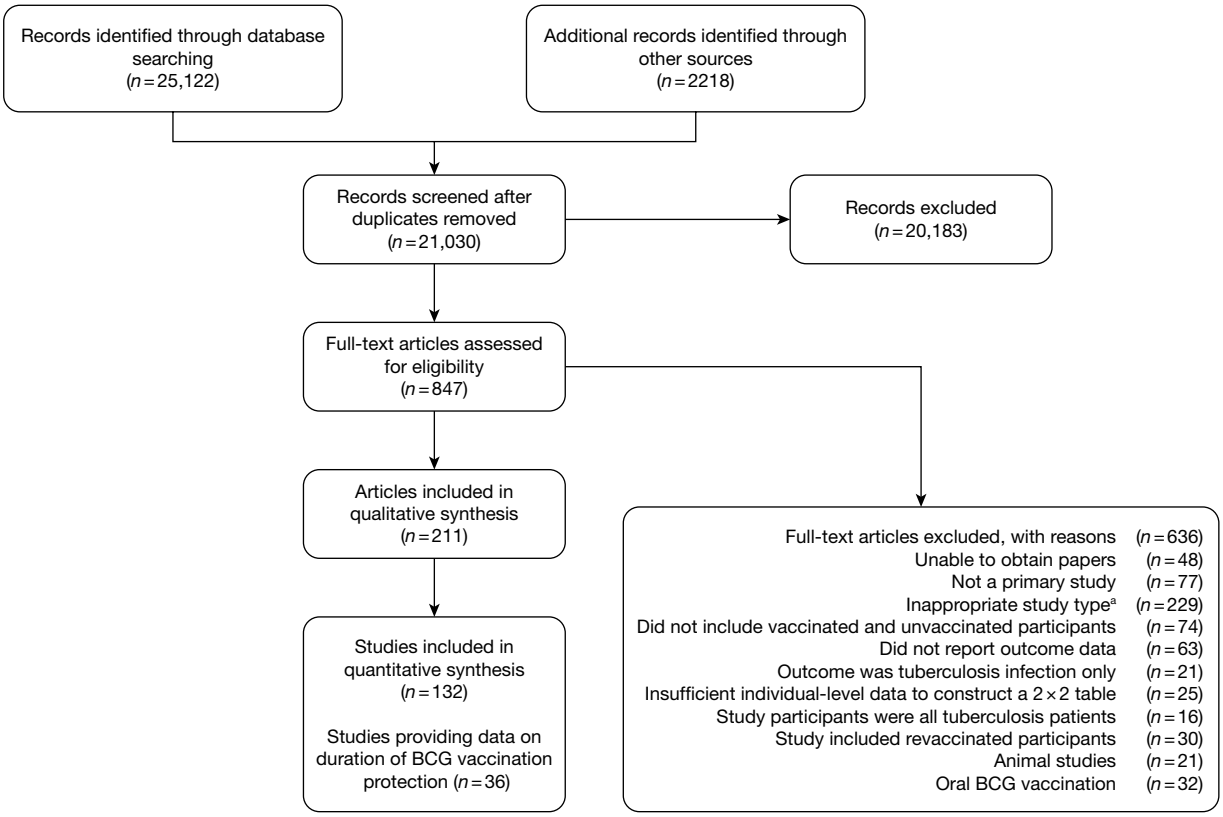

FIGURE 2 Flow diagram outlining the screening process for the review of BCG vaccination duration and efficacy. a, Inappropriate study types include ecological studies, case-series, and case–control studies with inappropriate vaccination and tuberculin testing protocols, in which tuberculin testing was performed prior to vaccination and only non-reactors were vaccinated or where control subjects were not considered to come from the same populations from which cases arose.

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extracted from the most informative or most recent article. Forty-eight of these additional papers provided further information on the studies, and 37 provided duplicate data on the 132 studies.

Overview of available evidence

The characteristics of the individual included studies are shown in *Appendix 3*.

A total of 132 studies provided data on the efficacy of BCG vaccination against tuberculosis outcomes. The included studies were categorised into six design types: 21 randomised control trials, 26 case–control studies, 38 cohort studies, 20 case population studies, 19 cross-sectional studies and eight outbreak studies.

Thirty-six studies gave sufficient data to estimate the duration of BCG vaccination protection. A majority of studies (51) provided data on pulmonary tuberculosis as a specific outcome, 13 of which gave data on BCG vaccination protection duration. Meningitis was an outcome reported in 34 studies, while 13 reported on miliary tuberculosis. Twenty-six studies provided data on extrapulmonary tuberculosis outcomes (with five giving sufficient data to evaluate duration of BCG vaccination protection), and 19 studies reported tuberculosis mortality as an outcome.

Randomised control trials

Fifty-eight references gave information on 21 individual RCT studies, with 18 references providing sufficient original data (three articles provided data on two separate studies). Thirty articles gave additional data on these 21 trials and 10 provided duplicate data. Quasi-randomisation was used in 13 trials, individualised randomisation in two, and the remaining six studies provided no details on the method of randomisation.

Eighteen trials provided data on pulmonary tuberculosis, six provided outcome data on tuberculosis meningitis and/or miliary tuberculosis (five on both outcomes and one on miliary tuberculosis only), six studies also provided outcome data for extrapulmonary tuberculosis (not recorded as tuberculosis meningitis or miliary tuberculosis) and six studies gave data on BCG vaccination efficacy against tuberculosis mortality. Thirteen of the trials were conducted in the USA and were initiated between 1933 and 1950.[5,12,15,44–50] Four trials were initiated in India between 1950 and 1988 (the latter is the publication date).[28,51–53] One trial each was conducted in Canada (started in 1933),[13] the UK (1950),[14] South Africa (1965)[54] and Haiti (1965)[55] *(Table 3)*.

The trial with the smallest number of participants ($n = 35$) was the US Mental Health Patients study.[44] The study with the most participants, with 73,459, was Chingleput.[28] The average number of participants was 14,826.

Case–control studies

Thirty-five articles[32,33,56–88] provided data on 26 case–control studies,[32,33,56–79] seven gave additional data[80–86] and two were duplicates.[87,88] Seven examined pulmonary tuberculosis,[56,62,66,70,72–74] 14 examined tuberculosis meningitis and/or miliary tuberculosis[57–62,66–69,71,72,74,76] (11 provided data only on tuberculosis meningitis[57–62,66–68,71,74]), seven provided data on other extrapulmonary tuberculosis outcomes,[56,62,66,72–74,78] and no case–control studies provided tuberculosis mortality data. Seven of the case–control studies were initiated in India between 1981 and 2005 (the latter is the publication date),[56–62] with two studies started in each of the UK (1965; 1991),[32,33] Canada (1975; 1979),[63,64] Thailand (1980; 1987)[65,66] and Brazil (1975; 1981)[67,68] and one study each in Papua New Guinea (1975),[69] Colombia (1977),[70] Republic of Korea (1979),[71] Argentina (1981),[72] Indonesia (1981),[73] Myanmar (1983),[74] Nepal (1983),[75] Japan (1988),[76] Saudi Arabia (1991),[77] Mexico (1991)[78] and Madagascar (1992).[79]

TABLE 3 Maximum duration of follow-up, latitude of study location and age at vaccination/stringency of tuberculin testing for all RCTs

Trial	Author	Duration	Years	Latitude	Age at vaccination and tuberculin testing stringency
Saskatchewan infants[13]	Ferguson	15 years	1933–48	>50°	Neonatal
New York infants, randomised[12]	Levine	11 years	1933–44	40–50°	Neonatal
Native American[5]	Aronson	63 years	1935–98	40–50°	School-age vaccination – stringent testing
Chicago Infants CCH[48]	Rosenthal	23 years	1937–60	40–50°	Neonatal
Turtle and Rosebud infants[45]	Aronson	8 years	1938–46	40–50°	Neonatal
Chicago medical students[46]	Rosenthal	4 years	1939–43	40–50°	Other age vaccination – stringent testing
Chicago nurses[47]	Rosenthal	5 years	1940–45	40–50°	Other age vaccination – stringent testing
Chicago Infants (TT HH)[48]	Rosenthal	12 years	1941–53	40–50°	Neonatal
Ida B Wells housing project[44]	Rosenthal	13 years	1942–56	40–50°	School-age vaccination – stringent testing
US mental health patients[44]	Rosenthal	4 years	1944–48	30–40°	Other age vaccination – stringent testing
Illinois mentally handicapped[50]	Bettag	12 years	1947–59	40–50°	Other age vaccination – stringent testing
Georgia (school)[49]	Shaw	20 years	1947–67	30–40°	School-age vaccination – stringent testing
Puerto Rican children[15]	Palmer	19 years	1949–68	10–20°	School-age vaccination – non-stringent testing
Madanapalle[53]	Frimodt-Moller	21 years	1950–71	10–20°	Other age vaccination – stringent testing
Georgia/Alabama[15]	Palmer	20 years	1950–70	30–40°	Other age vaccination – non-stringent testing
MRC[14]	MRC	20 years	1950–70	>50°	School-age vaccination – stringent testing
African gold miners[54]	Coetzee	3 years	1965–68	20–30°	Other age vaccination – non-stringent testing
Haiti[55]	Vandivière	3 years	1965–68	10–20°	Other age vaccination – non-stringent testing
Chingleput[28]	TBPT	15 years	1968–83	10–20°	Other age vaccination – non-stringent testing
Bombay infants[52]	Mehta	30 months	1976[a]	10–20°	Neonatal
Agra[51]	Mehrotra	5 years	1988[a]	20–30°	School-age vaccination – non-stringent testing

CCH, Cook County Hospital; TBPT, Tuberculosis Prevention Trial; TT HH, tuberculous households.
a Date of study publication was used if study start date was not available.

The case–control study with the smallest number of participants ($n = 63$) is the Delhi 1989–90 study,[57] whereas the largest case–control study (6293 participants) was the Saudi Arabian study.[77] The case–control studies had an average of 714 participants.

Cohort studies

A total of 65 papers[6,7,12,24,88–148] provided information on 38 individual cohort studies (13 prospectively recruited participants,[6,24,89,91,93,94,101,104,109,117,118,122,123] 20 did this retrospectively[7,90,92,95,96,100,102,103,105–108,110–116,119] and five were cohort studies in contacts of tuberculosis patients[97–99,120,121]). Eleven papers[12,125,132–138,140,147] gave additional data on these studies and 16[88,124,126–131,139,141–146,148] provided duplicate data. Twelve cohort studies[3,24,100,105,108,109,115–117,119,122,149] provided outcome data on pulmonary tuberculosis, whereas six[94,108,109,113,123,149] provided data on tuberculosis meningitis and/or miliary tuberculosis (four[94,109,123,149] on tuberculosis meningitis and one[108] on miliary tuberculosis only). Eight cohort studies[6,24,101,108,109,116,119,149] gave data on other forms of extrapulmonary tuberculosis, and nin e[91,94,109,111,113,114,116,122,123] had tuberculosis mortality as an outcome. The USA contributed seven cohort studies (initiated between 1927, the earliest date of a BCG study, and 1950),[89–95] while five studies were started in both the UK (between 1955 and 1985),[86–100] and in Norway (between 1927 and 1956),[101–104,150] four studies in Germany (between 1947 and 1954)[105–107,149] and three studies in France (between 1947 and 1956)[108–110] (*Table 4*). One cohort study was identified as undertaken in each of the following countries: Denmark (1936),[151] Italy (1938),[111] the Netherlands (1939),[102] Sweden (1941),[113] Uruguay (1943),[114] Ireland (1949),[115] Morocco (1950),[116] Algeria (1950),[117] Poland (1965),[118] Malawi (1979),[24] Jordan (1980),[119] Republic of Korea (1989),[120] Central African Republic (1989)[121] and Brazil (1996).[6] The smallest cohort study is the Dublin nurses,[115] with a

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TABLE 4 Maximum duration of follow-up of all cohort studies

Cohort studies	Author	Duration
Ancona children[111]	Mariotti	23 years
Bangui contacts[121]	Lanckriet	7 years
Bornholm[122]	Olsen	9 years
Boston nurses[84]	DeFriez	16 months
Bougie schoolchildren[117]	Sarrouy	3 years
Brazil REVAC[6]	Barreto	6 years
Chicago medical students[90]	Geiseler	43 years
Dublin nurses[115]	Counihan	6 years
Dusseldorf children[149]	Trub	15 years
Dutch nurses[112]	Bergsma	11 years
Edinburgh 1977 contacts[97]	Capewell	5 years
Edinburgh[96]	Capewell	8 years
Edinburgh contacts[98]	Rubilar	10 1/2
Hamburg children[105]	Ehrengut	7 years
Hesse 23 districts[106]	Daelen	5 years
Jordan[119]	Batieha	15 years
Seoul contacts[120]	Jin	2.5 years
Lyon students[108]	Despierres	7 years
Karonga[24]	Ponnighaus	10 years
Morocco children[116]	Gaud	2.5 years
New York infants[91]	Kereszturi	6 years
France schoolchildren[109]	Gernez-Rieux	20 years
Norway 1947[101]	Borgen	2 years
Norway[102]	Tverdal	10 years
Norwegian deported[103]	Oeding	
Oslo nurses[123]	Heimbeck	2 years
Philadelphia nurses[92]	Chakravarty	2 years
Richmond infants[93]	Kendig	7 years
Rzeszow children[118]	Kubit	
Siblings cohort[107]	Liebknecht	15 years
Strasbourg students[110]	Vaucher	3 years
Swedish conscripts[113]	Dahlstrom	6 years
Trysil Norway[104]	None	3 years
UK contacts[99]	Horne	2 years
Medical students UK[100]	Verney	3 years
Uruguay infants[114]	Gomez	10 years
US physicians[95]	Barrett-Connor	24 years
Virginia infants[94]	Kendig	20 years

REVAC, Brazilian revaccination study.
Date of study publication was used if study start date was not available.

total of 80 participants enrolled. The largest cohort study is the Norway 1956–73[93] study, with 1,047,550 participants enrolled.

Case population studies

In total, 23 references were included,[152–174] providing data on 20 case population studies (*Table 5*). One paper[159] gave details on three studies, four articles[171–174] provided additional data on these studies, and one[161] gave duplicate data. Four[156,158,160,162] of the 20 case population studies provided

TABLE 5 Maximum duration of follow-up of all case population studies

Study name	Author (year)	Case-finding duration	Case-finding start and end dates
Malaysia 0- to 19-year-olds[159]	WHO	3 years	1977–9
Malaysia meningitis[159]	WHO	3 years	1976–8
Korea neonatal[159]	WHO	1 year	1976–6
Britain surveys[153]	Sutherland	1 year	1973–3
		1 year	1978–8
		1 year	1983–3
Birmingham schoolchildren[152]	Springett	2 years	1954–8
		7 years	1956–62
		8 years	1962–9
Israel neonatal[162]	Zilber	4 years	1956–79
Canadian nurses[156]	Burril	11 years	1969–79
Brazil meningitis[166]	Martins	1 years	1983–3
South Asian adults[155]	Chaloner	8 years	1982–2000
Quebec meningitis[157]	Frappier	9 years	1949–56
Taiwan meningitis[169]	Chan	6 years	2002–7
Bydgoszcz children[160]	Krzyszkowska	4 years	1950–3
Singapore schoolchildren[165]	Chew	1 year	1972–2
France schoolchildren[168]	Schwoebel	1 year	1990–0
Manchester hospital[154]	Curtis	6 years	1975–80
Czechoslovakia meningitis[170]	Votjek	3 years	1954–8
Quebec pulmonary[158]	Frappier	5 years	1956–61
Ireland survey[167]	Kelly	5 years	1989–91
Cologne children[164]	Lotschert	10 years	1967–76
Hungary 4 to 14-year-olds[163]	Lugosi	1 year	1964–4

data specifically on pulmonary tuberculosis and five[157,159,166,169,170] on tuberculosis meningitis. Four case population studies were identified from the UK (started between 1956 and 1983),[152–155] three in Canada (1949; 1969),[156–158] two in Malaysia (1976; 1977)[159] and one each for Poland (1950),[160] Czechoslovakia (1954),[161] Israel (1956),[162] Hungary (1964),[163] Germany (1967),[164] Singapore (1972),[165] Republic of Korea (1976),[159] Brazil (1983),[166] Ireland (1986),[167] France (1990)[168] and Taiwan, Province of China (2002).[169]

Cross-sectional studies

Twenty-two articles were identified[175–196] and 12 provided original data on cross-sectional studies in the general population,[176,180–187,190,191,193] seven gave data on studies in contacts of tuberculosis patients,[175,177–179,188,189,192] and two gave duplicate data.[194,196] In total, 19 cross-sectional studies provided data on efficacy of BCG vaccination:[175–196] six on pulmonary tuberculosis,[178,181,182,187,189,193] six on the combined outcome of tuberculosis meningitis and/or miliary tuberculosis[177,181,182,184,186,190] (three reported data on both forms of tuberculosis,[177,186,190] two only on tuberculosis meningitis[184,186] and one on miliary tuberculosis only[181]); two studies reported data on other forms of extrapulmonary tuberculosis[181,182] and two on tuberculosis mortality.[186,187] Two studies were conducted in each of Spain (starting in 1969 and 1991*),[175,176] Togo (1988 and 1986*)[177,178] and Brazil (between 1988 and 2003).[179,180] Single studies were conducted in Japan (1949),[181] Belgium (1950),[182] Yugoslavia (1959),[183] France (1965),[184] Italy (1967),[185] India (1968),[186] Kenya (1979),[187] Thailand (1981),[188] Egypt (1986*),[189] South Africa (1999),[190] Colombia (2001),[191] Russia (2003)[192] and Lebanon (2004)[193] (*date of study publication was used if study start date was not available). The smallest cross-sectional study was the Naples classroom,[185] with 33 participants, whereas the greatest number of participants (4,264,400) was in the Bas-Rhin meningitis[184] study.

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Outbreak studies

Nine articles[197–205] provided data on eight outbreak studies, with one article[200] providing data on two separate outbreaks, and two articles[206,207] giving duplicate data. Three of these studies[197,198,201] provided data on pulmonary tuberculosis, one[199] on meningitis and miliary tuberculosis and one[200] on extrapulmonary tuberculosis. Three outbreaks occurred in Ireland between 1991 and 2009,[197–199] two in Canada (2004),[200] and one each in Sweden (1947),[201] Norway (1947)[202] and Denmark (1957).[203] The smallest outbreak included, Community I Canada outbreak,[200] involved only 40 individuals, whereas the Donegal school outbreak[199] involved a total of 1175 school children.

Efficacy of bacillus Calmette–Guérin vaccination

Results on the efficacy of BCG vaccination are divided first by study type (RCTs and observational studies), and within each study type are presented by type of tubercular disease/mortality outcome (pulmonary tuberculosis, all tuberculosis outcomes, meningeal and/or miliary tuberculosis, extrapulmonary tuberculosis and tuberculosis mortality) where results for these outcomes were available. Within each outcome, results are stratified according to study and participant characteristics. Meta-regression results for each variable examined, where available, are provided below the corresponding forest plot and refer to the summary table of meta-regression analyses performed, which can be found at the end of each tuberculosis disease/mortality outcome section.

Randomised control trials

Pulmonary tuberculosis

This section of the report first presents overall results, followed by results stratified according to study characteristics (latitude, age at vaccination/stringency of tuberculin testing and risk of diagnostic detection bias). Unstratified analyses are ordered by year trial started.

Figure 3 shows the results of 18 trials evaluating the efficacy of BCG vaccination against pulmonary tuberculosis, listed by date of study start. Nine studies were conducted in the USA,[5,44,45,48–50] four in India,[28,51–53] and the others in Canada,[13] Puerto Rico,[15] the UK,[14] Haiti[55] and South Africa.[54] There was substantial variation in the protective efficacy of BCG vaccination against pulmonary tuberculosis, ranging from substantial protection, as in the UK MRC[14] trial [rate ratio 0.22 (95% CI 0.16 to 0.31)], to absence of clinically important benefit, as in the large Chingleput[28] trial [rate ratio 1.05 (95% CI 0.88 to 1.25)].

Stratified analysis by latitude (10°), ordered by year study started

Figure 4 shows estimated effects of BCG vaccination against pulmonary tuberculosis, stratified by latitude of the study location (10° bands either side of the equator). In general, the protective effect of BCG vaccination was either absent or low in studies conducted close to the equator, whereas there was reasonably consistent evidence of good protection observed in studies conducted at latitudes exceeding 40°. Relatively high protection was observed in studies (Saskatchewan Infants[13] and MRC[14]) conducted above 50° latitude: rate ratio 0.22 (95% CI 0.16 to 0.30), corresponding to a VE of 78% (95% CI 70% to 84%). Latitude explained a substantial amount of the between-study variation in the protective effect of BCG vaccination.

Meta-regression analysis

Based on univariable meta-regression analyses, stratification on latitude appeared to explain 70% of the between-study variation (τ^2 values before and after stratification using 20° strata were 0.284 and 0.086, respectively) (*Table 6*). There was evidence ($p = 0.008$) that efficacy varied with latitude: rate ratios for studies between 0° and 20° latitude and between 20° and 40° latitude were, respectively, 2.45 (95% CI 1.42 to 4.21) and 2.17 (95% CI 1.14 to 4.10) times that of studies >40° latitude (thus VEs are correspondingly lower).

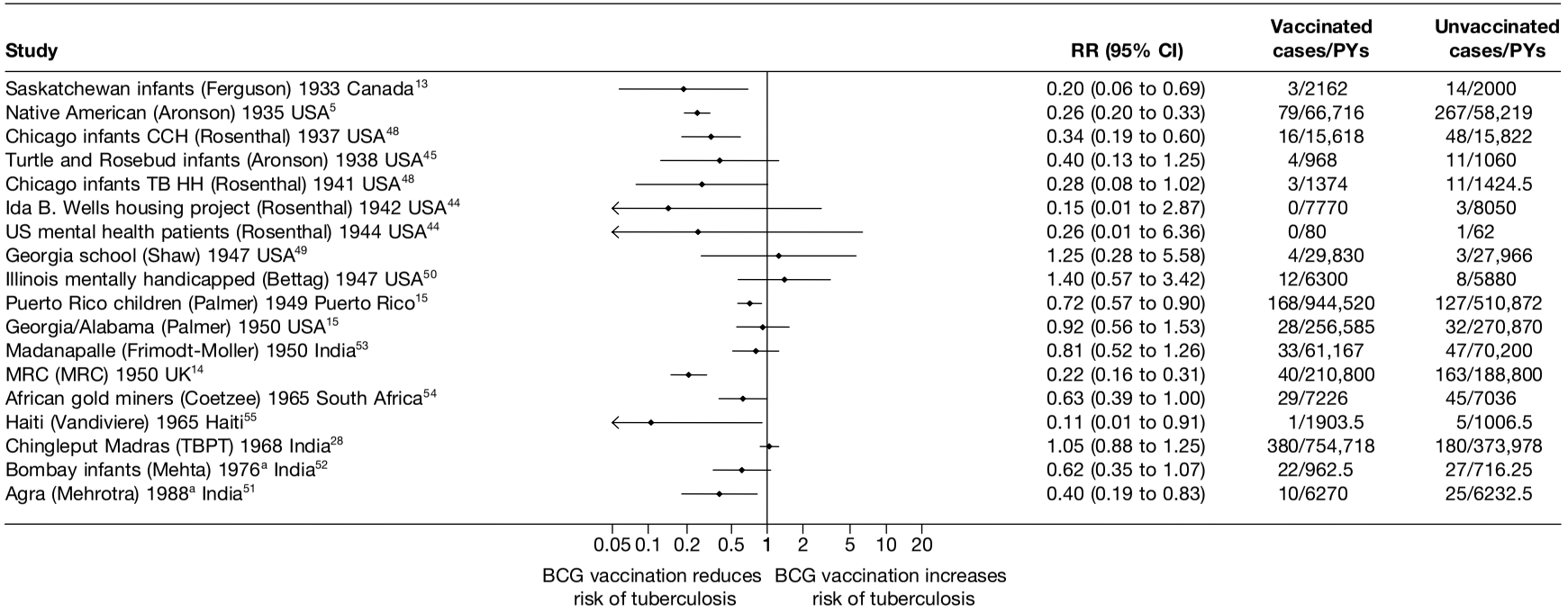

FIGURE 3 Rate ratios (with 95% CI) comparing the incidence of pulmonary tuberculosis among BCG vaccinated individuals with that in unvaccinated individuals for the longest duration of follow-up (see *Table 3*) in RCTs, by year of study start. a, Date of study publication was used if study start date was not available. CCH, Cook County Hospital; TB HH, tuberculosis households; TBPT, Tuberculosis Prevention Trial.

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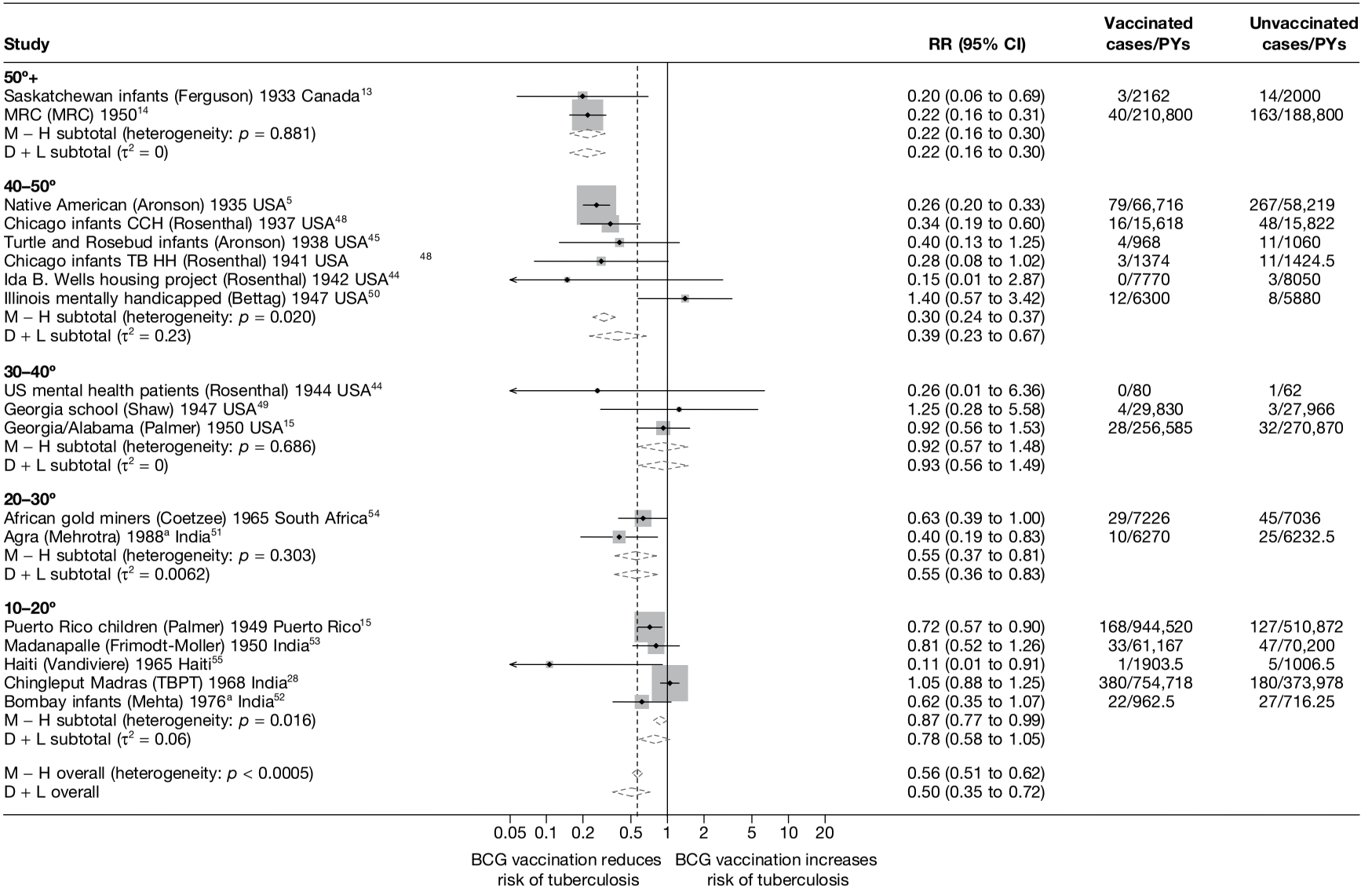

FIGURE 4 Rate ratios (with 95% CI) comparing the incidence of pulmonary tuberculosis among BCG vaccinated individuals with that in unvaccinated individuals for the longest duration of follow-up (see *Table 3*) in RCTs, stratified by latitude of study location (10° bands), ordered by year of study start. a, Date of study publication was used if study start date was not available. CCH, Cook County Hospital; D+L, DerSimonian and Laird method; M–H, Mantel–Haenszel method; TB HH, tuberculosis households; TBPT, Tuberculosis Prevention Trial.

Stratified analysis by age at vaccination and tuberculin testing stringency, ordered by year study started

Figure 5 shows estimated effects of BCG vaccination against pulmonary tuberculosis, stratified by the age at which vaccination was administered and the stringency of tuberculin testing performed, grouped into neonatal vaccination, school-aged vaccination, both stringent and less stringent, and an 'other' age group which includes studies in which older persons were vaccinated as well as those in which BCG vaccination, was given at any age, also divided into stringent and non-stringent tuberculin testing. Within these strata, there was little evidence of between-study heterogeneity, other than for studies with non-stringent tuberculin testing (school-age non-stringent testing $\tau^2 = 0.095$ and other age non-stringent testing $\tau^2 = 0.091$). In studies of school-age vaccination with stringent tuberculin testing prior to vaccination, the overall rate ratio was 0.26 (95% CI 0.18 to 0.37), corresponding to a good protective effect, with VE of 74% (95% CI 63% to 82%). There was also evidence of moderate levels of protection with neonatal vaccination [summary rate ratio 0.41 (95% CI 0.29 to 0.58), equivalent to a VE of 59% (95% CI 42% to 71%)]. Other strata showed less clear-cut evidence of protection, ranging from a moderate protection with rate ratio 0.59 (95% CI 0.65 to 1.01), equivalent to VE of 41% (95% CI –1% to 65%) in school-age vaccination studies with non-stringent tuberculin testing, to 0.88 (95% CI 0.59 to 1.31) equivalent to a VE of 12% (95% CI –0.31% to 41%) in studies of vaccination in other age groups with stringent tuberculin testing protocols.

Meta-regression analysis

Based on univariable meta-regression analyses, 85% of the between-study variation appeared to be explained by age at vaccination and tuberculin stringency (τ^2 before and after stratification 0.284 and 0.044 respectively) (see *Table 6*). There was clear evidence ($p < 0.003$) that the effect of BCG vaccination varied with age at vaccination/tuberculin testing stringency: the rate ratio in studies in the 'other' vaccination group with stringent tuberculin testing was estimated to be 2.38 (95% CI 1.09 to 5.18) times the overall rate ratio from studies with neonatal vaccination, while stringent tuberculin testing and school-age vaccination was 0.66 (95% CI 0.35 to 1.25) times that of neonatal vaccination studies.

Stratified analysis by risk of diagnostic detection bias, ordered by year study started

Figure 6 presents results from trials classified according to the level of risk of diagnostic detection bias. Among studies in which the outcome assessors were adequately blinded to the vaccination status of participants, or that performed active surveillance (which would act to lower the risk of diagnostic detection bias), there was substantial between-study variation, but the average protective efficacy of BCG vaccination against pulmonary tuberculosis was good [overall rate ratio 0.40 (95% CI 0.25 to 0.64), corresponding VE of 60% (95% CI 36% to 75%)] and was greater than for studies with higher risk of diagnostic detection bias, which showed a low protective effect [rate ratio 0.78 (95% CI 0.64 to 0.95), corresponding to VE of 22% (95% CI 5% to 37%)].

Meta-regression analysis

Meta-regression analyses stratifying on risk of diagnostic detection bias explained 18% of the heterogeneity between studies (null model $\tau^2 = 0.284$, after stratification $\tau^2 = 0.232$) (see *Table 6*). There was evidence (p-value = 0.036) that BCG vaccination efficacy varied according to the level of diagnostic detection bias introduced in the study design: studies with a higher risk of bias had a rate ratio 2.22 (95% CI 1.10 to 4.60) times that of studies with lower risk of bias (and therefore a correspondingly lower VE).

Results from univariable meta-regression analyses indicate that latitude and age at vaccination/tuberculin testing stringency explained the largest amount of between-study variation in overall BCG vaccination efficacy (τ^2 0.086 and 0.044 respectively, baseline τ^2 0.284). Bivariable analysis

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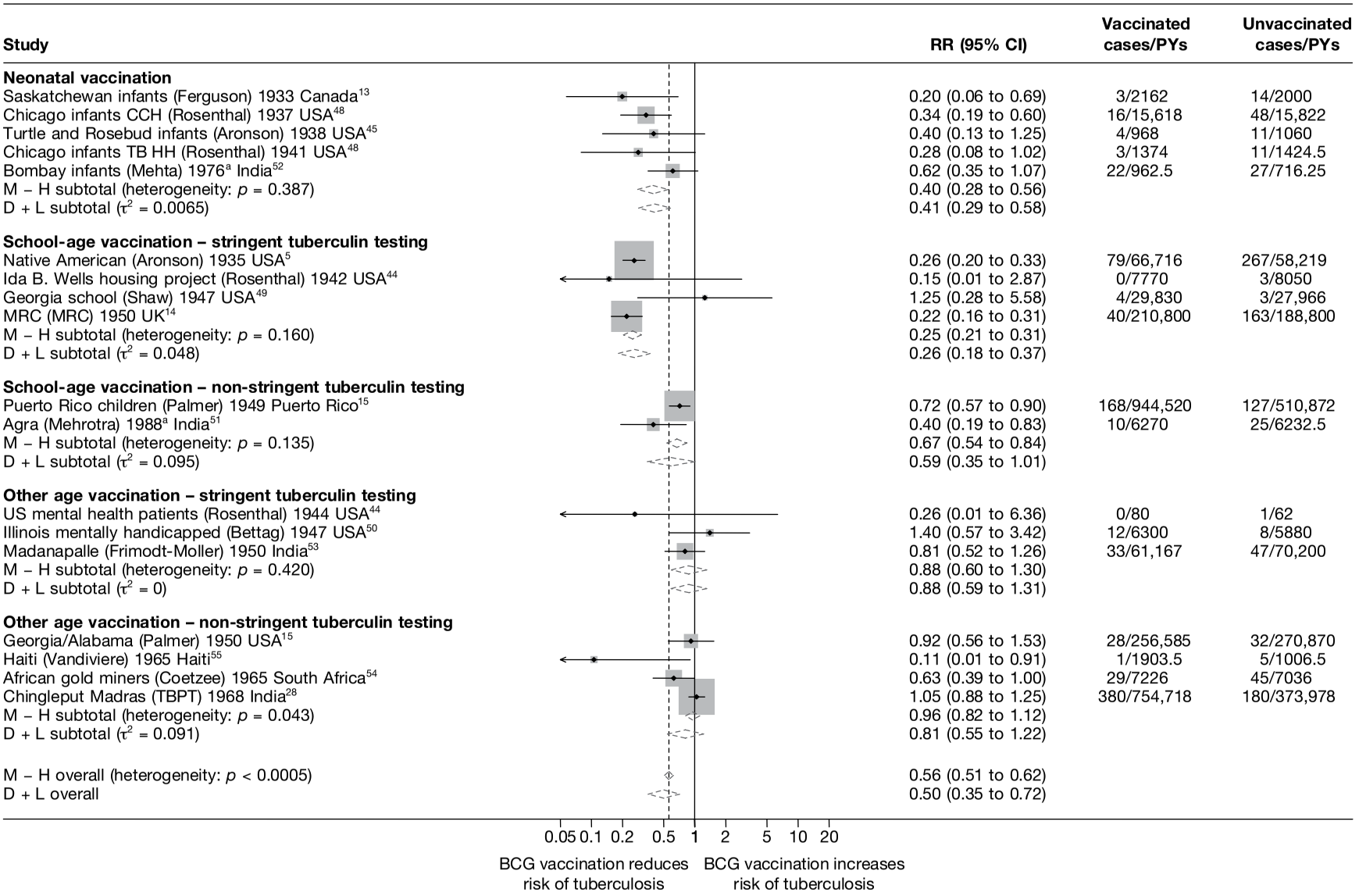

FIGURE 5 Rate ratios (with 95% CI) comparing the incidence of pulmonary tuberculosis among BCG vaccinated individuals compared with unvaccinated individuals for the longest duration of follow-up (see *Table 3*) in RCTs, stratified by age at vaccination/tuberculin testing stringency, ordered by year of study start. a, Date of study publication was used if study start date was not available. CCH, Cook County Hospital; D+L, DerSimonian and Laird method; M–H, Mantel–Haenszel method; TB HH, tuberculosis households; TBPT, Tuberculosis Prevention Trial.

showed that models including latitude and either the variables age at vaccination/tuberculin testing stringency or 'Was the allocation sequence adequately generated' accounted for the largest amount of between-study heterogeneity. The final multi-variable regression model, which explained all between-study variation ($\tau^2 = 0$) was one including the variables latitude, age at vaccination/tuberculin testing stringency and risk of diagnostic detection bias.

All tuberculosis disease morbidity outcomes

Figure 7 shows the overall results of 21 trials evaluating the efficacy of BCG vaccination against all tuberculosis morbidity outcomes, ordered by the year of study start.

Unstratified analysis ordered by year trial started

An additional three trials did not disaggregate results by type of disease, compared with results on pulmonary tuberculosis. Observation of data from all 21 RCTs shows that the estimates of BCG vaccination efficacy against all disease from tuberculosis (except death) vary considerably (see *Figure 7*). Similarly to the pulmonary tuberculosis outcome results, the observed effect varies from a good protective effect, as in the Native American,[5] Chicago Infants CCH[48] and MRC trials,[14] to an absence of protection against all tuberculosis morbidity outcomes, as in the Georgia School,[49] Chingleput[28] and in a residential school for people with learning difficulties (Illinois mentally handicapped[50]) trials. Most of the efficacy point estimates suggest that BCG vaccination reduces risk of tuberculosis, although the CIs are wide and include 1 in 14 of 21 studies.

Figures 8–11 present the results of RCTs stratified by latitude, age at vaccination/stringency of tuberculin testing and diagnostic detection bias, stringency of tuberculin testing and BCG strain lineage; the last was only possible to examine for all trials with all tuberculosis morbidity as the outcome.

Stratified analysis by latitude (10°), ordered by year study started

Figure 8 presents the overall efficacy of BCG vaccination reported in each controlled trial categorised into 10° bands of latitude. Overall, studies conducted > 40° latitude showed consistent evidence of a higher level of effect of BCG vaccination against all tuberculosis morbidity outcomes in comparison with studies conducted at lower latitudes. The highest level of protection was seen among studies conducted > 50°, with an overall rate ratio of 0.23 (95% CI 0.18 to 0.30) corresponding to a good VE of 77% (95% CI 70% to 82%). Latitude accounted for a substantial amount of the heterogeneity between studies.

Meta-regression analysis

Stratification only on latitude within which a study was conducted appeared to explain 38% of the variation in BCG vaccination protective effect estimates ($\tau^2 = 0.118$ after stratification by 20° bands of latitude (null model $\tau^2 = 0.292$) (*Table 8*). There was some evidence (p-value = 0.014) that efficacy varied with latitude. Studies in the 0–20° latitude groups had an overall estimated rate ratio 2.21 (95% CI 1.28 to 3.81) times that of studies conducted above 40° latitude. Similarly, the rate ratio for studies conducted in the 20–40° latitude group was 2.05 (95% CI 1.09 to 3.87) times the overall rate ratio for studies > 40° latitude.

Stratified analysis by age at vaccination and tuberculin testing stringency, ordered by year study started

Stratification of studies by age at vaccination and tuberculin testing stringency (*Figure 9*) shows that the estimated effect of BCG vaccination on all tuberculosis morbidity outcomes was substantial in studies of neonatal BCG vaccination [overall rate ratio 0.38 (95% CI 0.28 to 0.52)] corresponding to a good protection and VE of 62% (95% CI 48% to 72%). Similarly, studies of vaccination in school-age children with stringent tuberculin testing showed evidence of a good level of protection against all tuberculosis morbidity outcomes [overall rate ratio

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TABLE 6 Ratios of risk ratios (with 95% CI) comparing the incidence of pulmonary tuberculosis among vaccinated individuals compared with unvaccinated individuals for the longest duration of follow-up (see *Table 3*) in RCTs, according to univariable, two-variable and multivariable meta-regression analysis

Meta-regression results			Univariable model			Two-variable model			Multivariable model ($\tau^2 = 0.000$)	
Variable	Number of trials	Univariable rate ratios (95% CI)	Ratio of rate ratios (95% CI)	*p*-value	τ^2	Ratio of rate ratios[a] (95% CI)	*p*-value	τ^2	Ratio of rate ratios[b] (95% CI)	*p*-value
Null model	18				0.284			0.284		<0.001[c]
Latitude										
> 40°	8	0.31 (0.21 to 0.46)	1.00 (ref.)						1.00 (ref.)	
20–40°	5	0.68 (0.41 to 1.13)	2.17 (1.14 to 4.10)			Included in all models			1.17 (0.58 to 2.36)	
0–20°	5	0.77 (0.52 to 1.13)	2.45 (1.42 to 4.21)	0.008	0.086				1.73 (0.93 to 3.25)	0.054[d]
Age at vaccination/tuberculin testing stringency										
Neonatal	5	0.39 (0.24 to 0.64)	1.00 (ref.)			1.00 (ref.)			1.00 (ref.)	
School age/stringent	4	0.26 (0.17 to 0.40)	0.66 (0.35 to 1.25)			0.74 (0.52 to 2.67)			0.76 (0.45 to 1.26)	
School age/non-stringent	2	0.62 (0.38 to 1.01)	1.58 (0.80 to 3.13)			1.29 (0.64 to 2.61)			0.80 (0.37 to 1.72)	
Other age/stringent	3	0.94 (0.51 to 1.73)	2.38 (1.09 to 5.18)			1.83 (0.85 to 3.92)			1.60 (0.82 to 3.12)	
Other age/non-stringent	4	0.85 (0.58 to 1.24)	2.16 (1.17 to 3.98)	0.003	0.044	1.90 (0.97 to 3.73)	0.064[d]	0.000	1.75 (0.98 to 3.15)	0.013[d]
Diagnostic detection bias										
Lower risk of bias	13	0.43 (0.30 to 0.62)	1.00 (ref.)			1.00 (ref.)			1.00 (ref.)	
Higher risk of bias	5	0.95 (0.50 to 1.81)	2.22 (1.10 to 4.60)	0.036	0.232	1.71 (0.93 to 3.14)	0.077[d]	0.114	1.60 (1.01 to 2.54)	0.045[d]
Was the allocation sequence adequately generated?										
Lower risk of bias	1	1.05 (0.35 to 3.11)	1.00 (ref.)			1.00 (ref.)				
Higher risk of bias	17	0.48 (0.34 to 0.68)	0.46 (0.15 to 1.44)	0.169	0.253	0.64 (0.29 to 1.43)	0.255[d]	0.078		

Meta-regression results			Univariable model			Two-variable model			Multivariable model ($\tau^2 = 0.000$)	
Variable	Number of trials	Univariable rate ratios (95% CI)	Ratio of rate ratios (95% CI)	*p*-value	τ^2	Ratio of rate ratios[a] (95% CI)	*p*-value	τ^2	Ratio of rate ratios[b] (95% CI)	*p*-value
Was treatment allocation adequately concealed?										
Lower risk of bias	3	0.56 (0.22 to 1.41)	1.00 (ref.)			1.00 (ref.)				
Higher risk of bias	15	0.51 (0.34 to 0.75)	0.92 (0.34 to 2.49)	0.856	0.303	0.86 (0.40 to 1.83)	0.670[d]	0.091		
Was knowledge of the allocated intervention prevented during the study?										
Lower risk of bias	3	0.45 (0.20 to 1.02)	1.00 (ref.)			1.00 (ref.)				
Higher risk of bias	15	0.53 (0.36 to 0.80)	1.19 (0.48 to 2.96)	0.691	0.319	1.05 (0.48 to 2.05)	0.867[d]	0.128		
Are reports of the study free from the suggestion of selective outcome reporting?										
Lower risk of bias	17	0.50 (0.34 to 0.72)	1.00 (ref.)			1.00 (ref.)				
Higher risk of bias	1	0.81 (0.23 to 2.84)	1.62 (0.44 to 5.98)	0.445	0.299	1.09 (0.39 to 3.05)	0.860[d]	0.120		
Was ascertainment of cases complete?										
Lower risk of bias	15	0.51 (0.34 to 0.74)	1.00 (ref.)			1.00 (ref.)				
Higher risk of bias	3	0.59 (0.23 to 1.53)	1.17 (0.42 to 3.24)	0.756	0.310	0.80 (0.37 to 1.74)	0.551[d]	0.103		

ref., reference category; τ^2, estimated between-study variance.

a Adjusted for latitude category.

b Adjusted for all other variables in the model.

c Overall *p*-value for the model for the test of the hypothesis that none of the covariates is associated with the overall BCG vaccination efficacy.

d The *p*-value is for the test of the null hypothesis that there is no association between the covariate and the overall BCG vaccination efficacy.

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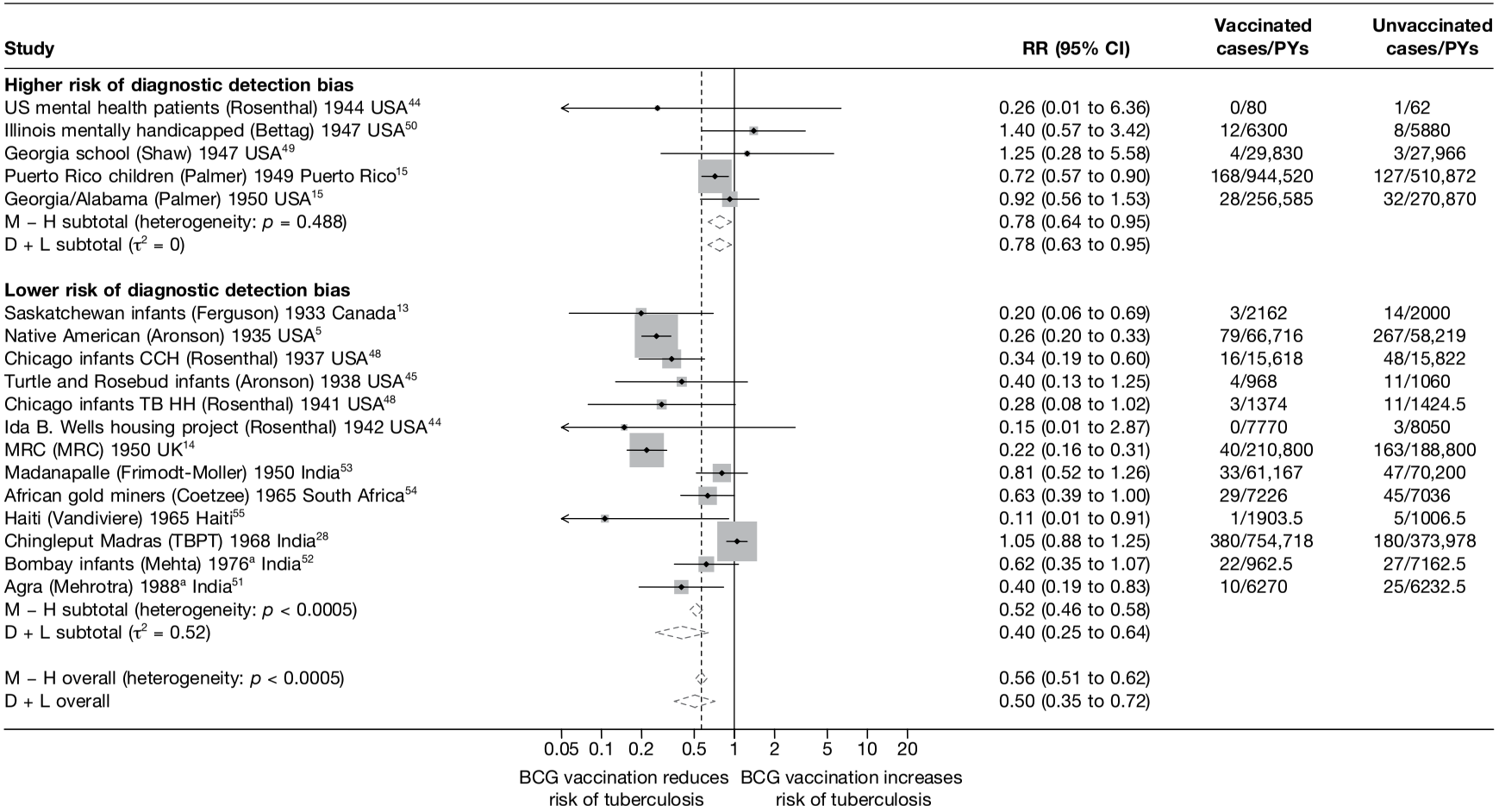

FIGURE 6 Rate ratios (with 95% CI) comparing the incidence of pulmonary tuberculosis among BCG vaccinated individuals compared with unvaccinated individuals for the longest duration of follow-up (see *Table 3*) in RCTs, stratified by risk of diagnostic detection bias,[b] ordered by year of study start. a, Date of study publication was used if study start date was not available; b, Diagnostic detection bias is considered to occur if the assessor of BCG vaccination outcome is not blinded to vaccination status. CCH, Cook County Hospital; D+L, DerSimonian and Laird method; M–H, Mantel–Haenszel method; TB HH, tuberculosis households; TBPT, Tuberculosis Prevention Trial.

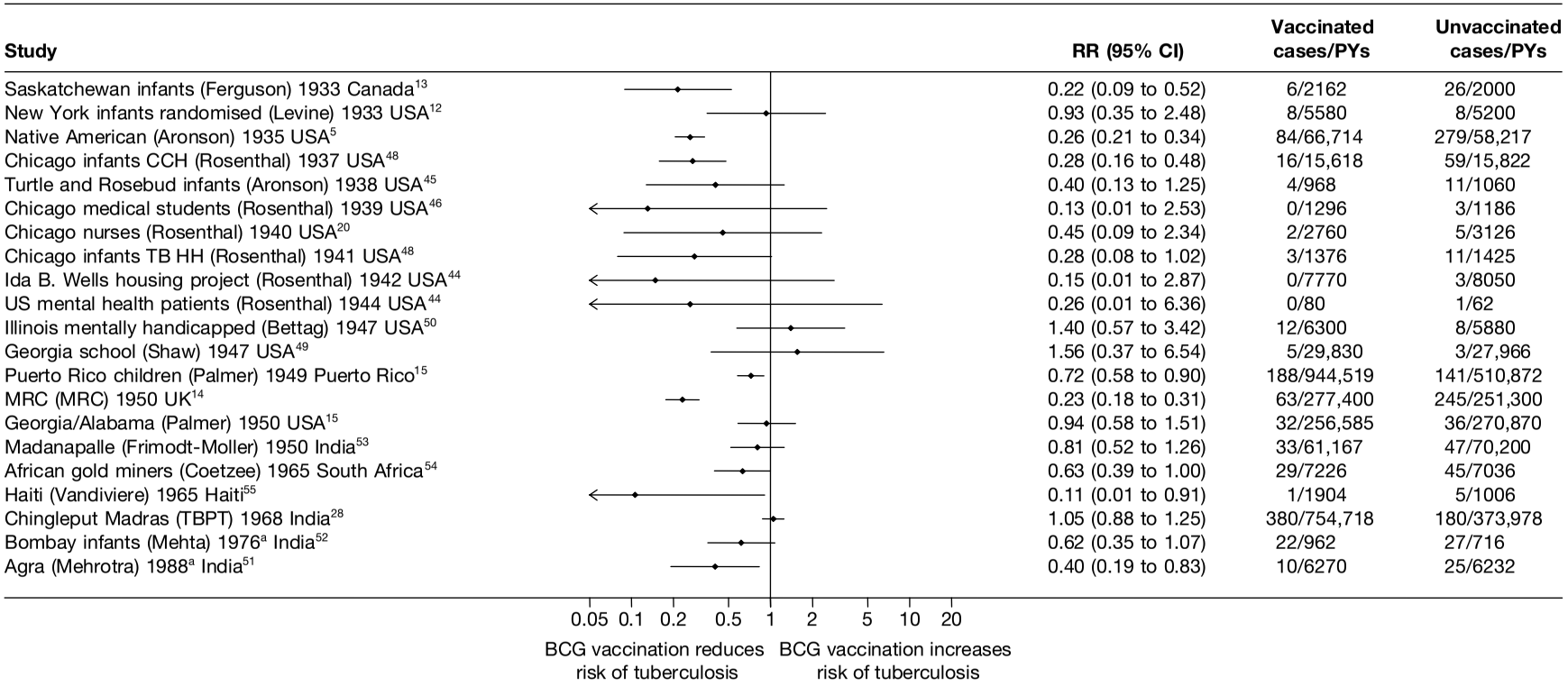

FIGURE 7 Rate ratios (with 95% CI) comparing the incidence of all tuberculosis morbidity outcomes among BCG vaccinated individuals with that in unvaccinated individuals for the longest duration of follow-up (see *Table 3*) in RCTs, ordered by year of study start. a, Date of study publication was used if study start date was not available. CCH, Cook County Hospital; TB HH, tuberculosis households; TBPT, Tuberculosis Prevention Trial.

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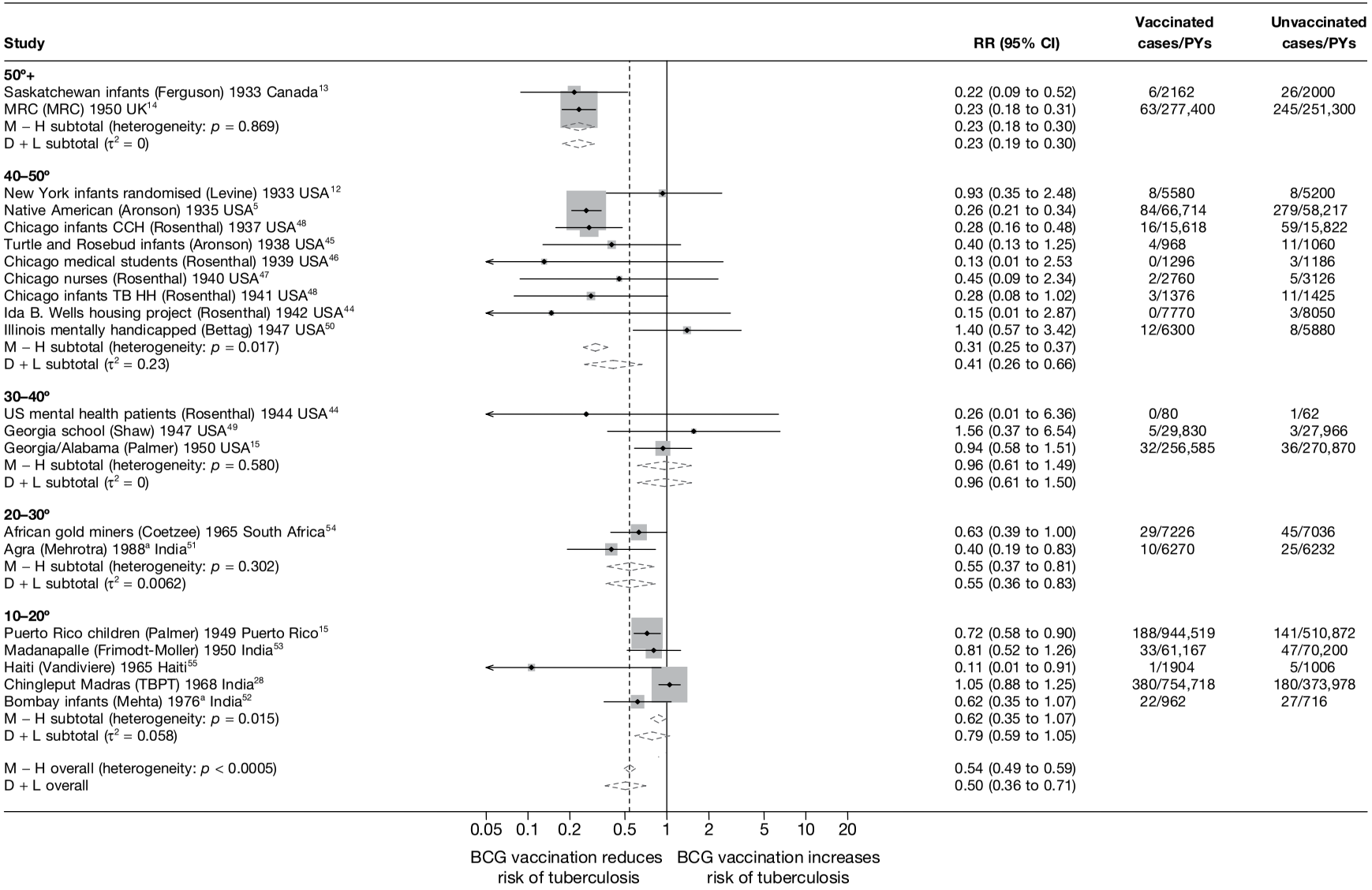

FIGURE 8 Rate ratios (with 95% CI) comparing the incidence of all tuberculosis morbidity outcomes among BCG vaccinated individuals with that in unvaccinated individuals for the longest duration of follow-up (see *Table 3*), in RCTs, stratified by latitude of study location (10° bands), ordered by year of study start. a, Date of study publication was used if study start date was not available. CCH, Cook County Hospital; D+L, DerSimonian and Laird method; M–H, Mantel–Haenszel method; TB HH, tuberculosis households; TBPT, Tuberculosis Prevention Trial.

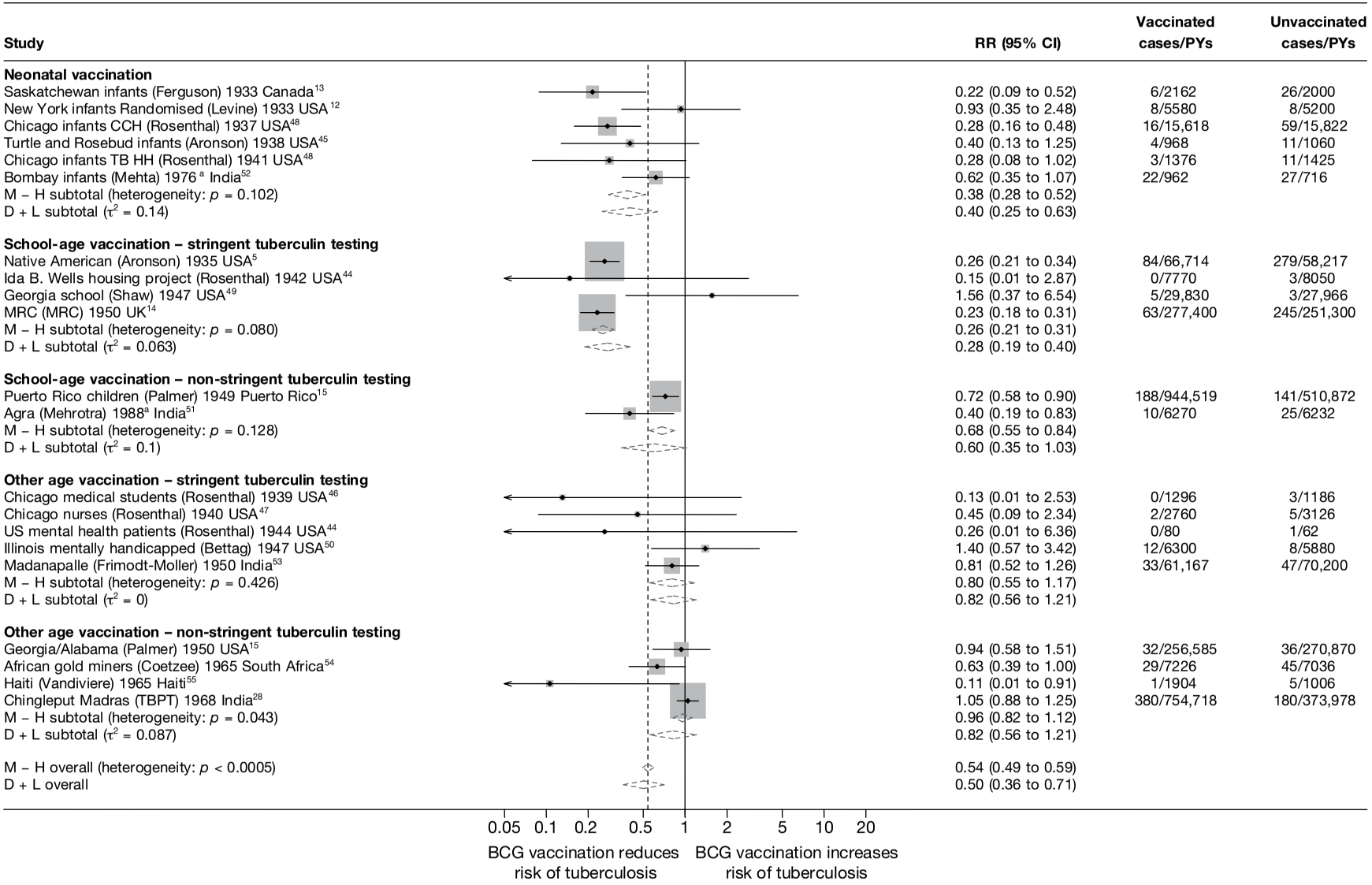

FIGURE 9 Rate ratios (with 95% CI) comparing the incidence of all tuberculosis morbidity outcomes among BCG vaccinated individuals with that in unvaccinated individuals for the longest duration of follow-up (see *Table 3*), in RCTs, stratified by age at vaccination, ordered by year of study start. a, Date of study publication was used if the study start date was not available. CCH, Cook County Hospital; D+L, DerSimonian and Laird method; M–H, Mantel–Haenszel method; TB HH, tuberculosis households; TBPT, Tuberculosis Prevention Trial.

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0.28 (95% CI 0.19 to 0.40)] equivalent to VE of 72% (95% CI 60% to 81%)]. Studies in which vaccination was performed both at school age without stringent tuberculin testing protocols, and in other age groups regardless of tuberculin testing stringency, showed low overall estimates of BCG vaccination efficacy. Overall levels of protection from studies in these categories were low, ranging from rate ratio 0.60 (95% CI 0.35 to 1.03) to rate ratio 0.82 (95% CI 0.56 to 1.21). Stratification on age at vaccination/tuberculin testing accounted for substantial amount of the heterogeneity in the estimates of effect of BCG vaccination; however, residual heterogeneity within strata remained ($\tau^2 = 0.14$ in the neonatal vaccination strata and $\tau^2 = 0.1$ in school-age vaccination non-stringent tuberculin testing).

Meta-regression analysis

Based on univariable meta-regression analyses, age at vaccination/tuberculin testing stringency appeared to account for 73% of the between-study variation (τ^2 after stratification = 0.080; null model $\tau^2 = 0.292$) (see *Table 8*). There was evidence that the effect of BCG vaccination varied with age at vaccination and tuberculin testing stringency (*p*-value 0.015). The rate ratio in studies of school-age vaccination with stringent tuberculin testing was 0.71 (95% 0.36 to 1.39) times that of the rate ratio for neonatal vaccination (and therefore VE correspondingly higher), whereas for vaccination in other age groups with stringent tuberculin testing the rate ratio was 2.23 (95% CI 1.01 to 4.92) times the overall rate ratio of that for neonatal vaccination studies (and VE correspondingly lower).

Stratified analysis by risk of diagnostic detection bias, ordered by year study started

Figure 10 shows estimated effects of the BCG vaccination on all tuberculosis morbidity outcomes, stratified by risk of diagnostic detection bias. Overall, the protective effect of BCG vaccination was lower in studies with a higher risk of bias, while there was reasonably consistent evidence of higher protection observed in studies with a 'lower risk of bias' (i.e. the assessors of the study outcome, usually the diagnosis of tuberculosis, were blinded to BCG vaccination status or active surveillance was conducted). There was considerable residual heterogeneity between studies within the same strata, despite stratification by risk of diagnostic detection bias. This risk of bias criteria did not explain any of the observed between-study variability.

Meta-regression analysis

Univariable meta-regression analyses appeared to suggest that very little of the between-study variance was explained by stratifying on this quality assessment criteria (τ^2 values before and after stratification were respectively 0.292 and 0.233) (see *Table 8*). There was weak evidence that BCG vaccination efficacy varied with risk of diagnostic detection bias (*p*-value = 0.028). Studies with a higher risk of diagnostic detection bias had an overall rate ratio 2.25 (95% CI 1.10 to 4.60) times that of studies with a lower risk of diagnostic detection bias.

Stratified analysis by bacillus Calmette–Guérin strain as per Brosch et al.,[41] ordered by year study started

Randomised controlled trials reporting the protective effect of BCG vaccination against all tuberculosis morbidity outcomes were also stratified according to the lineage of BCG strain used for vaccination of participants based on the criteria derived from Brosch *et al.*[41] (*Figure 11*). This stratification showed that the effect of BCG vaccination in studies in each stratum varied considerably from a clinically unimportant effect to some trials showing substantial protection. The pooled effect size was similar for studies using all strain families [Pasteur, which contains tandem duplication 1 (DU1) and tandem duplication 2 (DU2-I), and strains containing DU2-II, DU2-III and DU2-IV]. Stratification did not explain the between-study variation in BCG vaccination effect.

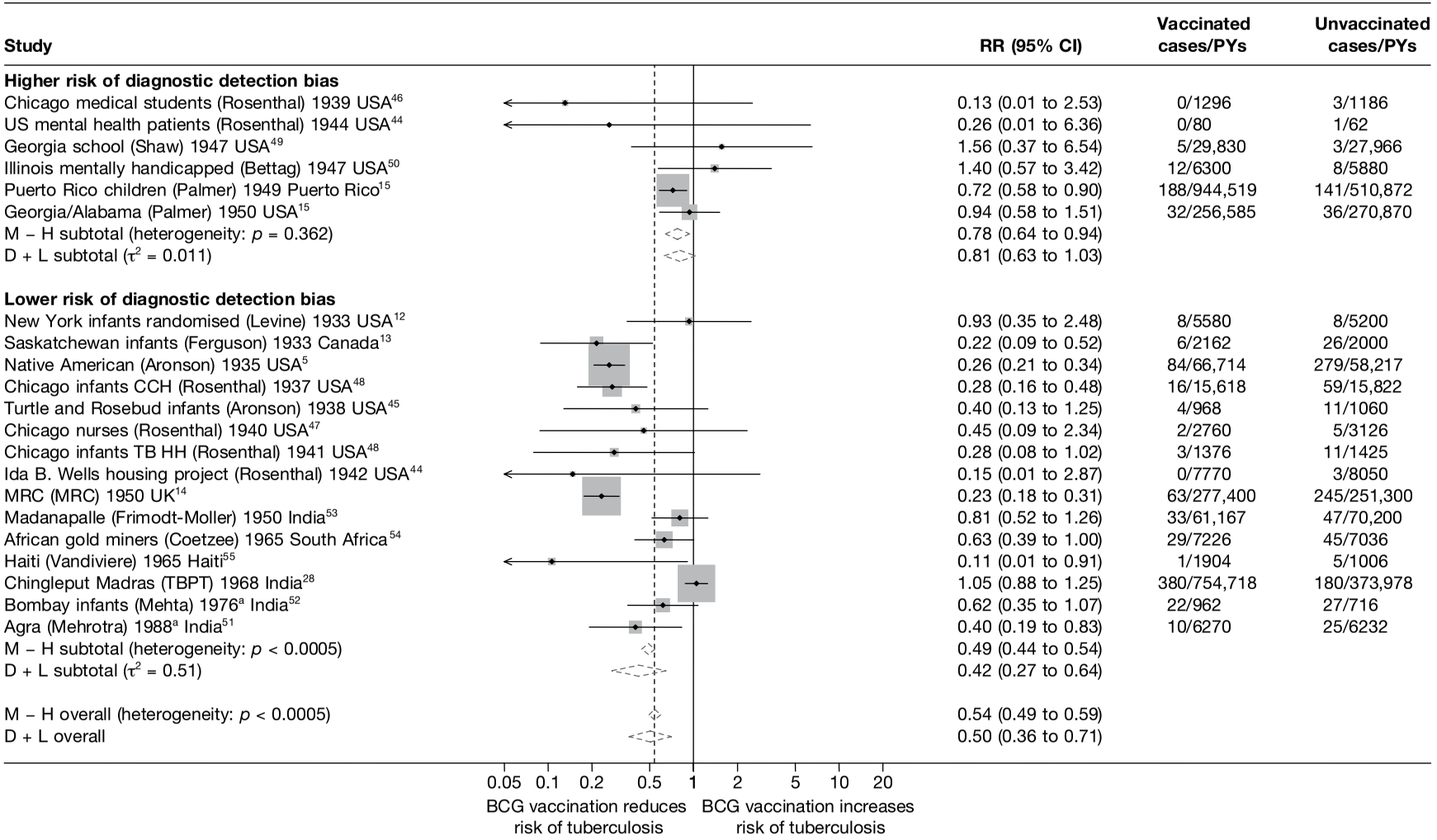

FIGURE 10 Rate ratios (with 95% CI) comparing the incidence of all tuberculosis morbidity outcomes among BCG vaccinated individuals with that in unvaccinated individuals for the longest duration of follow-up (see *Table 3*), in RCTs, stratified by risk of diagnostic detection bias,[b] ordered by year of study start. a, Date of study publication was used if study start date was not available; b, Diagnostic detection bias is said to occur if the assessor of BCG vaccination outcome is not blinded to vaccination status. CCH, Cook County Hospital; D+L, DerSimonian and Laird method; M–H, Mantel–Haenszel method; TB HH, tuberculosis Households; TBPT, Tuberculosis Prevention Trial.

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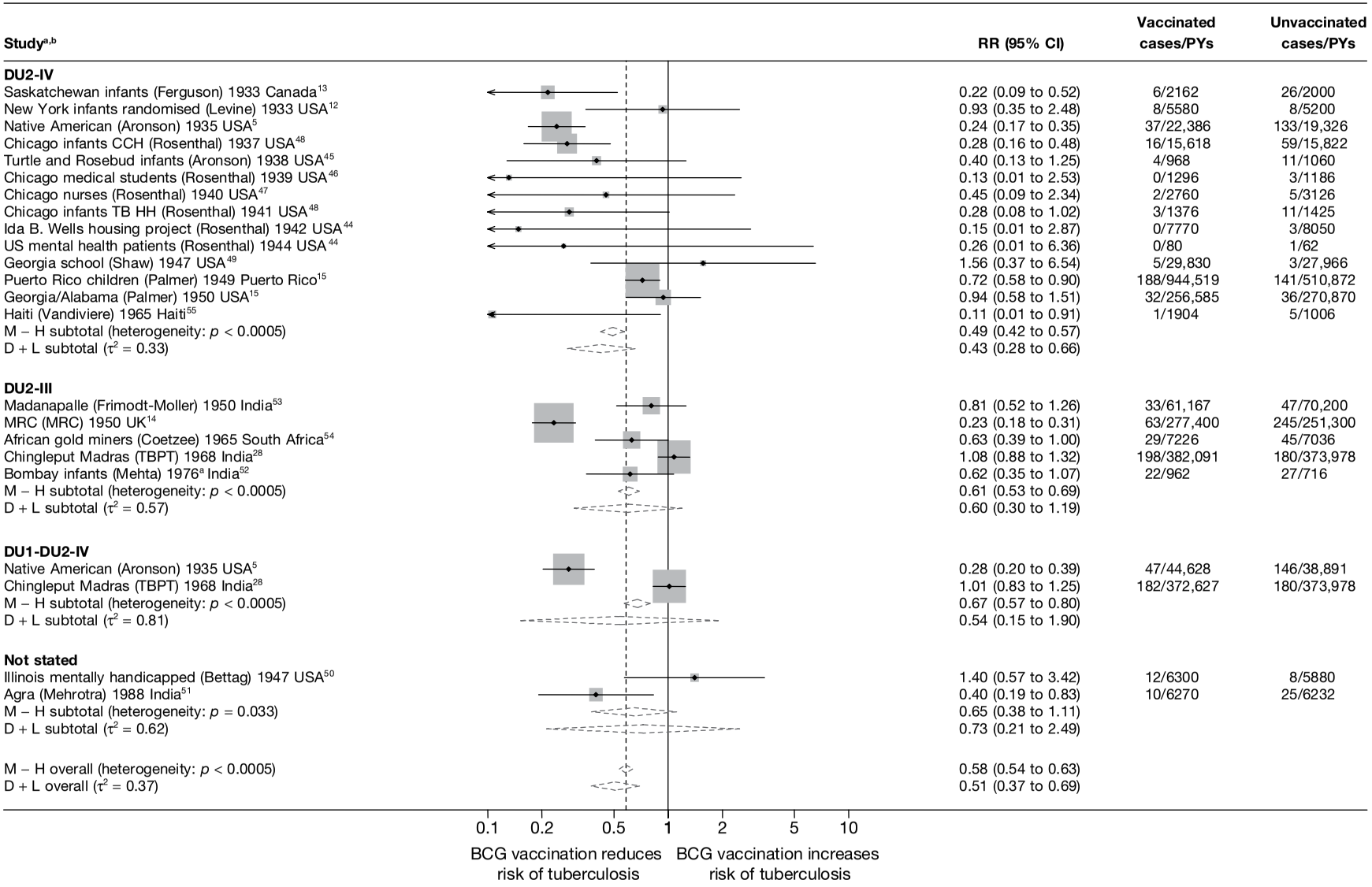

FIGURE 11 Rate ratios (with 95% CI) comparing the incidence of all tuberculosis morbidity outcomes among BCG vaccinated individuals with that in unvaccinated individuals for the longest duration of follow-up (see *Table 3*), in RCTs, stratified by BCG strain lineage, ordered by year of study start. a, As per Brosch *et al.*[41] b, Date of study publication was used if study start date was not available. The efficacy data for two trials (Native American[5] and Chingleput[28]), were provided for two different strains of BCG, accounting for two extra sets of results in this graph). CCH, Cook County Hospital; D+L, DerSimonian and Laird method; DU2-III[a], third form of tandem duplication 2; DU2-IV[a], fourth form of tandem duplication 2; M–H, Mantel–Haenszel method; TB HH, tuberculosis households; TBPT, Tuberculosis Prevention Trial.

Meta-regression analysis

Based on meta-regression analyses, BCG strain type did not account for the heterogeneity seen within the studies: τ^2 values before and after stratification on strain = 0.303 and 0.337, respectively. There was little evidence that BCG vaccination efficacy varied by strain (p-value = 0.614) (*Table 7*).

Scatterplot of vaccine efficacy by bacillus Calmette–Guérin strain type over time since trial started

Figure 12 shows VE for each trial plotted by vaccine strain and year the trial was started. We hypothesised that as the strains evolved over time, at least over the first few decades, the distribution of effect sizes would change over time. Not only was there no noticeable pattern over time, but also results showing trials according to strains used are distributed over a wide range of effect sizes.

Analysis by bacillus Calmette–Guérin strain

Results from univariable meta-regressions indicate that latitude, age at vaccination/tuberculin testing stringency and risk of diagnostic detection bias explained the largest amount of between-study variation in overall BCG vaccination efficacy with τ^2 values of 0.118, 0.080 and 0.233, respectively (baseline $\tau^2 = 0.292$). Bivariable analysis showed that models including latitude and the variables age at vaccination/tuberculin testing stringency explained the most between-study heterogeneity, reducing the τ^2 from 0.292 (null model) to 0.100. Results from the multivariable regression model including the variables latitude, age at vaccination/tuberculin testing stringency and risk of diagnostic detection bias explained more of the between-study variation observed, decreasing τ^2 from 0.292 to 0.037. There was strong evidence (p-value = 0.002), that these variables are associated with increased BCG vaccination efficacy.

Combined meningeal and/or miliary tuberculosis

The following section reports results of RCTs assessing the efficacy of BCG vaccination against meningeal and/or miliary tuberculosis outcomes.

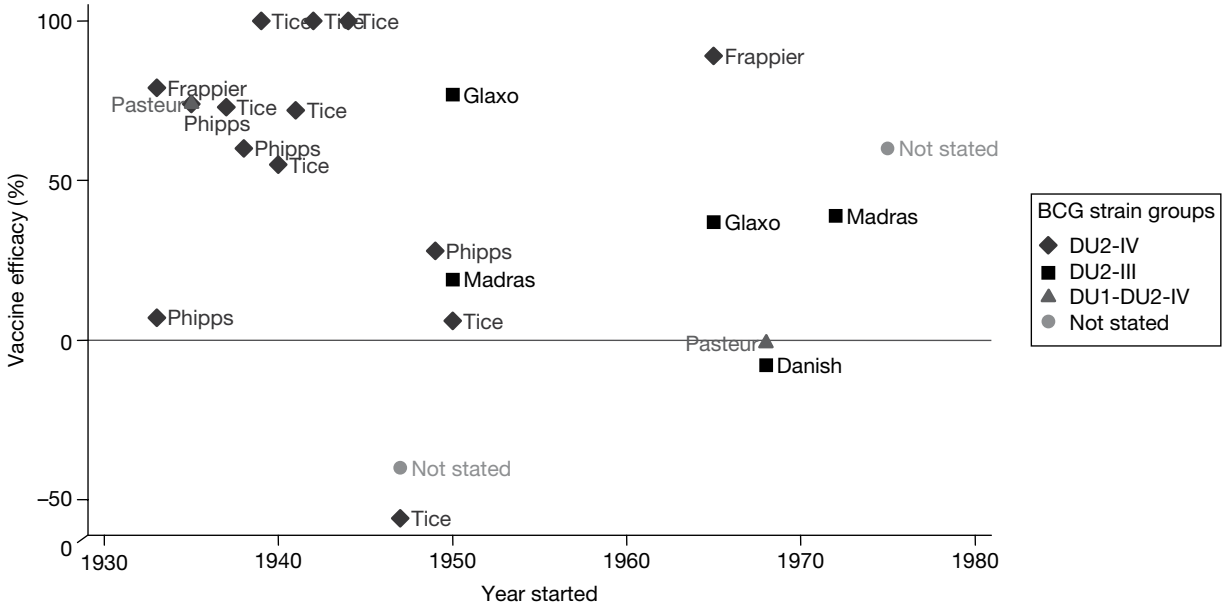

FIGURE 12 Scatterplot of study estimate of BCG vaccine efficacy over time of study start, by BCG strain category. DU2-III, third form of tandem duplication 2; DU2-IV, fourth form of tandem duplication 2; DU1-DU2-IV, tandem duplication 1 and fourth form of tandem duplication 2, according to Brosch *et al*.[41]

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TABLE 7 Ratios of risk ratios (with 95% CI) comparing the incidence of all tuberculosis morbidity outcomes among vaccinated individuals compared with unvaccinated individuals for the longest duration of follow-up (see *Table 3*) in RCTs, according to univariate meta-regression analysis, by BCG strain category

Variable	Number of results	Univariable rate ratios (95% CI)	Univariable model		
			Ratio of rate ratios (95% CI)	*p*-value	τ^2
Null model	23				0.322
BCG strain category[a,b]					
DU2-IV	14	0.45 (0.27 to 0.74)	1.00 (ref.)		
DU2-III	5	0.60 (0.32 to 1.10)	1.33 (0.61 to 2.91)		
DU1-DU2-IV	2	0.52 (0.20 to 1.31)	1.15 (0.40 to 3.29)		
Not stated	2	0.72 (0.24 to 2.74)	1.59 (0.48 to 5.33)	0.807	0.382

τ^2, estimated between-study variance; DU2-III, third form of tandem duplication 2; DU2-IV, fourth form of tandem duplication 2; DU1-DU2-IV, tandem duplication 1 and fourth form of tandem duplication 2; ref., reference category.

a The BCG strain categories were derived from the classification in Brosch *et al.*[41]

b There are 23 results for strain as it was possible to split the Native American[5] and Chingleput[28] results by the different strains used.

Unstratified analysis ordered by year trial started

The rate ratios and 95% CIs from the six trials assessing the efficacy of BCG vaccination on meningeal and/or miliary tuberculosis are shown in *Figure 13*. Most studies had very few events in the BCG group. Although there is evidence of variation, all point estimates apart from those of the Puerto Rico and Georgia/Alabama trials[15] were consistent with a high protective effect against these severe forms of tuberculosis disease. Two trials (Native American[5] and MRC[14]) provided stronger evidence of a protective effect of BCG vaccination against meningeal and/or miliary tuberculosis.

Stratified analysis by latitude (10°) group, ordered by year study started

Figure 14 shows the results of trials evaluating the effect of BCG vaccination on meningeal and/or miliary tuberculosis stratified according to 10° latitude groups. With the exception of two trials conducted between 10° and 40° in Puerto Rico[15] and Georgia/Alabama,[15] all other studies (conducted at higher latitudes) showed evidence of a high and consistent protective effect against meningeal and/or miliary tuberculosis. Studies conducted between 40° and 50° and > 50° latitude had a combined high VE of 90% (95% CI 71% to 97%) and 94% (95% CI 55% to 99%), respectively. Latitude appeared here to explain a substantial amount of the between-study variation in the effect of BCG vaccination, although the results should be interpreted with caution in view of the small number of studies contributing to this analysis.

Meta-regression analysis

Stratification on latitude appeared to explain the between-study heterogeneity (τ^2 values before and after stratification were 0.767 and 0.000, respectively); however, there were limited data to support the hypothesis that BCG vaccination efficacy varies according to latitude (*p*-value = 0.141); similarly, studies conducted between 20° and 40° latitude had a RR 60.58 (95% CI 0.34 to 10715.67) times than studies located at latitudes above 40° latitude, but the CIs were wide (*Table 9*).

Stratified analysis by age at vaccination and tuberculin testing stringency, ordered by year study started

Both school-age vaccination with stringent tuberculin testing and neonatal vaccination showed high BCG vaccination efficacy against meningeal and miliary tuberculosis, with the two neonatal vaccination studies showing a pooled rate ratio of 0.10 (95% CI 0.01 to 0.77) corresponding to a high VE of 90% (95% CI 67% to 99%). The two pooled studies of school-age vaccination with

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TABLE 8 Ratios of risk ratios (with 95% CI) comparing the incidence of all tuberculosis morbidity outcomes among vaccinated individuals compared with unvaccinated individuals for the longest duration of follow-up (see *Table 3*), according to univariable, two-variable and multivariable meta-regression analysis

			Univariable model			Two-variable model			Multivariable model ($\tau^2 = 0.037$)	
Variable	Number of trials	Univariable rate ratios (95% CI)	Ratio of rate ratios (95% CI)	*p*-value	τ^2	Ratio of rate ratios[a] (95% CI)	*p*-value	τ^2	Ratio of rate ratios[b] (95% CI)	*p*-value
Null model	21				0.292			0.292		0.002[c]
Latitude										
> 40°	5	0.34 (0.24 to 0.49)	1.00 (ref.)						1.00 (ref.)	
20–40°	5	0.70 (0.42 to 1.18)	2.05 (1.09 to 3.87)			Included in all models			1.38 (0.63 to 3.02)	
0–20°	11	0.76 (0.50 to 1.14)	2.21 (1.28 to 3.81)	0.014	0.118				1.80 (0.94 to 3.46)	0.143[d]
Age at vaccination/tuberculin testing stringency, combined										
Neonatal	6	0.40 (0.25 to 0.64)	1.00 (ref.)			1.00 (ref.)			1.00 (ref.)	
School age/stringent	4	0.28 (0.18 to 0.46)	0.71 (0.36 to 1.39)			0.80 (0.39 to 1.64)			0.77 (0.44 to 1.34)	
School age/non-stringent	2	0.60 (0.34 to 1.08)	1.52 (0.73 to 3.18)			1.02 (0.39 to 2.69)			0.71 (0.30 to 1.68)	
Other age/stringent	5	0.88 (0.47 to 1.69)	2.23 (1.01 to 4.92)			1.86 (0.79 to 4.36)			1.53 (0.74 to 3.16)	
Other age/non-stringent	4	0.83 (0.53 to 1.28)	2.08 (1.10 to 3.93)	0.015	0.080	1.41 (0.56 to 3.56)	0.354[d]	0.100	1.41 (0.68 to 2.93)	0.083[d]
Diagnostic detection bias										
Lower risk of bias	15	0.44 (0.31 to 0.61)	1.00 (ref.)			1.00 (ref.)			1.00 (ref.)	
Higher risk of bias	6	0.98 (0.52 to 1.84)	2.25 (1.10 to 4.60)	0.028	0.233	1.76 (0.95 to 3.28)	0.071[d]	0.132	1.77 (1.04 to 3.03)	0.036[d]
Was the allocation sequence adequately generated?										
Lower risk of bias	1	1.05 (0.35 to 3.14)	1.00 (ref.)			1.00 (ref.)				
Higher risk of bias	20	0.48 (0.34 to 0.68)	0.47 (0.15 to 1.48)	0.184	0.265	0.63 (0.25 to 1.57)	0.300[d]	0.125		
Was treatment allocation adequately concealed?										
Lower risk of bias	3	0.55 (0.22 to 1.39)	1.00 (ref.)			1.00 (ref.)				
Higher risk of bias	18	0.52 (0.36 to 0.74)	0.94(0.35 to 2.53)	0.898	0.311	0.94 (0.42 to 2.12)	0.876[d]	0.142		
Was knowledge of the allocated intervention prevented during the study?										
Lower risk of bias	3	0.45 (0.20 to 1.02)	1.00 (ref.)			1.00 (ref.)				
Higher risk of bias	18	0.54 (0.37 to 0.79)	1.20 (0.49 to 2.94)	0.676	0.324	1.13 (0.55 to 2.28)	0.728[d]	0.166		

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TABLE 8 Ratios of risk ratios (with 95% CI) comparing the incidence of all tuberculosis morbidity outcomes among vaccinated individuals compared with unvaccinated individuals for the longest duration of follow-up (see *Table 3*), according to univariable, two-variable and multivariable meta-regression analysis (*continued*)

			Univariable model			Two-variable model			Multivariable model ($\tau^2 = 0.037$)	
Variable	Number of trials	Univariable rate ratios (95% CI)	Ratio of rate ratios (95% CI)	*p*-value	τ^2	Ratio of rate ratios[a] (95% CI)	*p*-value	τ^2	Ratio of rate ratios[b] (95% CI)	*p*-value
Are reports of the study free from the suggestion of selective outcome reporting?										
Lower risk of bias	20	0.51 (0.36 to 0.72)	1.00 (ref.)			1.00 (ref.)				
Higher risk of bias	1	0.81 (0.23 to 2.82)	1.59 (0.44 to 5.81)	0.463	0.304	1.11 (0.37 to 3.29)	0.843[d]	0.156		
Was ascertainment of cases complete?										
Lower risk of bias	17	0.51 (0.36 to 0.74)	1.00 (ref.)			1.00 (ref.)				
Higher risk of bias	4	0.59 (0.23 to 1.52)	1.14 (0.42 to 3.14)	0.785	0.315	0.78 (0.35 to 1.75)	0.533[d]	0.138		

ref., reference category; τ^2, estimated between-study variance.

a Adjusted for latitude category.

b Adjusted for all other variables in the model.

c Overall *p*-value for the model for the test of the hypothesis that none of the covariates are associated with the overall BCG vaccination efficacy.

d The *p*-value is for the test of the null hypothesis that there is no association between the covariate and the overall BCG vaccination efficacy.

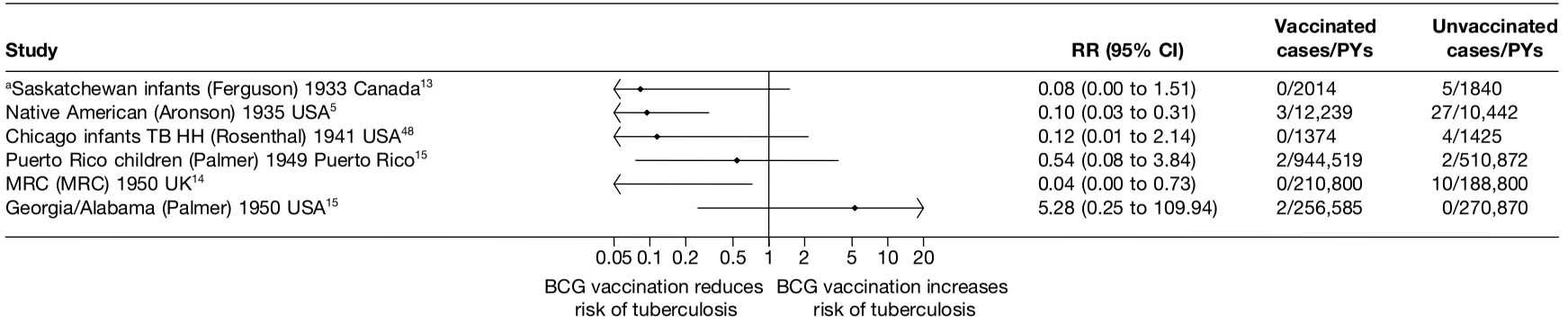

FIGURE 13 Rate ratios (with 95% CI) comparing the incidence of meningeal and/or miliary tuberculosis among BCG vaccinated individuals with that in unvaccinated individuals for the longest duration of follow-up (see *Table 3*) in RCTs, ordered by year of study start. a, The outcome is miliary tuberculosis only. TB HH, tuberculosis households.

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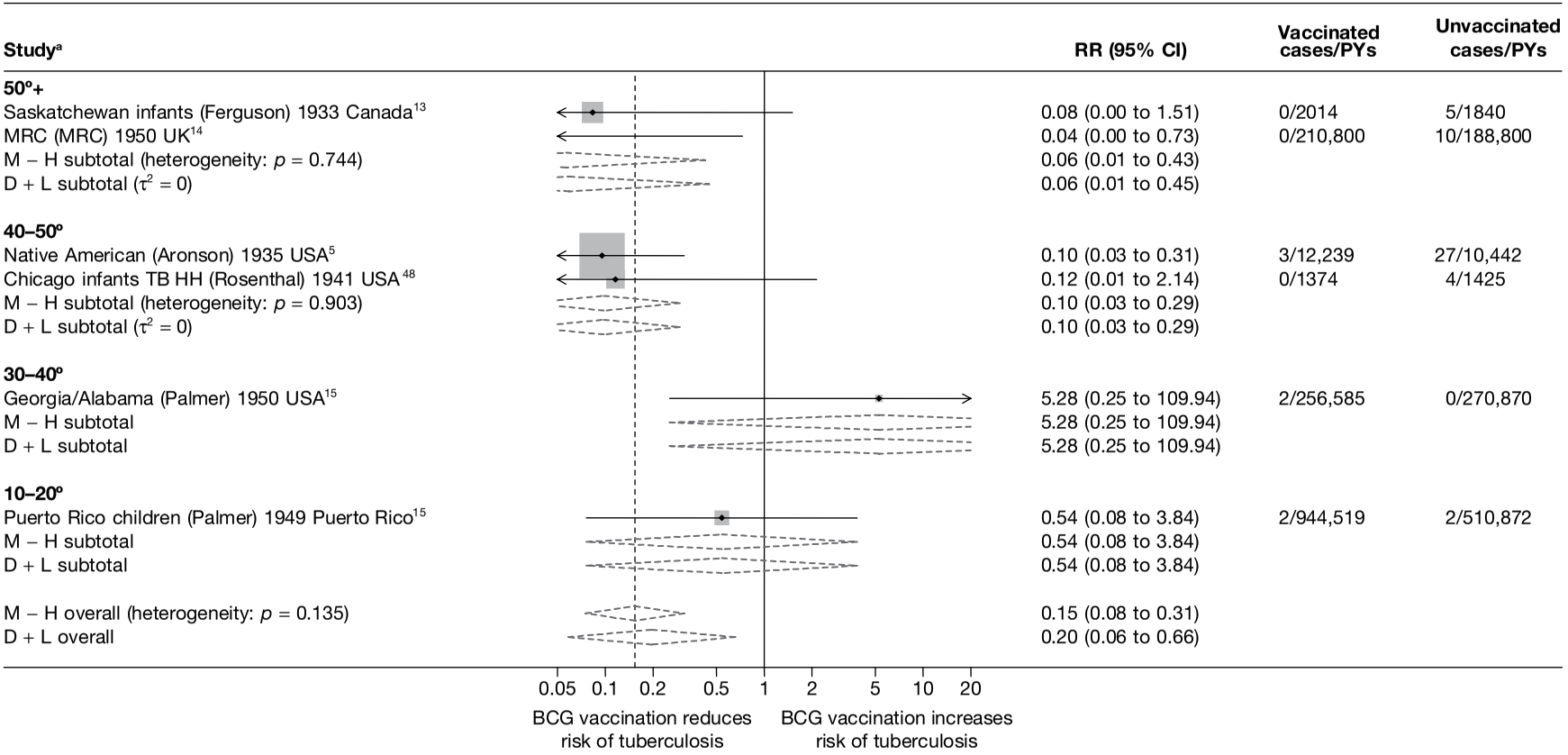

FIGURE 14 Rate ratios (with 95% CI) comparing the incidence of meningeal and/or miliary tuberculosis among BCG vaccinated individuals with that in unvaccinated individuals for the longest duration of follow-up (see *Table 3*) in RCTs, stratified by latitude of study location (10° bands), ordered by year of study start. a, The outcome is miliary tuberculosis only. D+L, DerSimonian and Laird method; M–H, Mantel–Haenszel method; TB HH, tuberculosis households.

stringent tuberculin testing gave a rate ratio of 0.08 (95% CI 0.03 to 0.25) also corresponding to a high VE of 92% (95% CI 75% to 97%). Only one study assessed BCG vaccination[15] at other ages with stringent and non-stringent tuberculin testing, respectively, showing little evidence of protection in the case of vaccination in other/all age groups with non-stringent tuberculin testing (*Figure 15*). Stratification on age at vaccination and tuberculin testing stringency appeared to explain a substantial amount of the between-study variation.

Meta-regression analysis

Based on meta-regression analyses, age at vaccination and stringency of tuberculin testing accounted for a substantial amount of the heterogeneity: τ^2 values before and after stratification = 0.767 and 0.000, respectively. However, there was insufficient evidence to test the hypothesis that BCG vaccination efficacy varied by age at vaccination/tuberculin testing stringency (*p*-value 0.282) (see *Table 9*).

Stratified analysis by risk of diagnostic detection bias, ordered by year study started

Results from trials were stratified according to risk of diagnostic detection bias (*Figure 16*). The most consistent protective effect was seen in studies with a lower risk of diagnostic detection bias. The overall rate ratio was 0.09 (95% CI 0.03 to 0.23), consistent with high VE of 91% (95% CI 77% to 97%), with little evidence of within-strata heterogeneity (*p*-value assuming a fixed-effects model = 0.959), whereas the trials with higher risk of bias showed an overall rate ratio of 1.26 (95% CI 0.14 to 11.27), equivalent to no clinical benefit. Diagnostic detection bias accounted for a substantial amount of the between-study variability.

Meta-regression analysis

Stratification on risk of diagnostic detection bias accounted for a very substantial amount of variability (τ^2 values before and after stratification = 0.767 and 0.000, respectively) (see *Table 9*). However, the evidence that BCG vaccination efficacy varied with risk of diagnostic detection bias was weak: studies with a higher risk of diagnostic detection bias had a rate ratio 12.13 (95% CI 0.81 to 181.79) times that of studies with a lower risk of bias, with the VE for studies at higher risk of diagnostic detection bias being correspondingly lower.

Results from univariable meta-regressions suggested that latitude, age at vaccination/tuberculin testing stringency and risk of diagnostic detection bias were closely correlated and could each explain the between-study variation in overall BCG vaccination efficacy against meningeal and/or miliary tuberculosis with a τ^2 value of 0.000.

Extrapulmonary tuberculosis

Studies providing data on outcomes of extrapulmonary tuberculosis which were not specified to be tuberculosis meningitis and/or miliary tuberculosis were analysed in the extrapulmonary tuberculosis section below.

Unstratified analysis ordered by year trial started

Figure 17 shows a forest plot for the six trials providing data on the efficacy of the BCG vaccination on any extrapulmonary tuberculosis disease (excluding those referring to miliary tuberculosis or tuberculosis meningitis). There was substantial variation in the protective efficacy of the BCG vaccination against extrapulmonary tuberculosis, ranging from a high protective effect [rate ratio 0.14 (95% CI 0.03 to 0.63)] in Saskatchewan Infants,[13] to absence of a clinically important benefit in the Georgia/Alabama trial[15] [rate ratio 1.06 (95% CI 0.26 to 4.22)].

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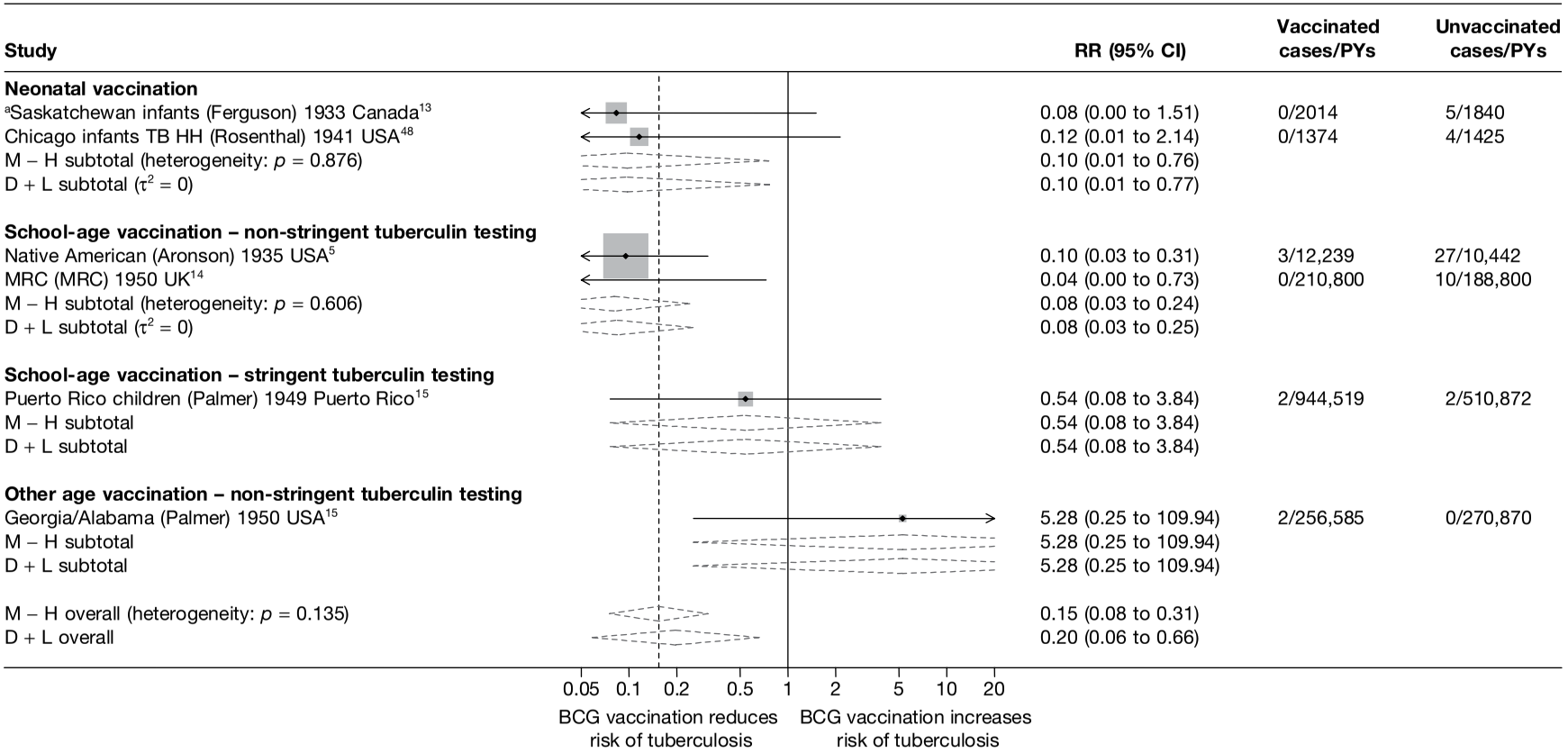

FIGURE 15 Rate ratios (with 95% CI) comparing the incidence of meningeal and/or miliary tuberculosis among BCG vaccinated individuals with that in unvaccinated individuals for the longest duration of follow-up (see *Table 3*) in RCTs, stratified by age at vaccination and tuberculin testing stringency, ordered by year of study start. a, The outcome is miliary tuberculosis only. CCH, Cook County Hospital; D+L, DerSimonian and Laird method; M–H, Mantel–Haenszel method; TB HH, tuberculosis households.

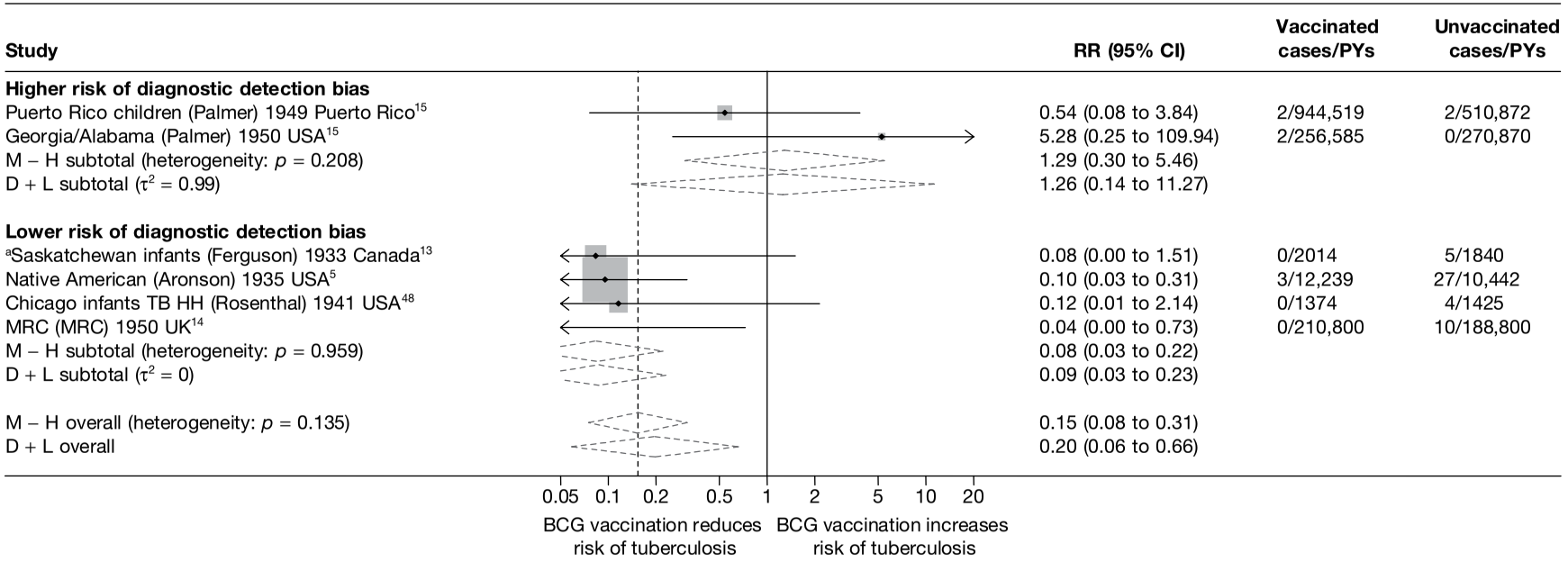

FIGURE 16 Rate ratios (with 95% CI) comparing the incidence of meningeal and/or miliary tuberculosis among BCG vaccinated individuals with that in unvaccinated individuals for the longest duration of follow-up (see *Table 3*) in RCTs, stratified by risk of diagnostic detection bias,[b] ordered by year of study start. a, Outcome is miliary tuberculosis only; b, Diagnostic detection bias occurs if the assessor of BCG vaccination outcome is not blinded to vaccination status. CCH, Cook County Hospital; D+L, DerSimonian and Laird method; M–H, Mantel–Haenszel method; TB HH, tuberculosis households.

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TABLE 9 Ratios of rate ratios (with 95% CI) comparing the incidence of meningeal and/or miliary tuberculosis among vaccinated individuals compared with unvaccinated individuals for the longest duration of follow-up (see *Table 3*) in RCTs, according to univariable meta-regression analysis

			Univariable model		
Variable	Number of trials	Univariable rate ratios (95% CI)	Ratio of rate ratios (95% CI)	*p*-value	τ^2
Null model	6				0.767
Latitude					
>40°	4	0.09 (0.01 to 0.73)	1.00 (ref.)		
20–40°	1	5.28 (0.01 to 4143)	60.58 (0.34 to 10,715)		
0–20°	1	0.54 (0.01 to 39.97)	6.21 (0.18 to 216.23)	0.141	0.000
Age at vaccination/tuberculin testing combined					
Neonatal	2	0.10 (0.00 to 60,173)	1.00 (ref.)		
School age/stringent	2	0.08 (0.00 to 104.89)	0.86 (0.01 to 143.64)		
School age/non-stringent	1	0.54 (0.00 to 178,373)	5.52 (0.01to 2819)		
Other age/stringent	0				
Other age/non-stringent	1	5.28 (0.00 to 1.87×10^9)	55.88 (0.02 to 168,840)	0.282	0.000
Diagnostic quality					
Lower risk of bias	4	0.09 (0.02 to 0.42)	1.00 (ref.)		
Higher risk of bias	2	1.06 (0.07 to 15.32)	12.13 (0.81 to 181.79)	0.063	0.000
Was the allocation sequence adequately generated?					
Lower risk of bias	0		1.00 (ref.)		
Higher risk of bias	6				0.767
Was treatment allocation adequately concealed?					
Lower risk of bias	1	0.12 (0.00 to 68.45)	1.00 (ref.)		
Higher risk of bias	5	0.22 (0.02 to 2.58)	1.89 (0.01 to 739.96)	0.783	1.268
Was knowledge of the allocated intervention prevented during the study?					
Lower risk of bias	1	0.10 (0.01 to 5.92)	1.00 (ref.)		
Higher risk of bias	5	0.27 (0.02 to 3.59)	2.82 (0.04 to 199.08)	0.536	1.178
Are reports of the study free from the suggestion of selective outcome reporting?					
Lower risk of bias	6		1.00 (ref.)		
Higher risk of bias	0				0.767
Was ascertainment of cases complete?					
Lower risk of bias	6		1.00 (ref.)		
Higher risk of bias	0				0.767

ref., reference category; τ^2, estimated between-study variance.

Stratified analysis by latitude (10°), ordered by year study started

Figure 18 shows the estimated effect of BCG vaccination from trials with extrapulmonary tuberculosis outcome data excluding tuberculosis meningitis and miliary tuberculosis, stratified by location using 10° bands of latitude of study. Overall, the protective effect of the BCG vaccination was low or absent in studies conducted nearer the equator, whereas there was strong evidence of higher protection observed in studies carried out at latitudes exceeding 40°. The highest protective effect was observed in studies conducted above 50° latitude: rate ratio 0.17 (95% CI 0.11 to 0.29), corresponding to a high VE of 83% (95% CI 71% to 89%). Stratification

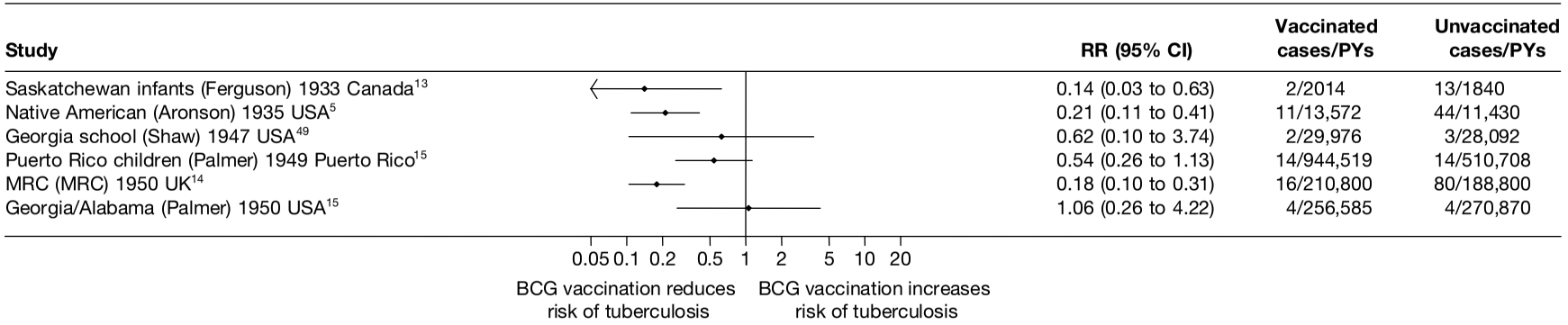

FIGURE 17 Rate ratios (with 95% CI) comparing the incidence of extrapulmonary tuberculosis among BCG vaccinated individuals with that in unvaccinated individuals for the longest duration of follow-up (see *Table 3*) in RCTs, ordered by year of study start.

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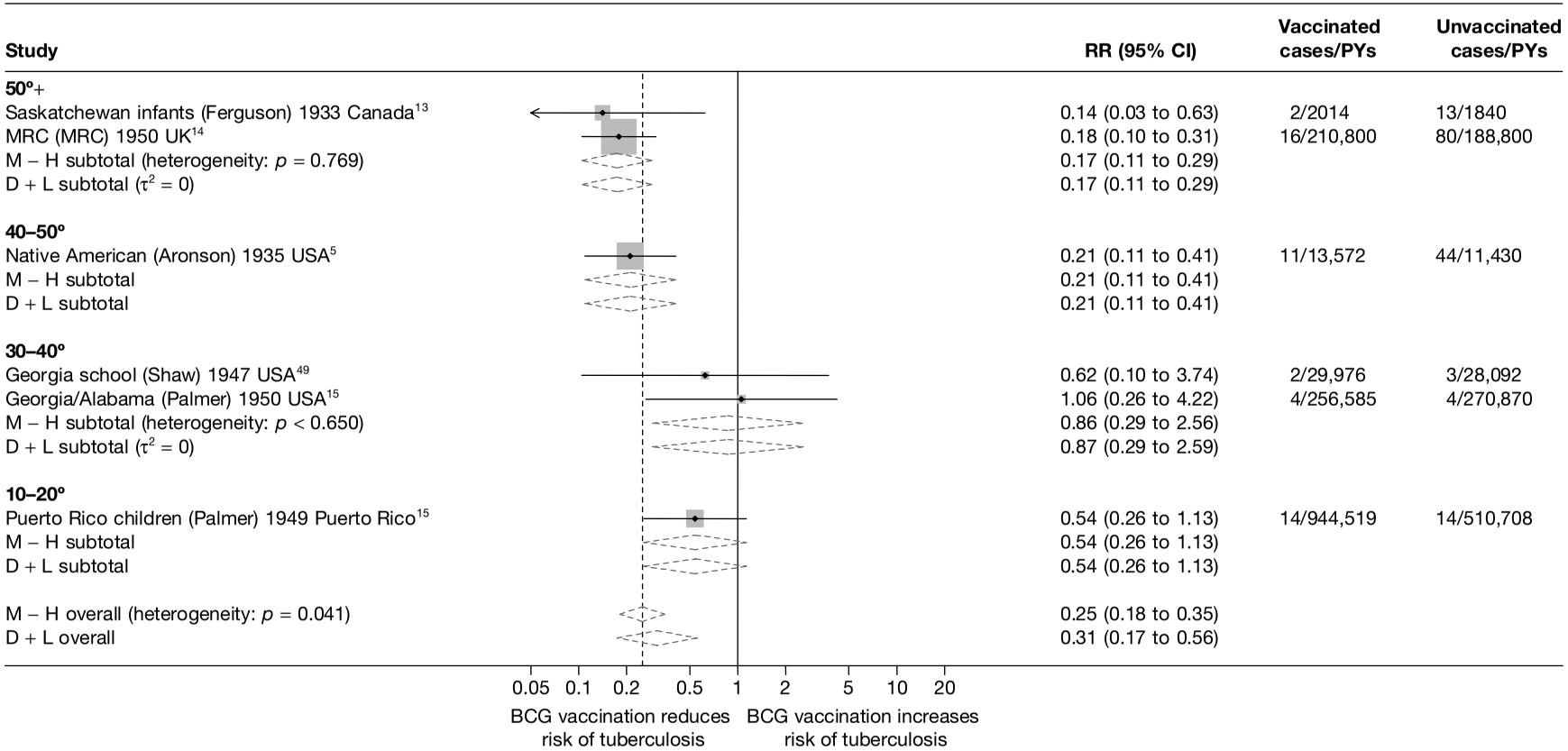

FIGURE 18 Rate ratios (with 95% confidence intervals) comparing the incidence of extrapulmonary tuberculosis among BCG vaccinated individuals with that in unvaccinated individuals for the longest duration of follow-up (see *Table 3*) in RCTs, stratified by latitude of study location (10° bands), ordered by year of study start. D+L, DerSimonian and Laird method; M–H, Mantel–Haenszel method.

by latitude appeared to explain a substantial amount of the between-study variation in effect of BCG vaccination.

Meta-regression analysis

The between-study variation in estimates was explained by stratification on latitude (τ^2 values before and after stratification on 20° latitude were 0.275 and 0.000, respectively) (see *Table 9*). There was some evidence of protection varying with latitude (p-value = 0.100): the overall rate ratio for the 0–20° latitude strata was 2.89 times (95% CI 0.74 to 11.37) the rate ratio for studies above 40° latitude (thus VE correspondingly lower). Similarly, the overall protective effect for the strata 20–40° was 4.64 (0.70 to 30.87) times lower that of studies above 40° latitude.

Stratified analysis by age at vaccination and tuberculin testing stringency, ordered by year study started

The results of trials with outcome data on extrapulmonary tuberculosis disease (excluding outcomes specified as miliary disease or tuberculosis meningitis) were stratified according to age at vaccination and tuberculin testing stringency (*Figure 19*). A consistent, high protective effect was seen in studies undertaking stringent tuberculin testing for school-age vaccination [rate ratio 0.20 (95% CI 0.14 to 0.30)] equivalent to a VE of 80% (95% CI 70% to 86%). The one study of BCG vaccination in neonates also showed substantial high protection with rate ratio 0.14 (95% CI 0.03 to 0.63) [VE equivalent to 86% (95% CI 37% to 97%)]. The Georgia/Alabama study[15] of vaccination in other age groups provided little evidence of an effect of BCG vaccination. This stratification accounted for a substantial amount of heterogeneity.

Meta-regression analysis

Based on meta-regression analyses, the between-study variation appeared to be explained by age at vaccination/tuberculin testing (null model $\tau^2 = 0.275$, after stratification $\tau^2 = 0.000$) (*Table 10*). There was little evidence, however, that the effect of BCG vaccination on extrapulmonary tuberculosis varied with age at vaccination and tuberculin testing (p-value = 0.245); the overall effect of BCG vaccination in those vaccinated at school-age with stringent tuberculin testing was 1.44 times (95% CI 0.05 to 42.74) that of neonatal vaccination studies.

Stratified analysis by risk of diagnostic detection bias, ordered by year study started

Figure 20 shows estimated effect of BCG vaccination on extrapulmonary tuberculosis (excluding tuberculosis meningitis and miliary tuberculosis) stratified according to risk of diagnostic detection bias. There was reasonably consistent evidence of higher protection against extrapulmonary tuberculosis observed in pooled results of the three studies with a lower risk of diagnostic detection bias [rate ratio 0.19 (95% CI 0.12 to 0.28)] corresponding to a VE of 81% (95% CI 72% to 88%). By contrast, all three trials that did not adequately mask vaccination status and without active surveillance showed, overall, less effective results. Risk of diagnostic detection bias appears to explain a substantial amount of the between-study variation in the protective effect of BCG vaccination.

Meta-regression analysis

Stratification on risk of diagnostic detection bias accounted for the between-study variation ($\tau^2 = 0.275$ and 0.000, before and after stratification respectively) (see *Table 10*). There was evidence (p-value = 0.032) that efficacy varied with risk of diagnostic detection bias: overall rate ratios for studies with a higher risk of diagnostic detection bias were 3.35 (95% CI 1.19 to 9.48) times that of studies with a lower risk and hence a lower VE.

Results from univariable meta-regressions indicate that latitude, age at vaccination/tuberculin testing stringency and risk of diagnostic detection bias each explained a large amount of between-study variation in overall BCG vaccination efficacy with a τ^2 value of 0.000 for each of

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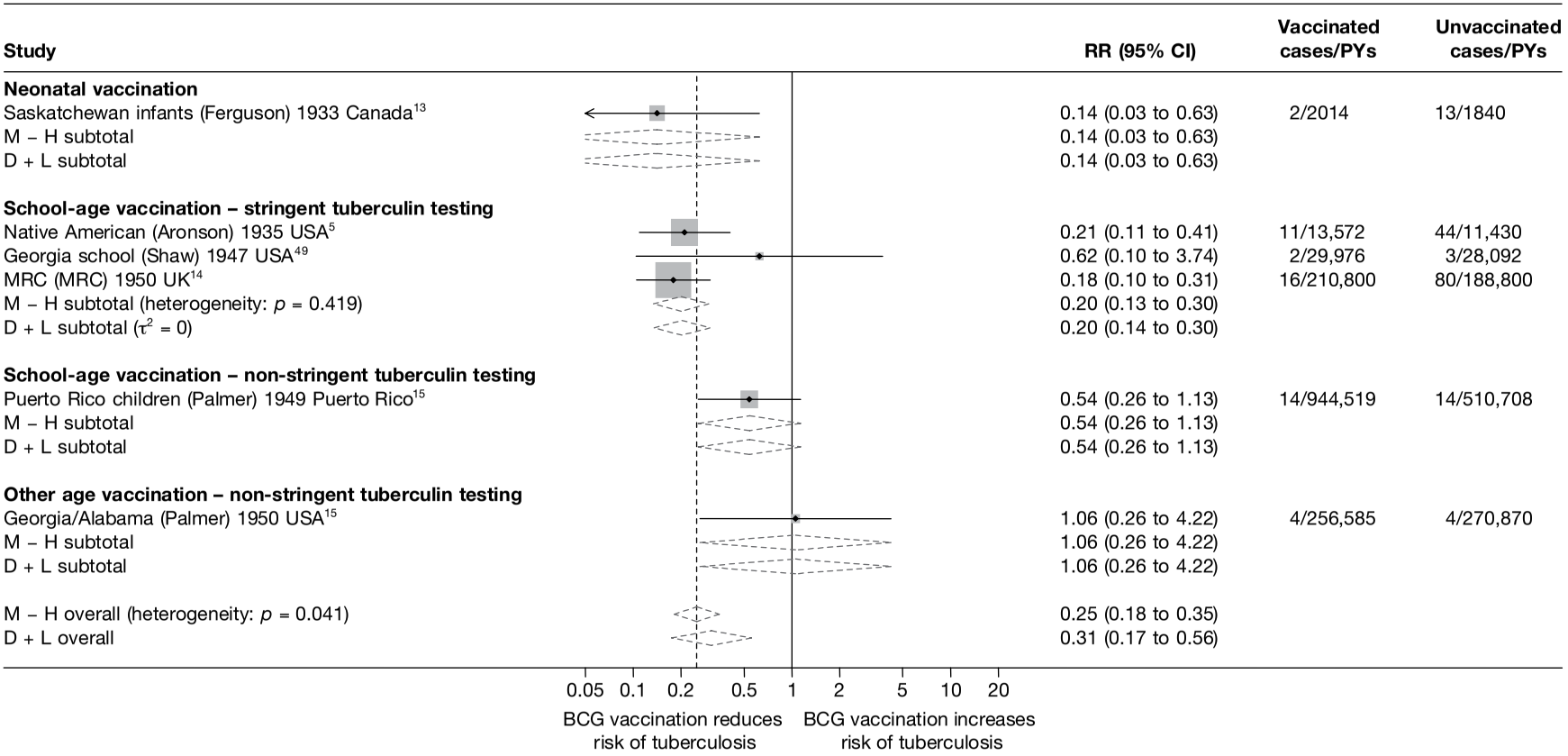

FIGURE 19 Rate ratios (with 95% CI) comparing the incidence of extrapulmonary tuberculosis among BCG vaccinated individuals with that in unvaccinated individuals for the longest duration of follow-up (see *Table 3*) in RCTs, stratified by age at vaccination/tuberculin testing stringency, ordered by year of study start. D+L, DerSimonian and Laird method; M–H, Mantel–Haenszel method.

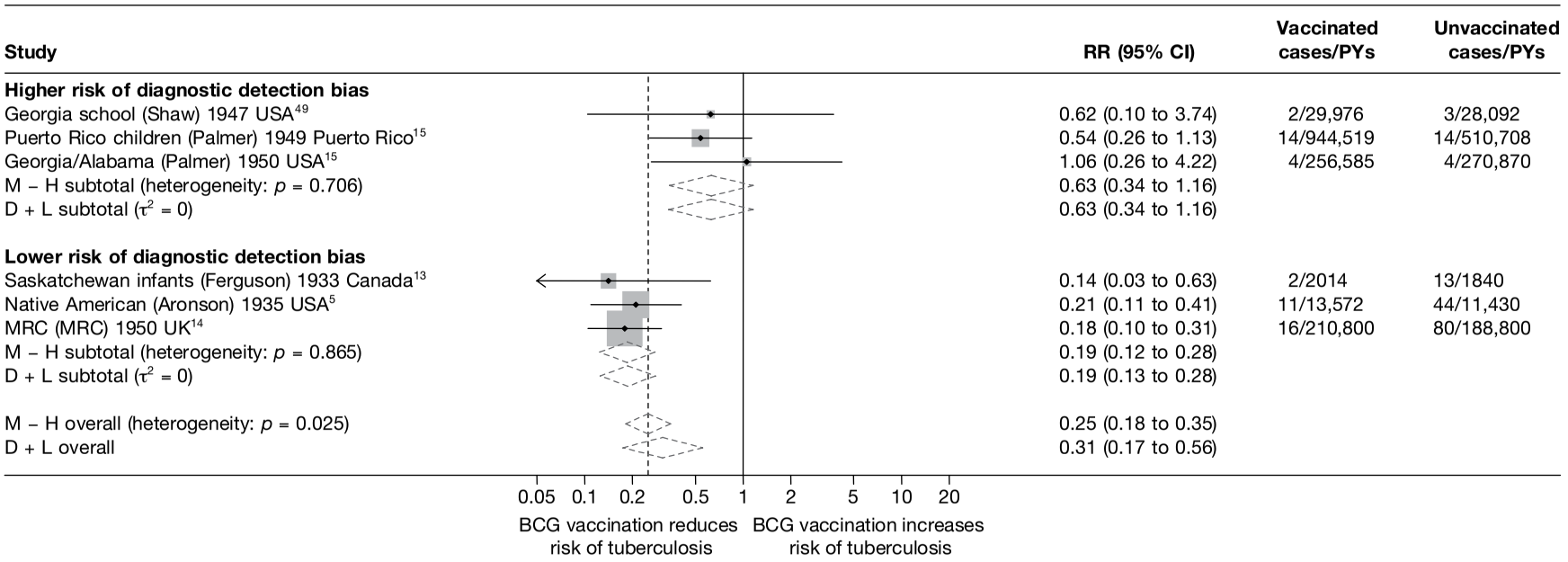

FIGURE 20 Rate ratios (with 95% CI) comparing the incidence of extrapulmonary tuberculosis among BCG vaccinated individuals with that in unvaccinated individuals for the longest duration of follow-up (see *Table 3*) in RCTs, stratified by risk of diagnostic detection bias,[a] ordered by year of study start. a, Diagnostic detection bias is said to occur if the assessor of BCG vaccination outcome is not blinded to vaccination status. D+L, DerSimonian and Laird method; M–H, Mantel–Haenszel method.

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TABLE 10 Ratios of risk ratios (with 95% CI) comparing the incidence of extrapulmonary tuberculosis among vaccinated individuals compared with unvaccinated individuals for the longest duration of follow-up (see *Table 3*) in RCTs, according to univariable meta-regression analysis

Variable	Number of trials	Univariable rate ratios (95% CI)	Univariable model		
			Ratio of rate ratios (95% CI)	*p*-value	τ^2
Null model	6				0.275
Latitude					
>40°	3	0.19 (0.08 to 0.45)	1.00 (ref.)		
20–40°	2	0.87 (0.08 to 9.61)	4.64 (0.70 to 30.87)		
0–20°	1	0.54 (0.11 to 2.74)	2.89 (0.74 to 11.37)	0.100	0.000
Age at vaccination/tuberculin testing combined					
Neonatal	1	0.14 (0.01 to 2183.96)	1.00 (ref.)		
School age/stringent	3	0.20 (0.01 to 2.82)	1.44 (0.05 to 42.74)		
School age/non-stringent	1	0.54 (0.01 to 65.86)	3.85 (0.10 to 148.06)		
Other age/stringent	0				
Other age/non-stringent	1	1.06 (0.01 to 8423.85)	7.51 (0.09 to 652.89)	0.245	0.000
Diagnostic quality					
Lower risk of bias	3	0.19 (0.10 to 0.36)	1.00 (ref.)		
Higher risk of bias	3	0.63 (0.23 to 1.70)	3.35 (1.19 to 9.48)	0.032	0.000
Was the allocation sequence adequately generated?					
Lower risk of bias	0				
Higher risk of bias	6				0.275
Was treatment allocation adequately concealed?					
Lower risk of bias	0				
Higher risk of bias	6				0.275
Was knowledge of the allocated intervention prevented during the study?					
Lower risk of bias	1	0.21 (0.02 to 2.03)	1.00 (ref.)		
Higher risk of bias	5	0.36 (0.11 to 1.19)	1.70 (0.18 to 15.90)	0.547	0.475
Are reports of the study free from the suggestion of selective outcome reporting?					
Lower risk of bias	6				
Higher risk of bias	0				0.275
Was ascertainment of cases complete?					
Lower risk of bias	6				
Higher risk of bias	0				0.275

ref., reference category; τ^2, estimated between-study variance.

these variables, compared with the baseline τ^2 value of 0.275. These results should be interpreted with caution in view of the small number of studies contributing to this analysis.

Tuberculosis mortality

Unstratified analysis ordered by year trial started

Only 8 of the 21 trials presented data on the effect of BCG vaccination on mortality from tuberculosis (*Figure 21*). The Native American trial[5] was the only study with a large number of events observed, all other studies having very few events and wide CIs. Two trials (Illinois

mentally handicapped[50] and Puerto Rico Children[15]) found a substantially increased risk of death in the vaccinated compared with unvaccinated group.

Stratified analysis by latitude (10°), ordered by year study started

Figure 22 shows estimated effects of BCG vaccination against tuberculosis mortality, stratified by latitude of study location. In general, the protection afforded by BCG vaccination is low or absent in studies close to the equator, while there was reasonable consistent evidence of higher levels of protection against mortality in studies conducted at latitude exceeding 40°. The overall effect for studies conducted above 50° was rate ratio 0.17 (95% CI 0.11 to 0.29), corresponding to a high protection [VE of 83% (95% CI 71% to 89%)]. Again this should be interpreted with caution in view of the small number of studies contributing to this analysis. A substantial amount of the between-study variation in protective effect of BCG vaccination appeared to be explained in part by latitude, although residual heterogeneity remained between studies conducted in the same latitude bands.

Meta-regression analysis

Stratifying these studies by latitude (20° bands) accounted for 45% of the between-study variation (null model $\tau^2 = 1.067$, after stratification $\tau^2 = 0.582$) (*Table 11*). There was, however, insufficient evidence on which to suggest that efficacy varied with latitude (p-value = 0.138). The estimate of the rate ratio for studies at latitudes 0–20° was 5.63 (95% CI 0.48 to 66.58) times that of studies of > 20° latitude, pointing towards a corresponding lower VE.

Stratified analysis by age at vaccination and tuberculin testing stringency, ordered by year study started

The results in *Figure 23* show the effect of BCG vaccination on tuberculosis mortality, stratified by age at which vaccination was administered and stringency of the tuberculin testing method. The most consistent protective effect of BCG vaccination was seen in neonatal vaccination and school-age vaccination with stringent tuberculin testing [overall good protection with rate ratio from five studies of 0.34 (95% CI 0.12 to 0.92) corresponding to a VE of 66% (95% CI 8% to 88%) and rate ratio from one study of 0.26 (95% CI 0.17 to 0.40) corresponding to a VE of 74% (95% CI 60% to 83%), respectively]. There was no evidence of a protective effect of BCG vaccination in the one study each of 'other' age groups of vaccination, with stringent or non-stringent tuberculin testing. Stratification by age at vaccination appeared to explain some of the between-study variation observed.

Meta-regression analysis

Based on meta-regression analyses, age at vaccination and tuberculin testing stringency accounted for 31% of the between-study variation observed (null model $\tau^2 = 1.067$, after stratification $\tau^2 = 0.731$) (see *Table 11*). There was, however, insufficient evidence (p-value = 0.369) that BCG vaccination efficacy against tuberculosis mortality varied according to age at vaccination/tuberculin testing stringency. The point estimate of effect (rate ratio) for studies of school-age vaccination with stringent tuberculin testing was 0.53 (95% CI 0.02 to 13.26) times that of neonatal vaccination studies, whereas rate ratio for BCG vaccination at other ages with stringent tuberculin testing was 3.81 (95% CI 0.07 to 202.48) times higher and VE correspondingly lower.

Stratified analysis by risk of diagnostic detection bias, ordered by year study started

Figure 24 presents the estimated effects of BCG vaccination on tuberculosis mortality stratified by risk of diagnostic detection bias. The most consistent protective effect was seen in studies assessed as having a lower risk of diagnostic detection bias, with rate ratio 0.32 (95% CI 0.17 to 0.59), corresponding to a good protective effect [VE of 68% (95% CI 41% to 83%)], whereas

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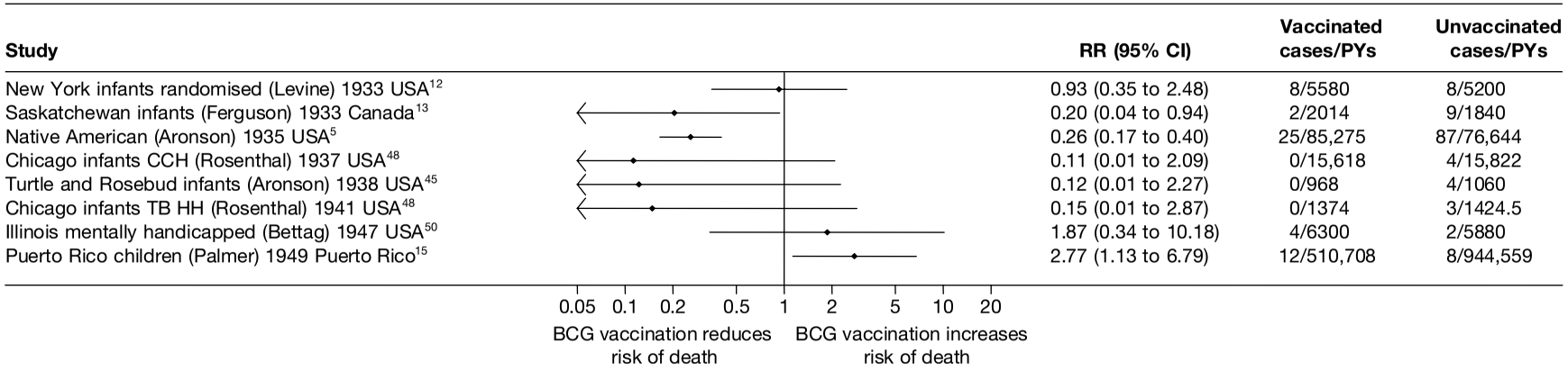

FIGURE 21 Rate ratios (with 95% CI) comparing the incidence of tuberculosis mortality among BCG vaccinated individuals with that in unvaccinated individuals for the longest duration of follow-up (see *Table 3*) in RCTs, ordered by year of study start. CCH, Cook County Hospital; TB HH, tuberculosis households.

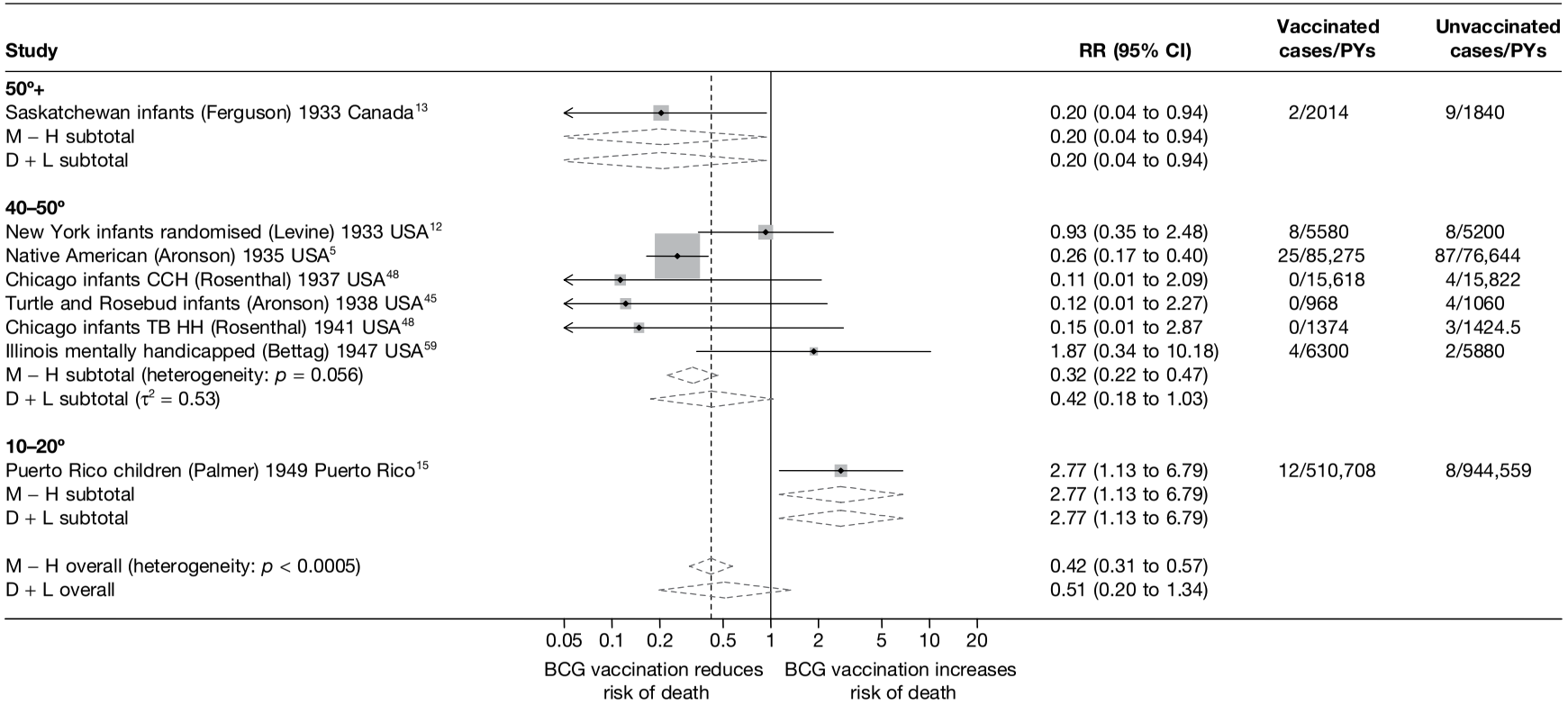

FIGURE 22 Rate ratios (with 95% CI) comparing the incidence of tuberculosis mortality among BCG vaccinated individuals with that in unvaccinated individuals for the longest duration of follow-up (see *Table 3*), in RCTs stratified by latitude of study location (10° bands), ordered by year of study start. CCH, Cook County Hospital; D+L, DerSimonian and Laird method; M–H, Mantel–Haenszel method; TB HH, tuberculosis households.

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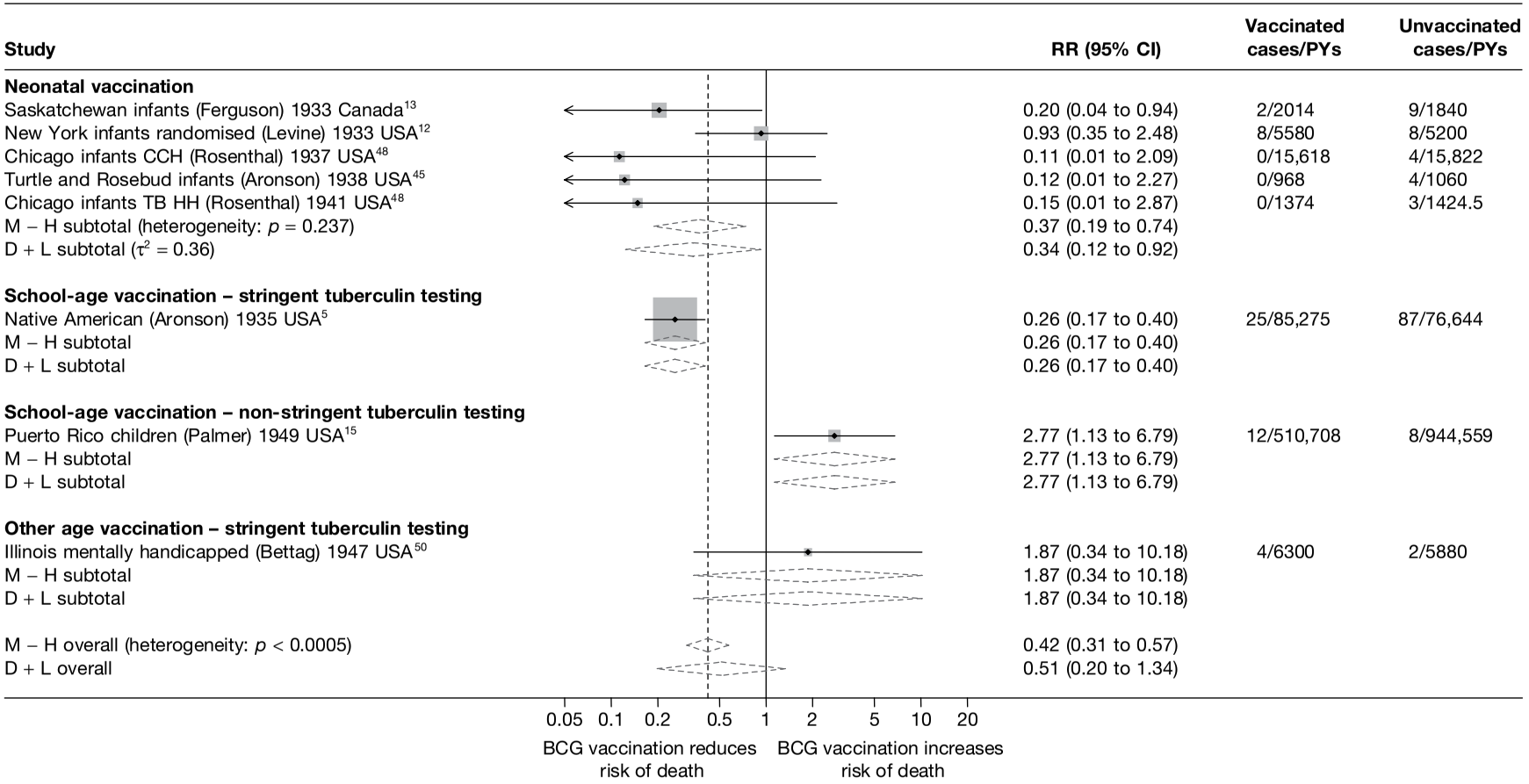

FIGURE 23 Rate ratios (with 95% CI) comparing the incidence of tuberculosis mortality among BCG vaccinated individuals with that in unvaccinated individuals for the longest duration of follow-up (see *Table 3*) in RCTs, stratified by age at vaccination/tuberculin testing stringency, ordered by year of study start. CCH, Cook County Hospital; D+L, DerSimonian and Laird method; M–H, Mantel–Haenszel method; TB HH, tuberculosis households.

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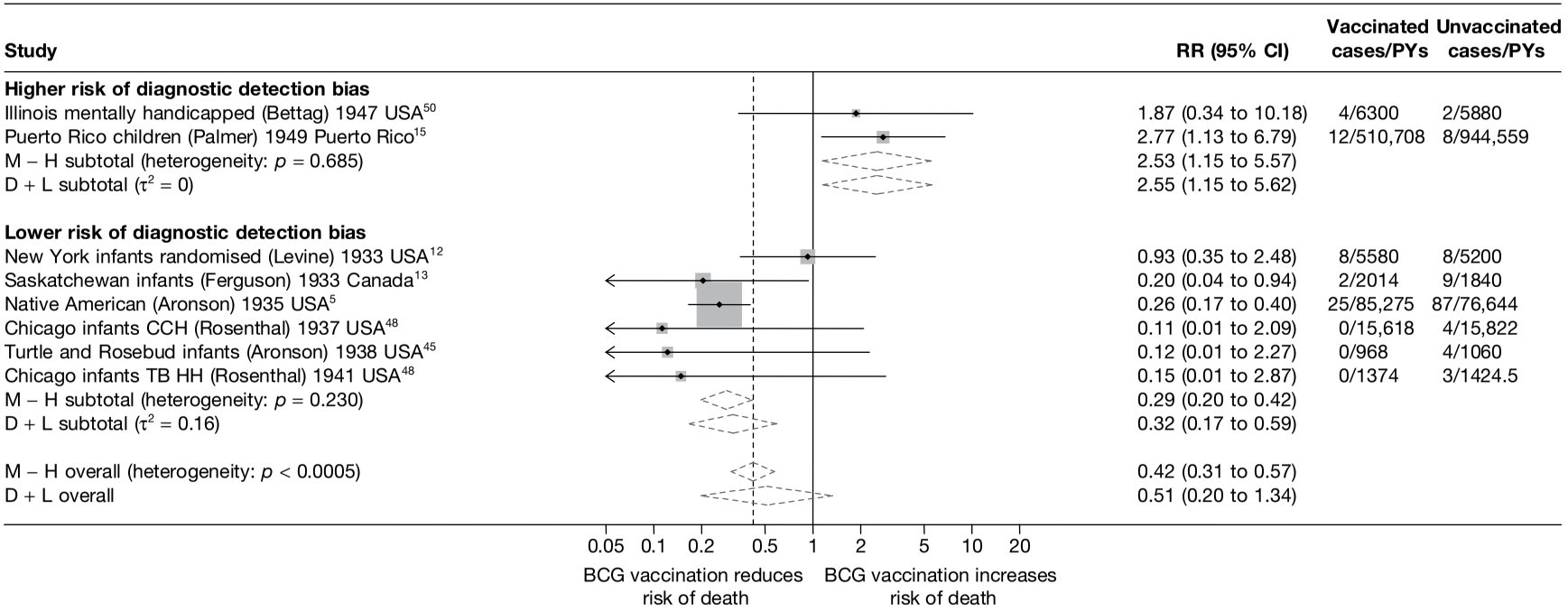

FIGURE 24 Rate ratios (with 95% CI) comparing the incidence of tuberculosis mortality among BCG vaccinated individuals with that in unvaccinated individuals for the longest duration of follow-up (see *Table 3*) in RCTs, stratified by risk of diagnostic detection bias,[a] ordered by year of study start. a, Diagnostic detection bias occurs if the assessor of BCG vaccination outcome is not blinded to vaccination status. CCH, Cook County Hospital; D+L, DerSimonian and Laird method; M–H, Mantel–Haenszel method; TB HH, tuberculosis households.

there was an absence of protective effect of BCG vaccination in two trials with a higher risk of diagnostic detection bias. Stratification on risk of diagnostic detection bias appeared to explain a substantial amount of the between-study variation, although residual heterogeneity remained within strata.

Meta-regression analysis

Stratification on risk of diagnostic detection bias accounted for 76% of the between-study variation (null model $\tau^2 = 1.067$, after stratification $\tau^2 = 0.260$) (see *Table 11*). There was more evidence (p-value = 0.034) that efficacy varied with latitude: rate ratio for studies with higher risk of bias was 6.65 (95% CI 1.22 to 36.09) times greater than that of studies with a lower risk of bias.

Results from univariable meta-regressions indicate that latitude, age at vaccination/tuberculin testing stringency and risk of diagnostic detection bias each appeared to explain some of the between-study heterogeneity in overall BCG vaccination efficacy with τ^2 values 0.582, 0.731 and 0.260, respectively, compared with the baseline τ^2 value (1.067), but only with risk of diagnosis detection bias was there sufficient strong evidence of an effect.

Observational studies

Pulmonary tuberculosis

A variety of observational studies have assessed the effectiveness of BCG vaccination in protecting against pulmonary tuberculosis: eight eligible case–control studies (in which eligibility was that control subjects were selected from the same population from which cases arose), 12 eligible cohort studies (in which the comparison group was tuberculin negative individuals at the start of follow-up), four case population studies (where the rate in BCG vaccinated was compared with rates in the estimated tuberculin negative populations), six cross-sectional studies and three outbreak studies. These studies were conducted in a range of countries between 1936 and 2004. *Figures 25–28* present the unstratified results of these observational studies, ordered chronologically by date of study start. While there is some degree of variation in the estimates of effectiveness of BCG vaccination, the majority of studies for each study design showed evidence consistent with a protective effect of BCG vaccination against pulmonary tuberculosis.

Estimates of protection by BCG vaccination against pulmonary tuberculosis varied across the eight case–control studies, ranging from a strong protective effect in Thailand[65] [OR 0.30 (95% CI 0.24 to 0.38)], to clinical benefit in Bangalore children[56] [OR 0.88 (95% 0.53 to 1.17)]. In 11 of the 12 cohorts in *Figure 26* there was strong evidence of a protective effect, ranging from rate ratio 0.56 (95% CI 0.39 to 0.81) in the control arm of the Brazil revaccination study[6] [equivalent to VE of 44% (95% CI 19% to 61%)] to rate ratio 0.01 (95% CI 0.00 to 0.14) in UK medical students[100] [VE 99% (95% CI 86% to 100%)], with one study from Karonga, Malawi[24] showing no evidence of clinical benefit. Two of the case population studies, those conducted in Poland[160] and Canada (Quebec Pulmonary[158]), showed evidence of a high level of protection against pulmonary tuberculosis, whereas the other two studies showed some evidence of a protective effect. Four of the six cross-sectional studies found strong evidence of BCG vaccination reducing the risk of pulmonary tuberculosis (see *Figure 28*), with the Kenyan[187] and Lebanese children[193] studies suggesting no clinical benefit from BCG vaccination. Two of the three outbreak studies suggested limited clinical benefit from BCG vaccination, whereas the Cork toddler outbreak[198] showed evidence of a protective effect [rate ratio 0.09 (95% CI 0.01 to 1.52)].

Unstratified analysis ordered by year study started

Case–control studies

See *Figure 25*.

Cohort studies

See *Figure 26*.

TABLE 11 Ratios of risk ratios (with 95% CI) comparing the incidence of tuberculosis mortality among vaccinated individuals compared with unvaccinated individuals for the longest duration of follow-up (see *Table 3*) in RCTs, according to univariable meta-regression analysis

			Univariable model		
Variable	**Number of trials**	**Univariable rate ratios (95% CI)**	**Ratio of rate ratios (95% CI)**	***p*-value**	τ^2
Null model	8				1.067
Latitude					
>40°	7	0.49 (0.14 to 1.69)	1.00 (ref.)		
20–40°	0				
0–20°	1	2.77 (0.28 to 27.27)	5.63 (0.48 to 66.58)	0.138	0.582
Age at vaccination/tuberculin testing stringency					
Neonatal	5	0.49 (0.04 to 5.37)	1.00 (ref.)		
School age/stringent	1	0.26 (0.02 to 4.31)	0.53 (0.02 to 13.26)		
School age/non-stringent	1	2.77 (0.13 to 60.59)	5.67 (0.19 to 170.89)		
Other age/stringent	1	1.87 (0.04 to 89.71)	3.81 (0.07 to 202.48)		
Other age/non-stringent	0			0.369	0.731
Diagnostic detection bias					
Lower risk of bias	6	0.36 (0.13 to 1.02)	1.00 (ref.)		
Higher risk of bias	2	2.45 (0.57 to 10.47)	6.65 (1.22 to 36.09)	0.034	0.260
Was the allocation sequence adequately generated?					
Lower risk of bias	0				
Higher risk of bias	8				1.067
Was treatment allocation adequately concealed?					
Lower risk of bias	1				
Higher risk of bias	7				
Was knowledge of the allocated intervention prevented during the study?					
Lower risk of bias	1	0.25 (0.02 to 2.73)	1.00 (ref.)		
Higher risk of bias	7	1.07 (0.26 to 4.38)	4.13 (0.30 to 56.56)	0.232	0.790
Are reports of the study free from the suggestion of selective outcome reporting?					
Lower risk of bias	8				
Higher risk of bias	0				1.067
Was ascertainment of cases complete?					
Lower risk of bias	8				
Higher risk of bias	0				1.067

ref., reference category; τ^2, estimated between-study variance.

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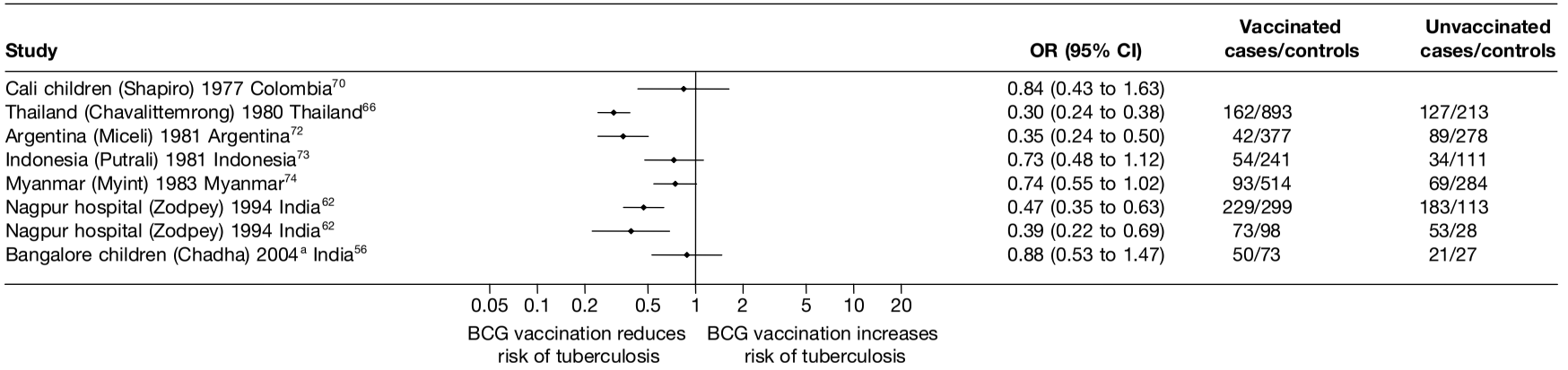

FIGURE 25 Odds ratios (with 95% CI) comparing the BCG vaccination status of pulmonary tuberculosis cases and control subjects in case–control studies, ordered by year of study start. a, Date of study publication was used if study start date was not available.

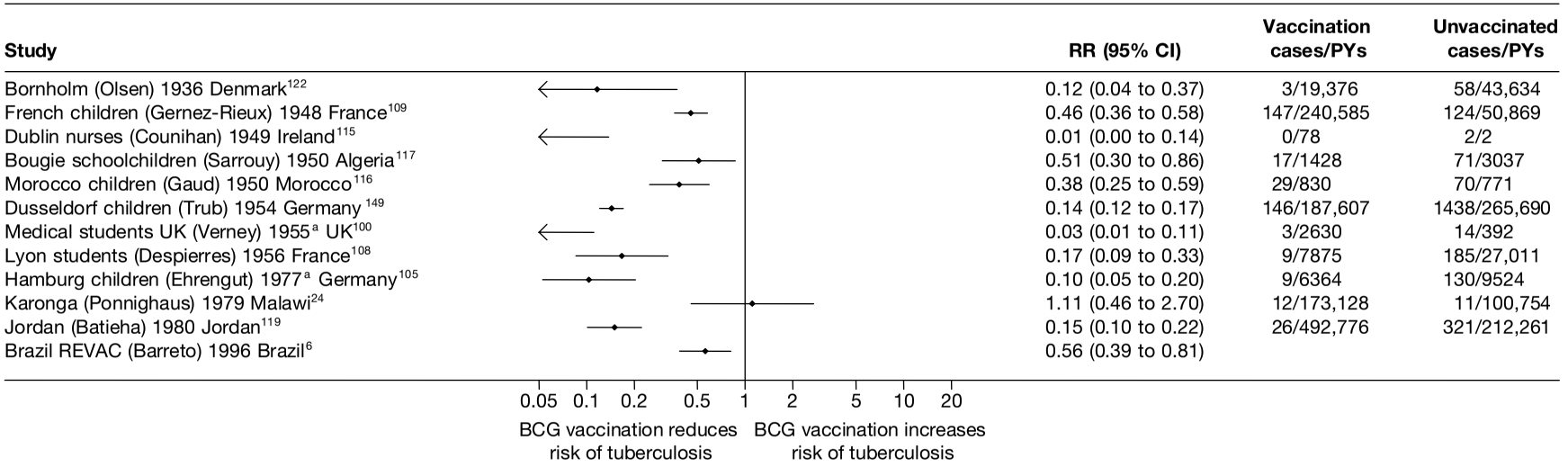

FIGURE 26 Rate ratios (with 95% CI) comparing the incidence of pulmonary tuberculosis among BCG vaccinated individuals with that in unvaccinated individuals for the longest duration of follow-up (see *Table 4*) in cohort studies, ordered by year of study start. a, Date of study publication was used if study start date was not available.

Case population studies
See *Figure 27*.

Cross-sectional studies
See *Figure 28*.

Outbreak studies
See *Figure 29*.

Stratified analysis by latitude (10°), ordered by year study started
Forest plots in *Figures 30–33* present results from observational studies on the protective effect of BCG vaccination against pulmonary tuberculosis stratified by 10° latitude bands of study location. No case–control studies were identified above 40° of latitude, but there was reasonable evidence of the strongest protective effect in all studies, apart from the cross-sectional ones, at latitudes further from the equator. All outbreak studies were located above 50° latitude.

Meta-regression analysis
Using such an analysis, however, indicated that stratification on latitude explained only a small amount (9%) of the between-study heterogeneity within case–control studies (null model $\tau^2 = 0.141$, after stratification $\tau^2 = 0.128$). There was little evidence to suggest that BCG vaccination effectiveness varies with latitude (p-value = 0.199) in this study type (*Table 12*). Latitude explained a more substantial amount of heterogeneity (42%) in cohort studies (τ^2 values before and after stratification = 0.872 and 0.509, respectively, *Table 13*), and some evidence (p-value = 0.060) that BCG vaccination effectiveness varies with latitude and with study design (retrospective cohort studies were more likely to show a protective effect than prospective cohort studies). None of the between-study variation seen within cross-sectional studies was found to be associated with latitude (τ^2 values before and after stratification = 0.249 and 0.599, respectively (*Table 14*). There were an insufficient number of case population studies to undertake meta-regression analyses.

Case–control studies
See *Figure 30*.

Cohort studies
See *Figure 31*.

Case population studies
See *Figure 32*.

Cross-sectional studies
See *Figure 33*.

Stratified analysis age at vaccination, ordered by year study started
Estimated effects of BCG vaccination on pulmonary tuberculosis from observational studies were stratified by age at vaccination (*Figures 34–37*). Only one case–control study of pulmonary tuberculosis did not have neonatal BCG vaccination (*Figure 34*). This study did not show a protective effect of vaccination, whereas the pooled estimate of neonatal vaccination studies was consistent with a moderate protective effect: OR 0.53 (95% CI 0.39 to 0.72), equivalent to a VE of 47% (95% CI 28% to 61%).

Results from the cohort studies showed some variation with neonatal BCG vaccination appearing to provide a good protective effect [rate ratio 0.21 (95% CI 0.08 to 0.56)], compared with school-age vaccination [rate ratio 0.35 (95% CI 0.21 to 0.58)] (see *Figure 35*). Results from studies of

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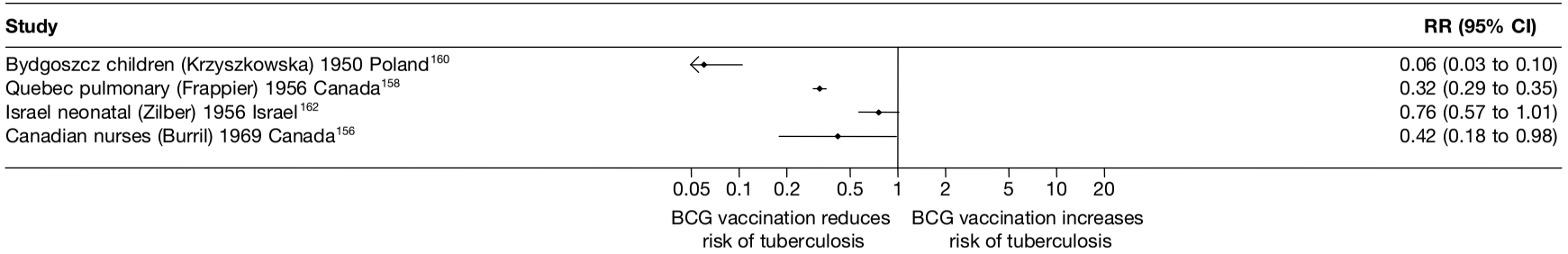

FIGURE 27 Rate ratios (with 95% CI) comparing the incidence of pulmonary tuberculosis among BCG vaccinated individuals with that in unvaccinated individuals for the longest duration of follow-up (see *Table 5)* in case population studies, ordered by year of study start.

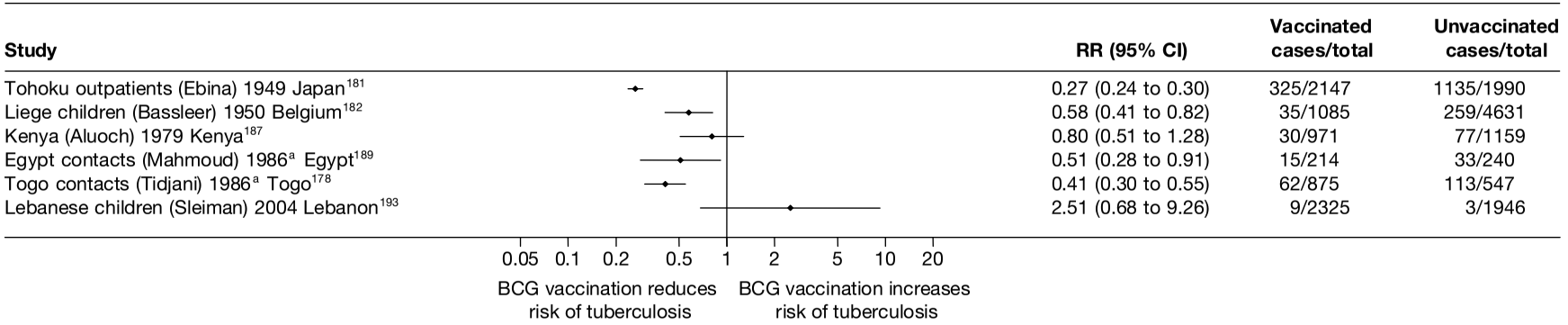

FIGURE 28 Risk ratios (with 95% CI) comparing the prevalence of pulmonary tuberculosis among BCG vaccinated individuals with that in unvaccinated individuals in cross-sectional studies, ordered by year of study start. a, Date of study publication was used if study start date was not available.

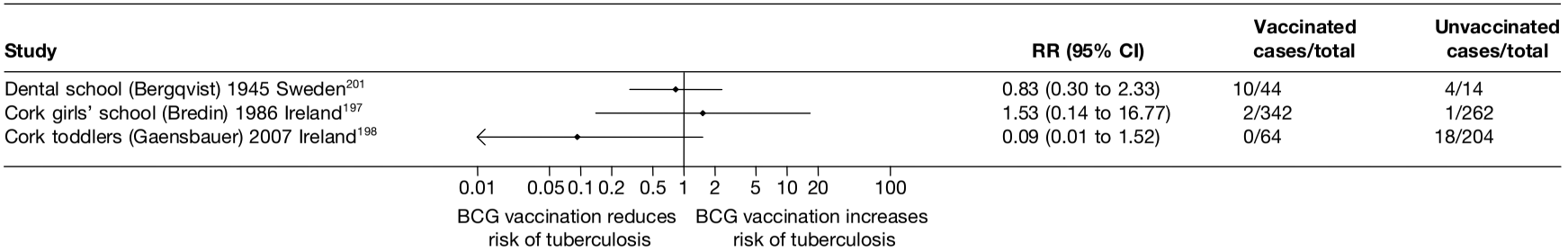

FIGURE 29 Risk ratios (with 95% CI) comparing the incidence of pulmonary tuberculosis among BCG vaccinated individuals with that in unvaccinated individuals in outbreak studies, ordered by year of study start.

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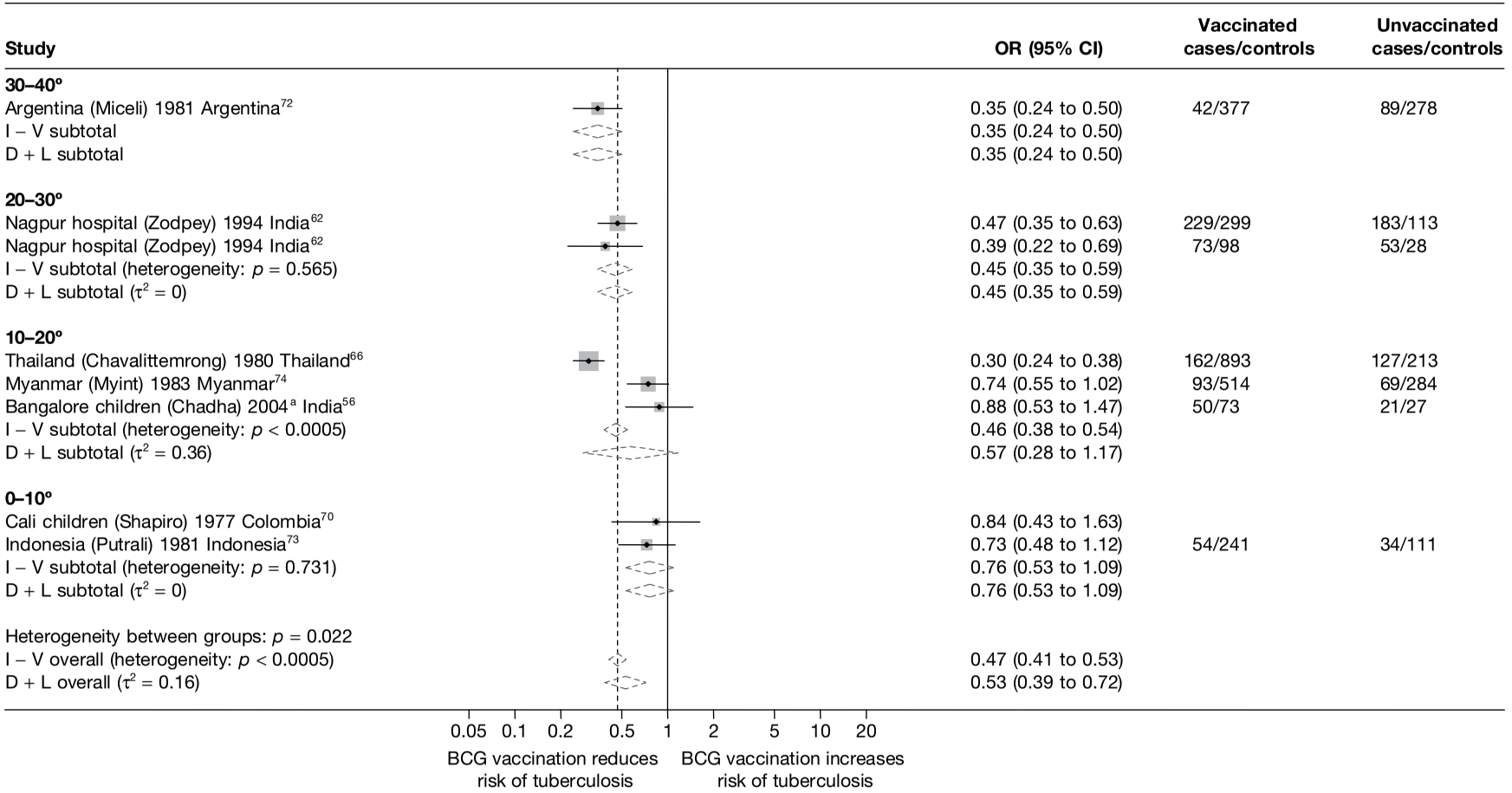

FIGURE 30 Odds ratios (with 95% CI) comparing the BCG vaccination status of pulmonary tuberculosis cases and control subjects in case–control studies, stratified by latitude of study location (10° bands), ordered by year of study start. a, Date of study publication was used if study start date was not available. D+L, DerSimonian and Laird method; I–V, inverse variance method.

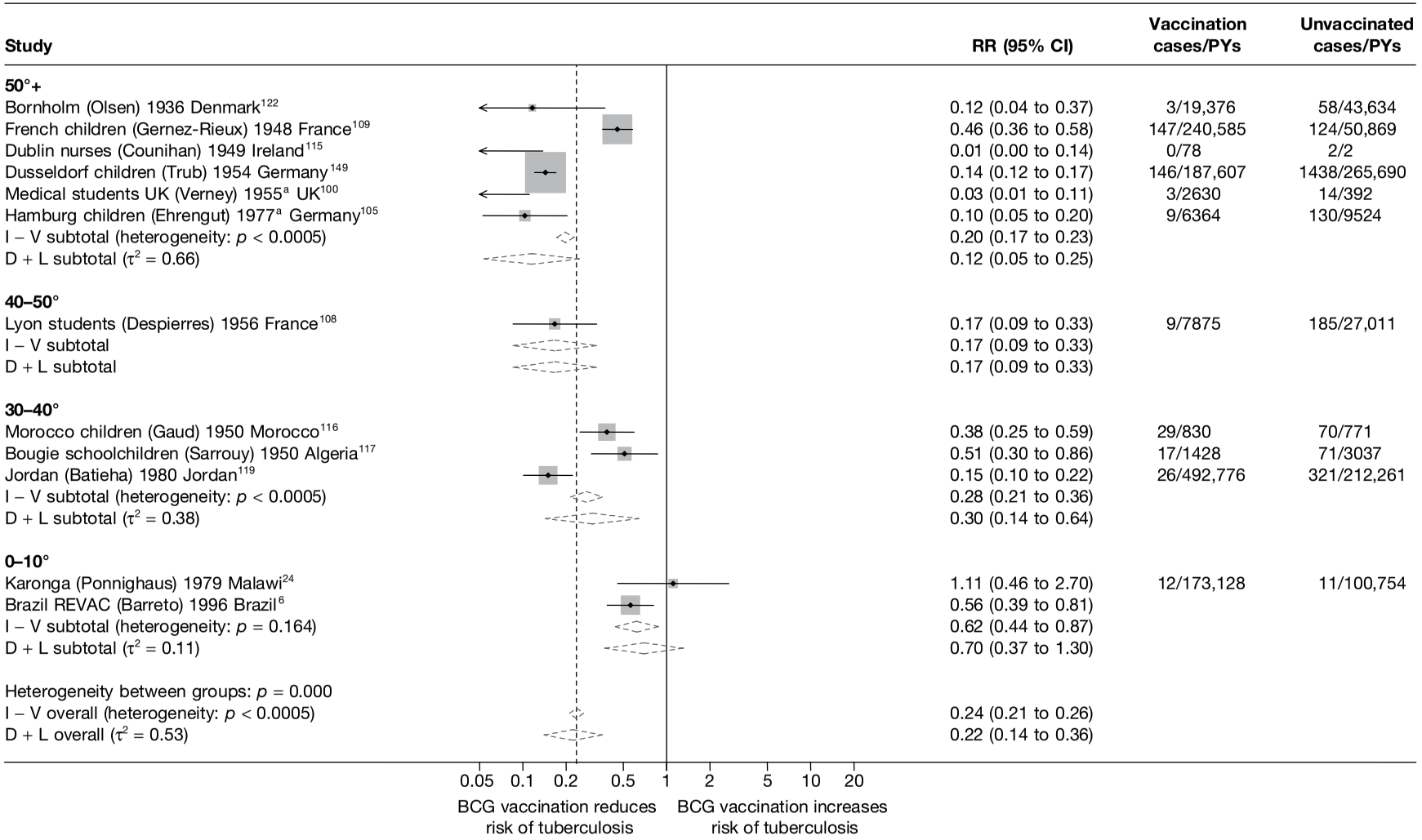

FIGURE 31 Rate ratios (with 95% CI) comparing the incidence of pulmonary tuberculosis among BCG vaccinated individuals with that in unvaccinated individuals for the longest duration of follow-up (see *Table 4*) in cohort studies, stratified by latitude of study location (10° bands), ordered by year of study start. a, Date of study publication was used if study start date was not available. D + L, DerSimonian and Laird method; I–V, inverse variance method.

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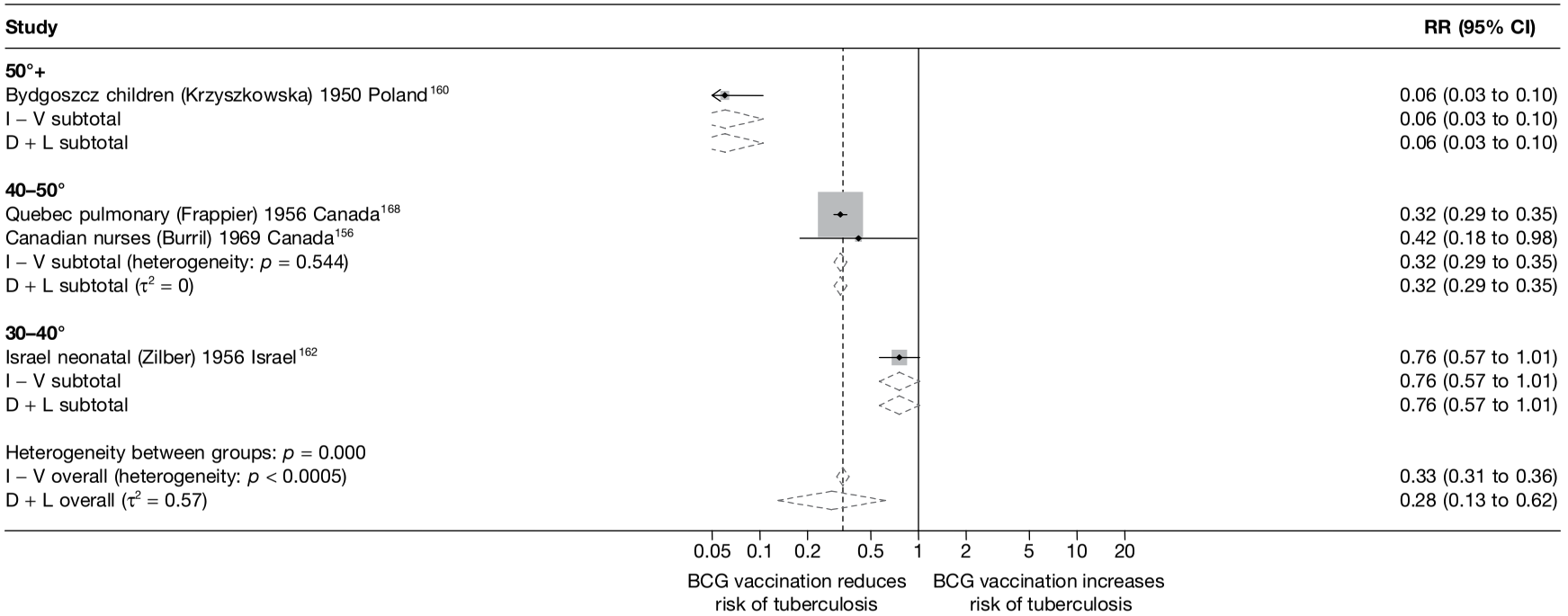

FIGURE 32 Rate ratios (with 95% CI) comparing the incidence of pulmonary tuberculosis among BCG vaccinated individuals with that in unvaccinated individuals for the longest duration of follow-up (see *Table 5*) in case population studies, stratified by latitude of study location (10° bands), ordered by year of study start. D+L, DerSimonian and Laird method; I–V, inverse variance method.

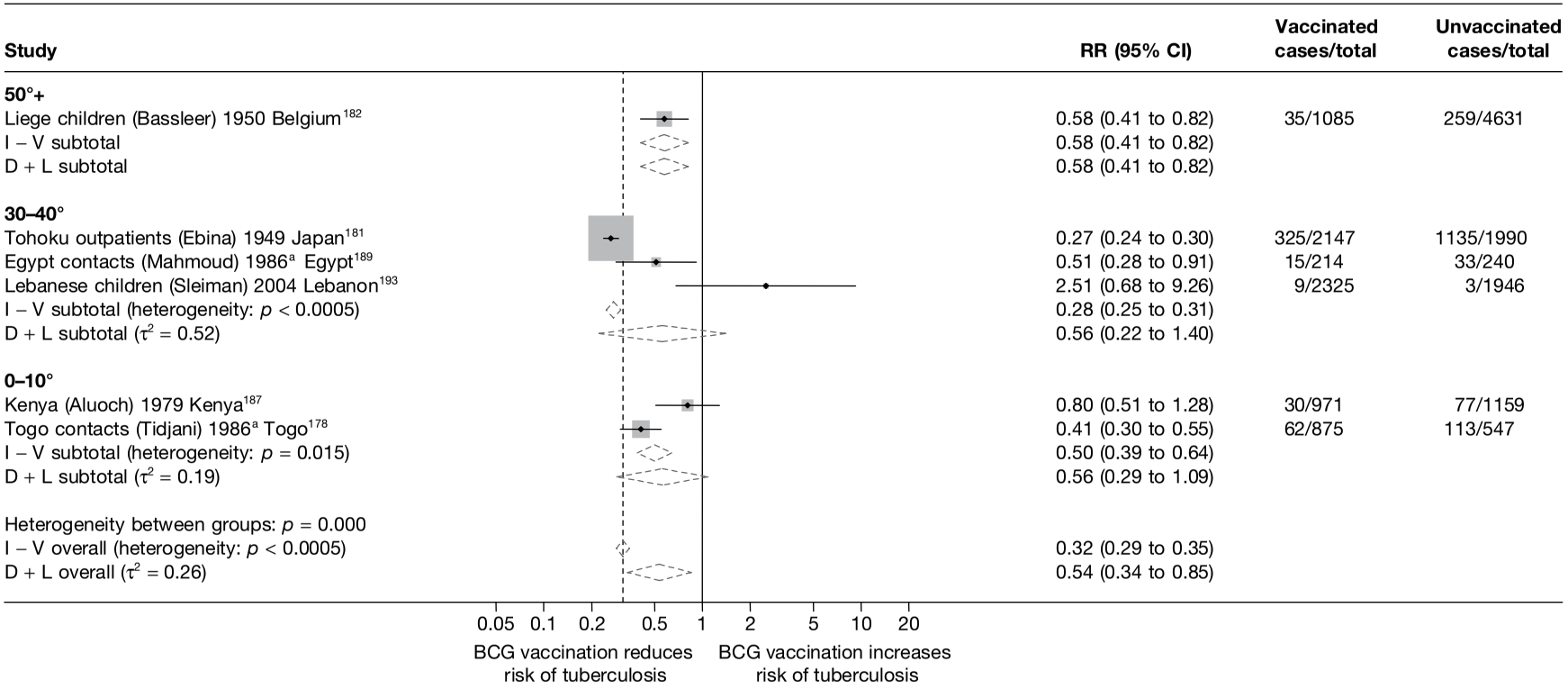

FIGURE 33 Risk ratios (with 95% CI) comparing the prevalence of pulmonary tuberculosis among BCG vaccinated individuals with that in unvaccinated in cross-sectional studies, stratified by latitude of study location (10° bands), ordered by year of study start. a, Date of study publication was used if study start date was not available. D+L, DerSimonian and Laird method; I–V, inverse variance method.

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vaccination in other age groups showed highly protective effect, with the rate ratio ranging from 0.01 (95% CI 0.00 to 0.14) in the Dublin nurses study[115] to 0.12 (95% CI 0.04 to 0.37) in the Bornholm study.[122]

One of the two case population studies evaluating neonatal BCG vaccination (Bydgoszcz children),[160] suggested a very high level of effectiveness, whereas the other (Israel neonatal) study,[162] showed very little reduction in the risk of pulmonary tuberculosis, similar to the other two case population studies of school-age and other age vaccination, respectively. Only one of the cross-sectional studies assessed the effect of neonatal vaccination on pulmonary tuberculosis and showed a moderate protective effect, as did the two investigating school-age vaccination. Little protection was noted in those examining vaccinations in other age groups (see *Figure 37*). Similarly, little protection was noted in the outbreak study in other age groups (*Figure 39*), whereas overall moderate efficacy was seen in neonatal vaccination outbreak studies.

Meta-regression analysis

Using this method, stratification on age at vaccination accounted for only some of the heterogeneity in cohort studies (τ^2 values before and after stratification were 0.872 and 0.546, respectively, see *Table 13*) and some evidence (p-value = 0.049) that age at vaccination is associated with the size of BCG vaccination protective effect.

Case–control studies

See *Figure 34*.

Cohort studies

See *Figure 35*.

Case population studies

See *Figure 36*.

Cross-sectional studies

See *Figure 37*.

Outbreak studies

See *Figure 38*.

Stratified analysis by study design, ordered by year study started

Cohort studies

Figure 39 presents estimated effects of BCG vaccination against pulmonary tuberculosis in cohort studies, stratified by study design. The strongest protective effect of BCG vaccination was seen in retrospective cohort studies with rate ratio 0.15 (95% CI 0.13 to 0.18), corresponding to a high level of protection with a VE of 85% (95% CI 82% to 87%). Stratification by study design accounted for a substantial amount of heterogeneity, but residual between-study variation remained, particularly in the retrospective cohort study group.

Meta-regression analysis

Stratification on study design for cohorts explained 61% of the between-study variation observed within these studies (τ^2 null model = 0.872, τ^2 values after stratification on study design = 0.342) (see *Table 13*). There was evidence that BCG vaccination effectiveness varies depending on cohort study design (p-value = 0.018). The overall rate ratio for retrospective cohort studies was 0.27 (95% CI 0.10 to 0.76) times the overall rate ratio for prospective studies, corresponding to a protective effect approximately 73% higher in retrospective compared with prospective studies.

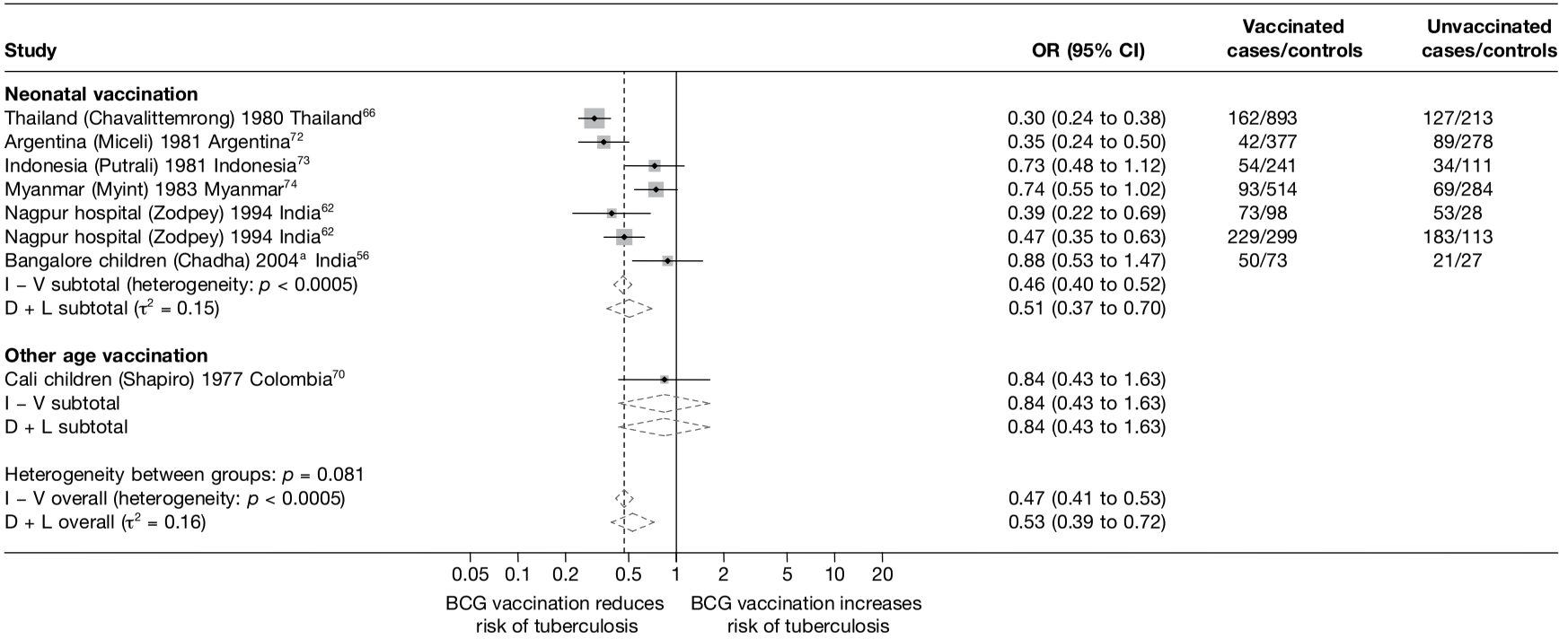

FIGURE 34 Odds ratios (with 95% CI) comparing the BCG vaccination status of pulmonary tuberculosis cases and control subjects in case–control studies, stratified by age at vaccination, ordered by year of study start. a, Date of study publication was used if study start date was not available. D+L, DerSimonian and Laird method; I–V, inverse variance method.

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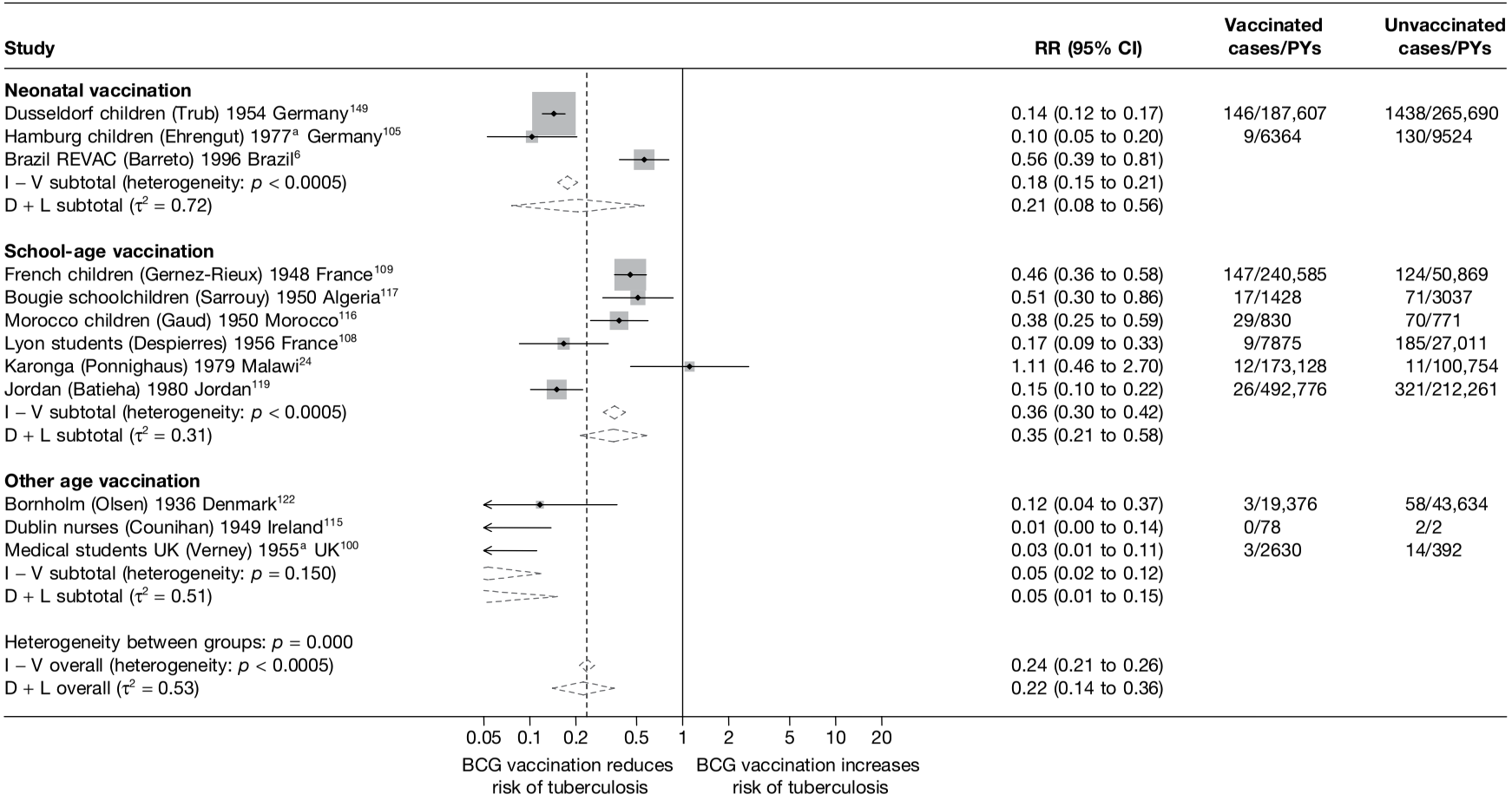

FIGURE 35 Rate ratios (with 95 CI) comparing the incidence of pulmonary tuberculosis among BCG vaccinated individuals with that in unvaccinated individuals for the longest duration of follow-up (see *Table 4*) in cohort studies, stratified by age at vaccination, ordered by year of study start. a, Date of study publication was used if study start date was not available. D+L, DerSimonian and Laird method; I–V, inverse variance method.

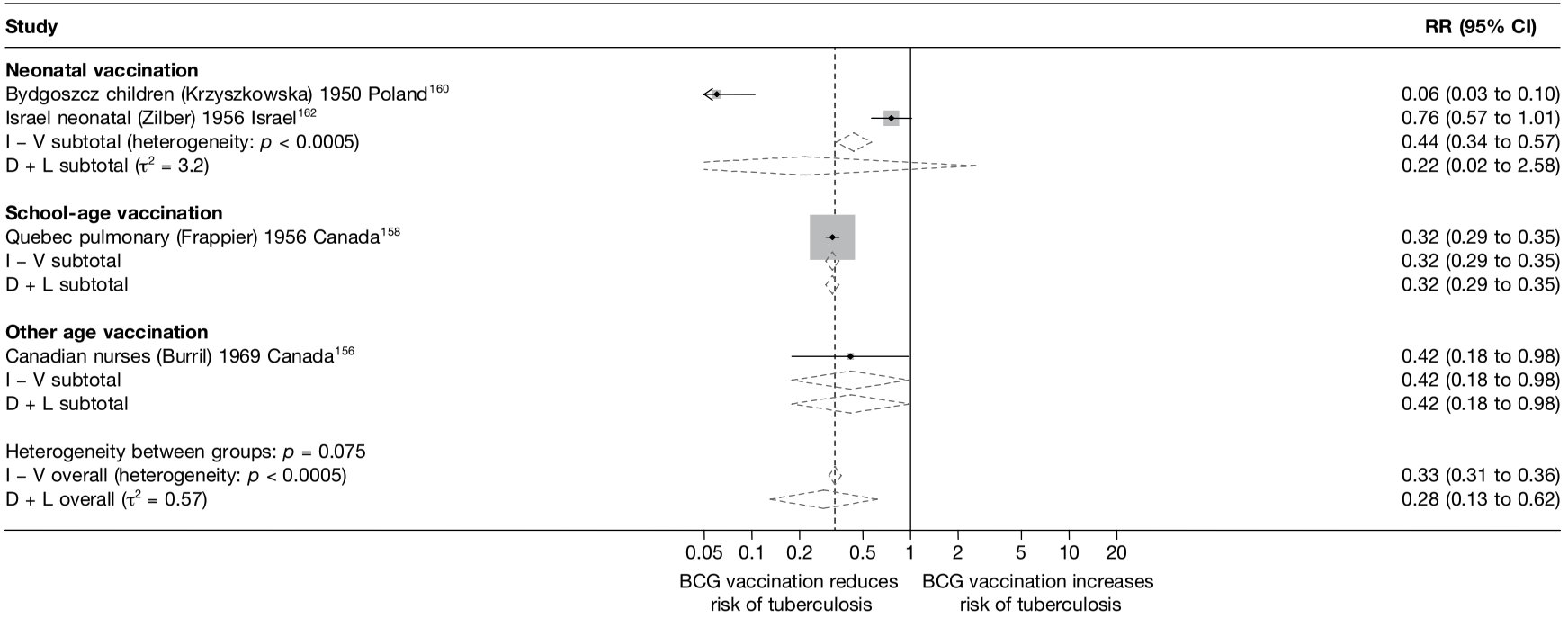

FIGURE 36 Rate ratios (with 95% CI) comparing the incidence of pulmonary tuberculosis among BCG vaccinated individuals with that in unvaccinated individuals for the longest duration of follow-up (see *Table 5*) in case population studies, stratified by age at vaccination, ordered by year of study start. D + L, DerSimonian and Laird method; I–V, inverse variance method.

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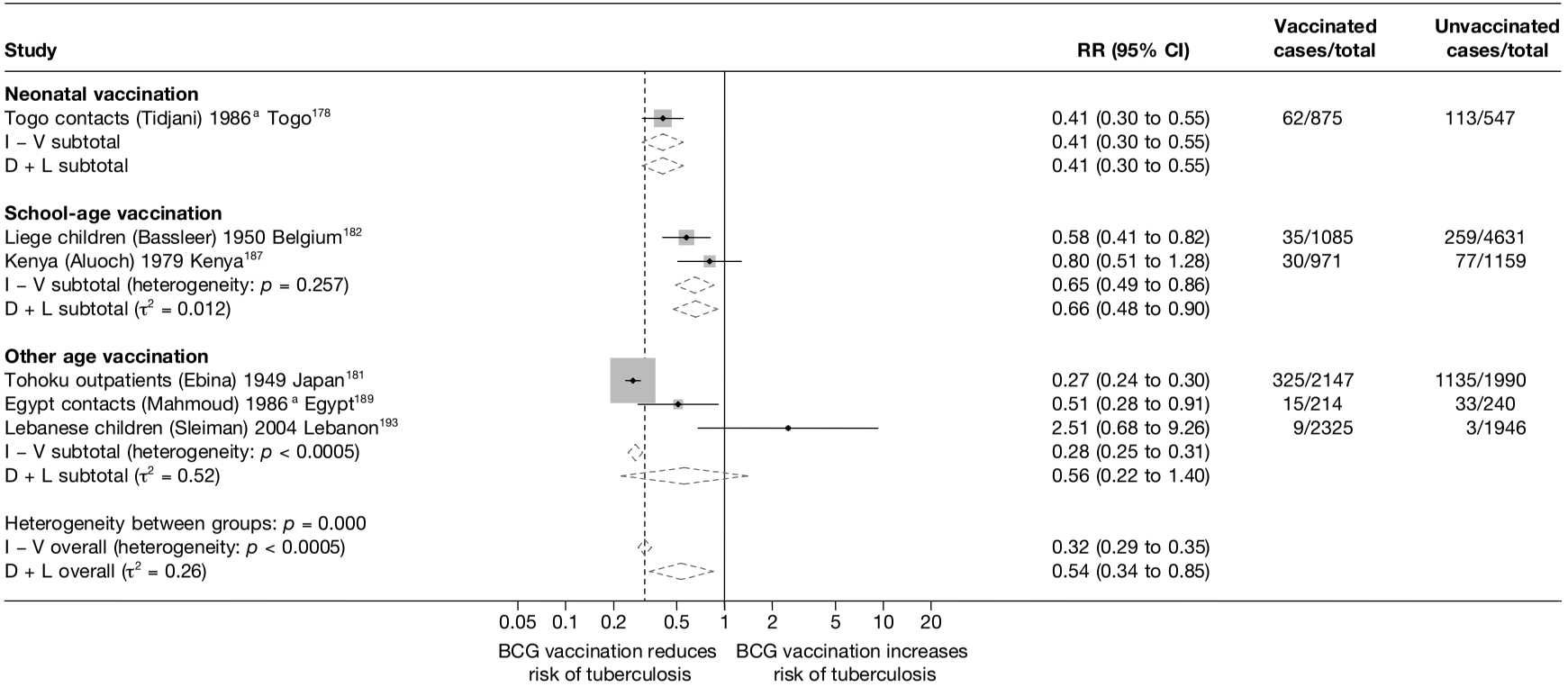

FIGURE 37 Risk ratios (with 95% CI) comparing the prevalence of pulmonary tuberculosis among BCG vaccinated individuals with that in unvaccinated individuals in cross-sectional studies, stratified by age at vaccination, ordered by year of study start. a, Date of study publication was used if study start date was not available. D+L, DerSimonian and Laird method; I–V, inverse variance method.

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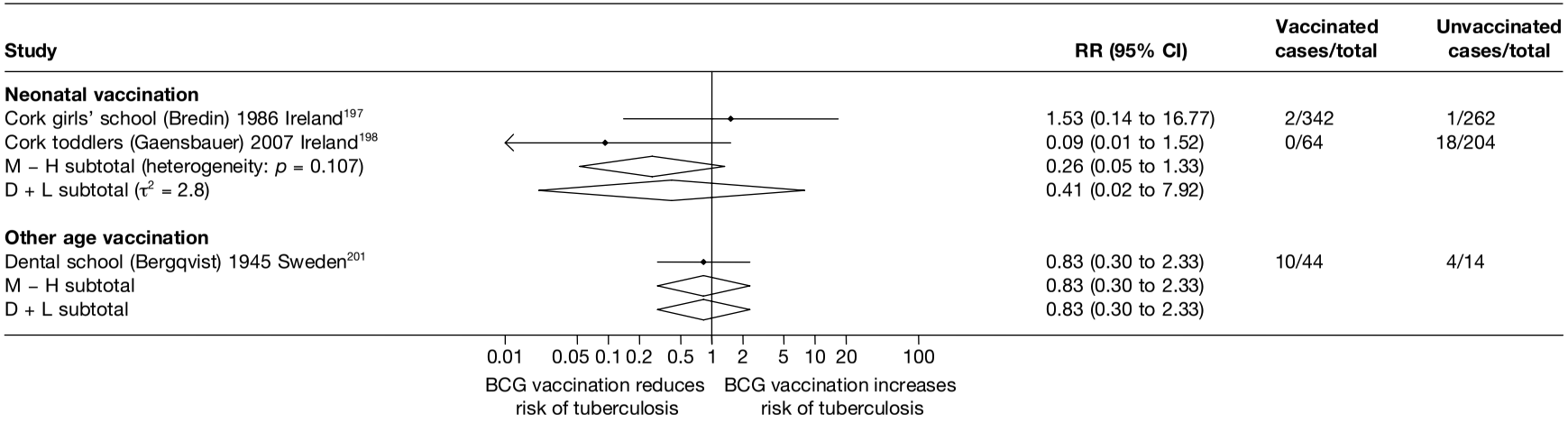

FIGURE 38 Risk ratios (with 95% CI) comparing the prevalence of pulmonary tuberculosis among BCG vaccinated individuals with that in unvaccinated individuals in outbreak studies, stratified by age at vaccination, ordered by year of study start. D+L, DerSimonian and Laird method; I–V, inverse variance method.

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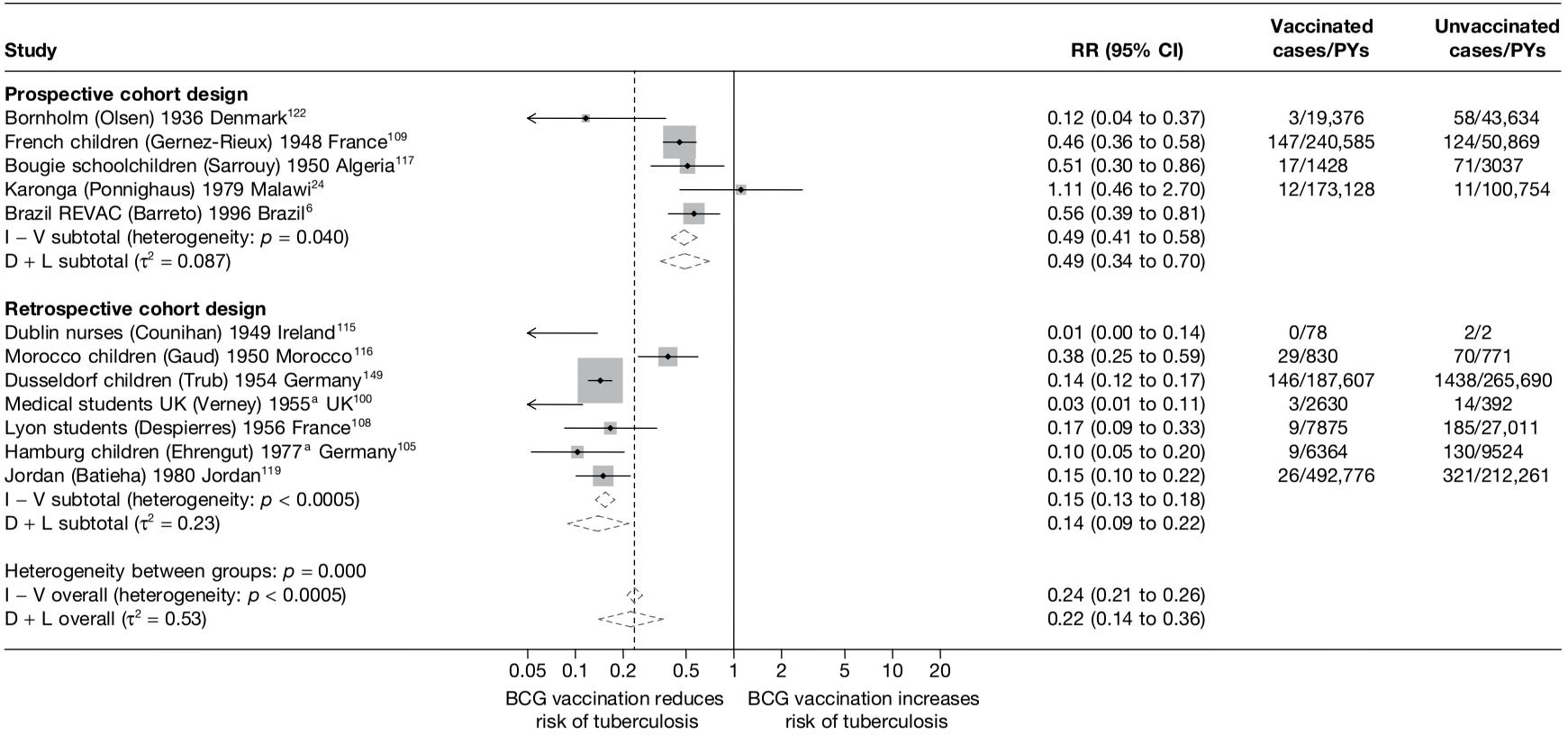

FIGURE 39 Rate ratios (with 95% CI) comparing the incidence of pulmonary tuberculosis among BCG vaccinated individuals with that in unvaccinated individuals for the longest duration of follow-up (see *Table 4*) in cohort studies, stratified by cohort study design, ordered by year of study start. a, Date of study publication was used if study start date was not available. D+L, DerSimonian and Laird method; I–V, inverse variance method.

Meta-regression analysis

Case–control studies

The small number of studies in each of the observational study design categories precludes any detailed modelling. Univariate meta-regression analysis was used to explore possible reasons for heterogeneity of the findings more formally. For case–control studies (see *Table 12*), apart from the finding that latitude explained only a small amount of the between-study variation in overall BCG vaccination effectiveness with a τ^2 value 0.128 compared with the baseline τ^2 value (0.141), there was little evidence that any of other the study level variables were associated with the size of protective effect of BCG vaccination against pulmonary tuberculosis.

Cohort studies

Results from cohort studies univariable meta-regression analysis (see *Table 13)* indicated that latitude and cohort study type explained the largest amount of between-study variation in overall BCG vaccination effectiveness with a τ^2 values of 0.509 and 0.342, respectively, compared with the baseline τ^2 value of 0.872. There was some evidence that latitude (p-value = 0.060), age at vaccination (p-value = 0.049), 'Were methods of case ascertainment identical for vaccinated and unvaccinated group?' (p-value = 0.067), 'Was diagnostic detection bias present?' (p-value = 0.067), 'Were results adjusted for socioeconomic status?' (p-value = 0.058) and study type (p-value = 0.018) were also associated with the size of effect of BCG vaccination.

Cross-sectional studies

Results from univariable meta-regression analysis of cross-sectional studies (see *Table 14*) indicate that no variables explained the between-study variation in overall BCG vaccination effectiveness. There was no evidence that any of these factors were associated with increased BCG vaccination effectiveness.

All tuberculosis morbidity outcomes

Unstratified analysis ordered by year study started

More observational studies assessed the effectiveness of BCG vaccination in preventing all forms of tuberculosis: 16 case–control studies, 32 cohort studies, 12 case population studies, 13 cross-sectional studies and seven outbreak studies (*Figures 40–44*). All case–control studies showed evidence of protection against all forms of tuberculosis disease (see *Figure 40*). Similarly, the majority of cohort studies found a protective effect of BCG vaccination on all tuberculosis morbidity outcomes (see *Figure 41*), with only four showing no evidence of a clinical benefit from BCG vaccination. The observed effect varied from a high protective effect (rate ratio 0.01; 95% CI 0.00 to 0.05), in the German Siblings cohort,[107] to no clinical benefit (rate ratio 6.08; 95% CI 0.00 to 5.97e7) in the Edinburgh study.[96] All case population studies showed evidence of a strong protective effect of BCG vaccination against all tuberculosis morbidity outcomes (see *Figure 42*) and the majority of cross-sectional studies, except for the Surui Indians[180] study, found evidence of substantial protection against tuberculosis (see *Figure 43*). The majority of outbreak studies provided evidence of a protective effect against all forms of tuberculosis morbidity (see *Figure 43*).

Case–control studies

See *Figure 40.*

Cohort studies

See *Figure 41.*

Case population studies

See *Figure 42.*

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TABLE 12 Ratios of ORs (with 95% CIs) comparing the BCG vaccination status of pulmonary tuberculosis cases and control subjects in case–control studies, according to univariable meta-regression analysis

Variable	Number of studies	Univariable ORs (95% CI)	Univariable model		
			Ratio of ORs (95% CI)	*p*-value	τ^2
Null model	8				0.141
Latitude					
40°+	0				
20–40°	3	0.40 (0.22 to 0.74)	1.00 (ref.)		
0–20°	5	0.62 (0.39 to 1.01)	1.55 (0.74 to 3.26)	0.199	0.128
Age at vaccination					
Neonatal	7	0.50 (0.33 to 0.76)	1.00 (ref.)		
School age	0				
Other	1	0.84 (0.23 to 3.08)	1.66 (0.46 to 6.08)	0.374	0.141
Was disease status blinded to BCG assessors?					
Lower risk of bias	0				
Higher risk of bias	8				0.141
Were vaccination definitions the same for cases and control subjects?					
Lower risk of bias	6	0.57 (0.35 to 0.91)	1.00 (ref.)		
Higher risk of bias	2	0.43 (0.19 to 1.00)	0.77 (0.31 to 1.90)	0.500	0.160
Were cases and control subjects determined independently of BCG vaccination status?					
Lower risk of bias	5	0.52 (0.30 to 0.89)	1.00 (ref.)		
Higher risk of bias	3	0.55 (0.28 to 1.10)	1.07 (0.47 to 2.45)	0.853	0.171
Were results adjusted for SES?					
Yes	5	0.53 (0.31 to 0.90)	1.00 (ref.)		
No	3	0.53 (0.26 to 1.07)	1.01 (0.44 to 2.33)	0.985	0.171
If a matched design was used, was a matched analysis performed?					
Unmatched design	1	0.30 (0.12 to 0.80)	1.00 (ref.)		
Matched design – matched analysis	3	0.52 (0.27 to 1.00)	1.69 (0.57 to 5.03)		
Matched design – matched analysis	4	0.63 (0.37 to 1.08)	2.07 (0.74 to 5.77)	0.279	0.106

ref., reference category, τ^2, estimated between-study variance.

Cross-sectional studies

See *Figure 43*.

Outbreak studies

See *Figure 44*.

Stratified analysis by latitude (10°), ordered by year study started

Figures 45 and *46* present the estimated effects of case–control and cohort studies against all tuberculosis morbidity outcomes stratified by latitude. Studies on all types of tuberculosis morbidity, unlike pulmonary tuberculosis studies, showed evidence of high effectiveness with no defined pattern of latitude effect on BCG vaccination effectiveness.

TABLE 13 Ratios of rate ratios (with 95% CI) comparing the incidence of pulmonary tuberculosis among vaccinated individuals compared with unvaccinated individuals for the longest duration of follow-up (see *Table 4*) in cohort studies, according to univariable meta-regression analysis

Variable	Number of studies	Univariable rate ratios (95% CI)	Univariable model		
			Ratio of rate ratios (95% CI)	*p*-value	τ^2
Null model	12				0.872
Latitude					
>40°	7	0.12 (0.06 to 0.27)	1.00 (ref.)		
20–40°	3	0.31 (0.11 to 0.87)	2.46 (0.68 to 8.90)		
0–20°	2	0.75 (0.19 to 2.92)	6.08 (1.31 to 28.10)	0.060	0.509
Age at vaccination					
Neonatal	3	0.20 (0.07 to 0.54)	1.00 (ref.)		
School age	6	0.36 (0.17 to 0.76)	1.83 (0.53 to 6.37)		
Other	3	0.05 (0.01 to 0.19)	0.24 (0.04 to 1.32)	0.049	0.546
Was follow-up independent of vaccination status?					
Lower risk of bias	6	0.25 (0.09 to 0.70)	1.00 (ref.)		
Higher risk of bias	6	0.17 (0.06 to 0.52)	0.70 (0.16 to 3.10)	0.604	0.993
Was case ascertainment blinded to vaccination status?					
Lower risk of bias	0				
Higher risk of bias	12				0.872
Were methods of case ascertainment identical for vaccinated and unvaccinated group?					
Lower risk of bias	10	0.28 (0.14 to 0.54)	1.00 (ref.)		
Higher risk of bias	2	0.06 (0.01 to 0.28)	0.22 (0.04 to 1.14)	0.067	0.524
Were losses to follow-up similar in each group?					
Lower risk of bias	3	0.23 (0.05 to 1.15)	1.00 (ref.)		
Higher risk of bias	9	0.20 (0.08 to 0.48)	0.87 (0.14 to 5.27)	0.869	0.982
Was diagnostic detection bias present?					
Lower risk of bias	5	0.39 (0.16 to 0.95)	1.00 (ref.)		
Higher risk of bias	7	0.13 (0.06 to 0.30)	0.33 (0.10 to 1.10)	0.067	0.551
Were results adjusted for SES?					
Yes	2	0.75 (0.17 to 3.20)	1.00 (ref.)		
No	10	0.17 (0.09 to 0.33)	0.22 (0.05 to 1.06)	0.058	0.572
Study type					
Prospective	5	0.13 (0.07 to 0.26)	1.00 (ref.)		
Retrospective	7	0.47 (0.22 to 1.04)	0.27 (0.10 to 0.76)		
Contact	0			0.018	0.342

ref., reference category; τ^2, estimated between-study variance.

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TABLE 14 Ratios of risk ratios (with 95% CI) comparing the incidence of pulmonary tuberculosis among vaccinated individuals compared with unvaccinated individuals in cross-sectional studies, according to univariable meta-regression analysis

Variable	Number of studies	Univariable RRs (95% CI)	RRRs (95% CI)	*p*-value	τ^2
Null model	6				0.249
Latitude					
>40°	2	0.58 (0.01 to 22.59)	1.00 (ref.)		
20–40°	3	0.57 (0.06 to 5.61)	0.99 (0.04 to 24.13)		
0–20°	1	0.57 (0.04 to 7.72)	0.99 (0.04 to 27.52)	0.999	0.599
Age at vaccination					
Neonatal	1	0.41 (0.01 to 12.42)	1.00 (ref.)		
School age	2	0.68 (0.06 to 7.95)	1.66 (0.07 to 37.37)		
Other	3	0.55 (0.06 to 4.83)	1.36 (0.07 to 26.99)	0.878	0.500
Was disease status blinded to BCG assessors?					
Lower risk of bias	0		1.00 (ref.)		
Higher risk of bias	6				0.249
Were vaccination definitions the same for cases and control subjects?					
Lower risk of bias	4	0.66 (0.23 to 1.88)	1.00 (ref.)		
Higher risk of bias	2	0.38 (0.11 to 1.38)	0.58 (0.14 to 2.45)	0.350	0.252
Were cases and control subjects determined independently of BCG vaccination status?					
Lower risk of bias	6		1.00 (ref.)		
Higher risk of bias	0				0.249
Were results adjusted for SES?					
Yes	0				
No	6				0.249
Study type					
Non-contact	4	0.61 (0.19 to 1.92)	1.00 (ref.)		
Contact	2	0.45 (0.10 to 2.15)	1.35 (0.25 to 7.29)	0.650	0.359

ref., reference category, τ^2, estimated between-study variance.

Figures 47 and *48* show forest plots of the results of case population and cross-sectional studies, respectively, stratified by 10° latitude. The majority of case population studies were conducted in sites located above 50° latitude. The small number of case population studies in each stratum other than the above 50° latitude band limits any conclusion, although there was some evidence that the protective effect was strongest in studies conducted at latitudes furthest away from the equator. The majority of cross-sectional studies show a protective effect of BCG vaccination against tuberculosis; however, there was no clear evidence of variation by latitude. Stratification by latitude therefore appeared to explain very little of the heterogeneity in both case population and cross-sectional studies. All outbreak studies were conducted above 50° latitude.

Meta-regression analysis

Meta-regression with stratification on latitude partially explained the heterogeneity between case–control studies (null model $\tau^2 = 0.208$; after stratification by 20° latitude group $\tau^2 = 0.180$)

(*Table 15*). Latitude also accounted for a proportion of the heterogeneity between cohort studies (null model $\tau^2 = 0.253$; after stratification by 20° latitude group $\tau^2 = 0.185$) (*Table 16*) but there was little evidence (p-value = 0.174) that effectiveness varied by latitude. There was some evidence (p-value = 0.069) that BCG vaccination protection against all tuberculosis varies according to latitude in cohort studies: the overall rate ratios for the 0–20° and 20–40° latitude groups were, respectively, 2.30 (95% CI 1.10 to 4.78) and 0.94 (95% CI 0.53 to 1.68) times the overall rate ratio in the 40° and above group. Based on meta-regression analysis (*Table 17*), stratification on latitude did not account for any of the between-study variation seen in case population studies (τ^2 values before and after stratification by 20° group were 0.619 and 0.683, respectively) or cross-sectional studies (τ^2 values before and after stratification by 20° group 0.716 and 0.754, respectively) (*Table 18*).

Case–control studies

See *Figure 45*.

Cohort studies

See *Figure 46*.

Case population studies

See *Figure 47*.

Cross-sectional studies

See *Figure 48*.

Stratified analysis by age at vaccination, ordered by year study started

Forest plots showing the results of observational studies stratified by the age at which BCG vaccination was given to participants are presented in *Figures 49* and *52*. All but one case–control study evaluated the effect of neonatal BCG vaccination against all forms of tuberculosis (see *Figure 49*). This study did not show a protective effect, whereas the estimates of neonatal vaccination studies ranged from substantial protection, as in Nepal[75] [OR 0.11 (95% CI 0.07 to 0.17)], to reduced protection [OR 0.69 (95% CI 0.47 to 1.01)], in Madagascar children.[79] Estimates of effect from cohort studies indicated that, in general, the level of protection was similar among studies investigating neonatal BCG vaccination [rate ratio 0.22 (95% CI 0.12 to 0.40)], and school-age vaccination [rate ratio 0.24 (95% CI 0.17 to 0.34)] (the results being based only on tuberculin-negative participants at study start), corresponding to VE of 76% (95% CI 66% to 83%). The Karonga study[124] did not show evidence of a protective effect from school-age vaccination, and the majority of studies failed to detect a substantial protective effect from BCG vaccination in other age groups. The majority of case population studies showed strong protective effects of BCG vaccination against all forms of tuberculosis, ranging from rate ratio 0.05 (95% CI 0.04 to 0.08) in the Bydgoszcz children[160] neonatal vaccination study to rate ratio of 0.80 (95% CI 0.72 to 0.89) in the Ireland Survey study of school-age BCG vaccination.[167] All cross-sectional studies evaluated either neonatal or school-age vaccination. Both groups were associated with substantial protection against tuberculosis; the highest level was observed in studies evaluating the vaccination of school-age children [RR 0.16 (95% CI 0.04 to 0.65)], equivalent to VE of 84% (95% CI 35% to 96%) (see *Figure 52*). Age at vaccination appears to explain very little of the heterogeneity seen between case–control studies, whereas evidence of substantial heterogeneity remained after stratification for age at vaccination for all study designs. In outbreak studies, there was little evidence of a clinical benefit from neonatal vaccination, whereas outbreaks in which vaccination was undertaken at school age showed evidence of a high protective effect RR of 0.02 (95% CI 0.01 to 0.07), equivalent to VE of 98% (95% CI 93% to 99%).

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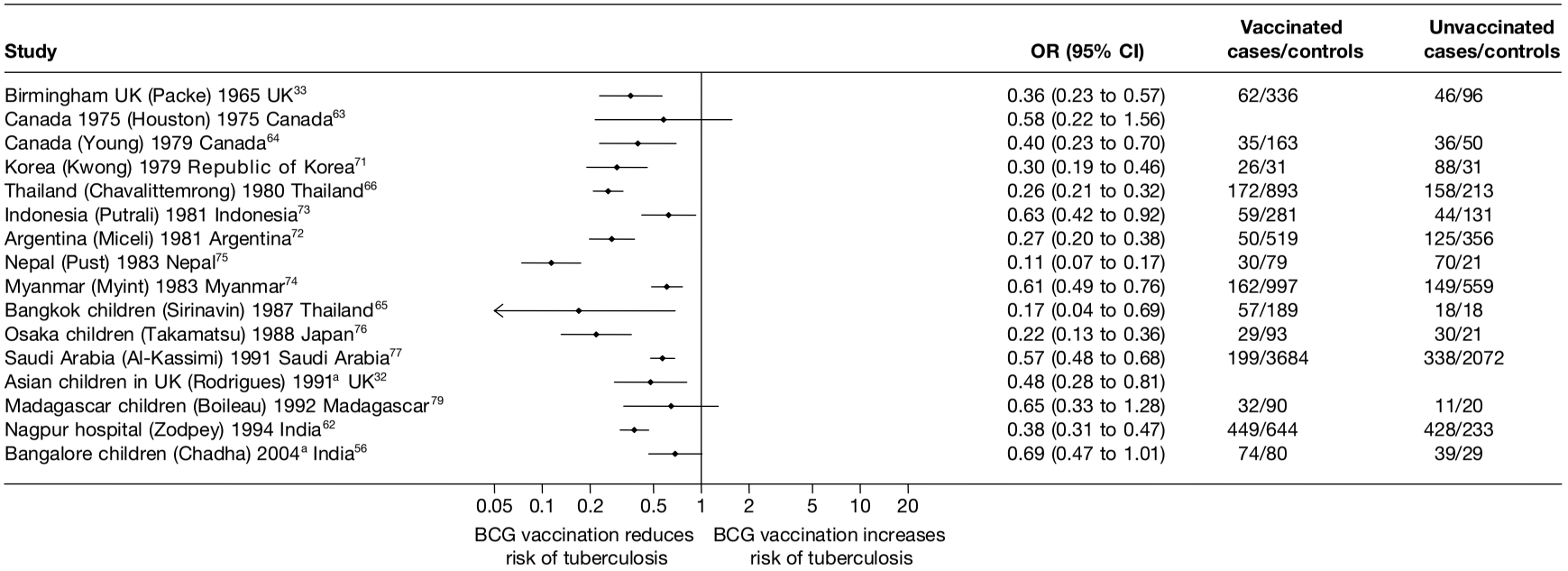

FIGURE 40 Odds ratios (with 95% CI) comparing the BCG vaccination status of all tuberculosis outcome cases and control subjects in case–control studies, ordered by year of study start. a, Date of study publication was used if study start date was not available.

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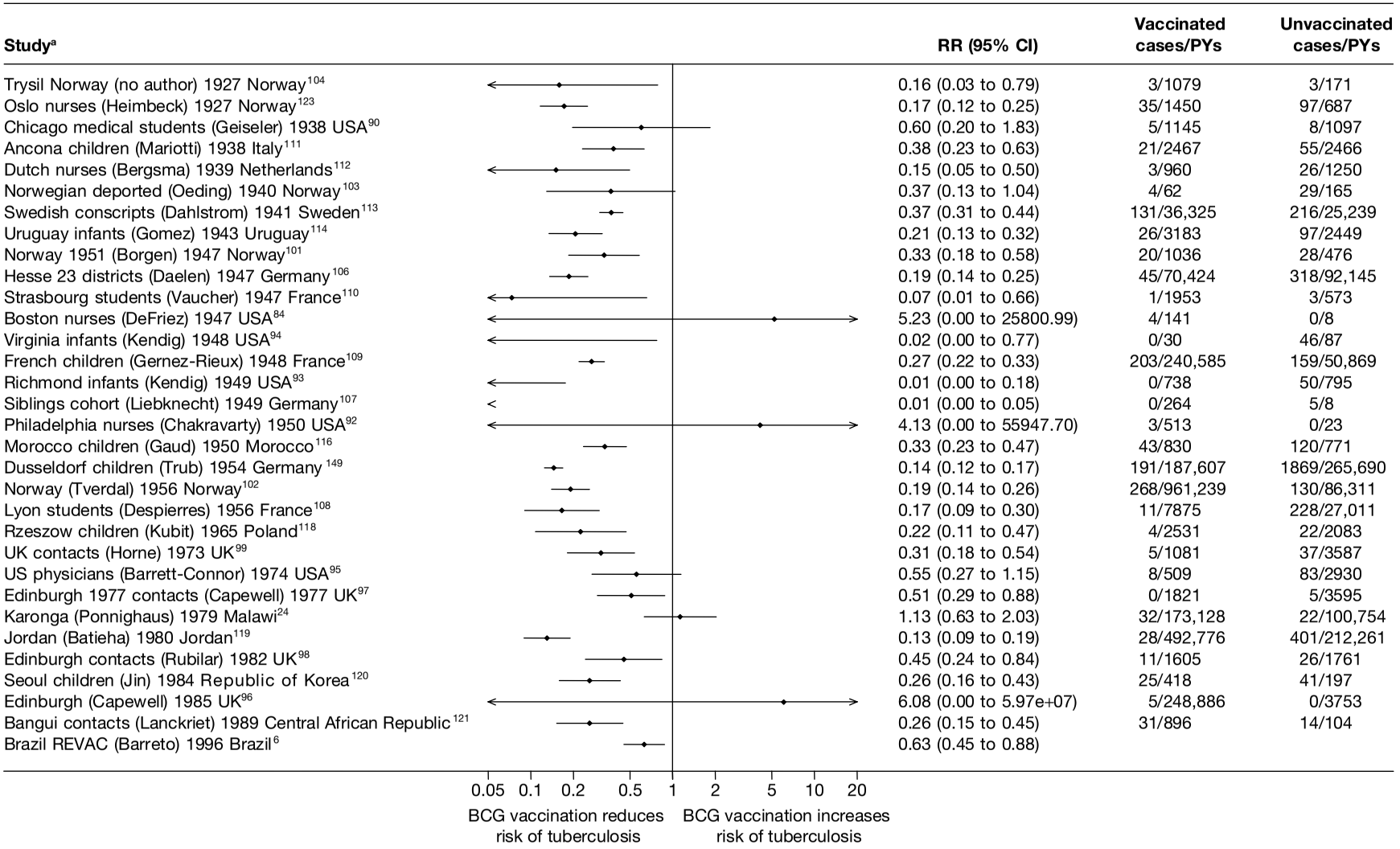

FIGURE 41 Rate ratios (with 95% CI) comparing the incidence of all tuberculosis morbidity outcomes among BCG vaccinated individuals with that in unvaccinated individuals for the longest duration of follow-up (see *Table 4*) in cohort studies, ordered by year of study start. a, Date of study publication was used if study start date was not available.

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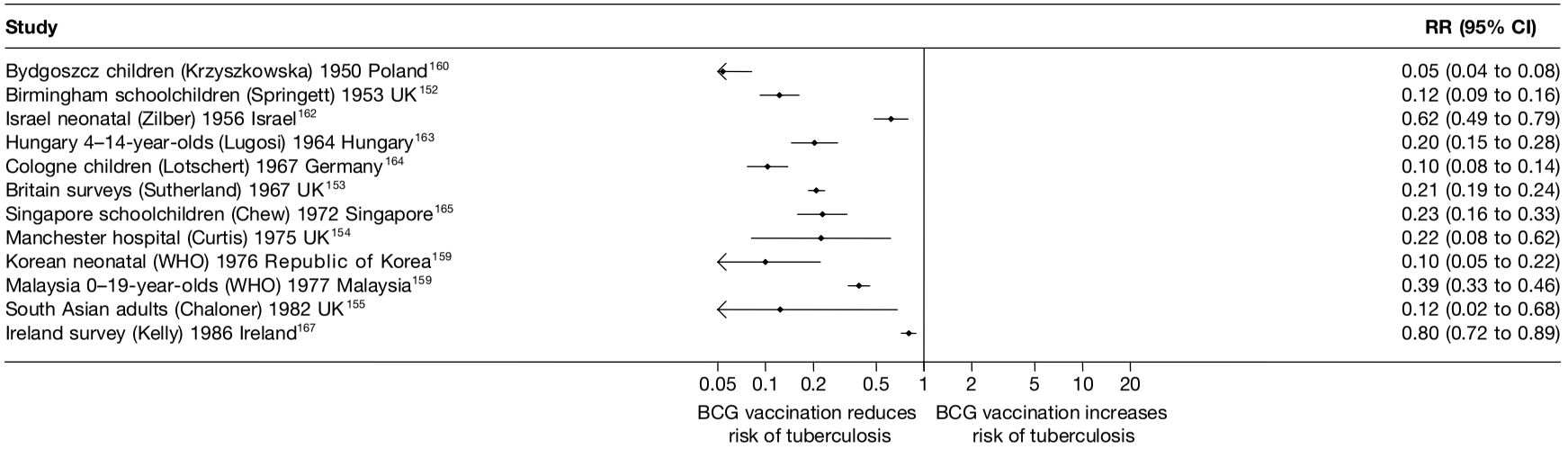

FIGURE 42 Rate ratios (with 95% CI) comparing the incidence of all tuberculosis morbidity outcomes among BCG vaccinated individuals with that in unvaccinated individuals for the longest duration of follow-up (see *Table 5*) in case population studies, ordered by year of study start.

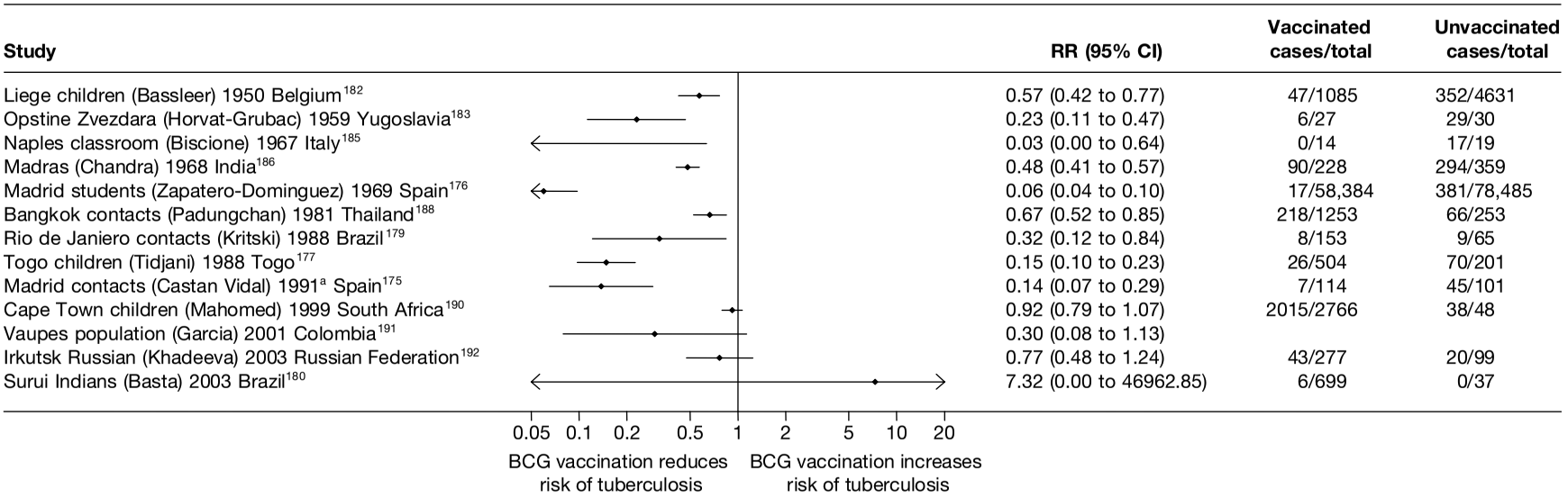

FIGURE 43 Risk ratios (with 95% CI) comparing the prevalence of all tuberculosis morbidity outcomes among BCG vaccinated individuals with that in unvaccinated individuals, in cross-sectional studies ordered by year of study start. a, Date of study publication was used if study start date was not available.

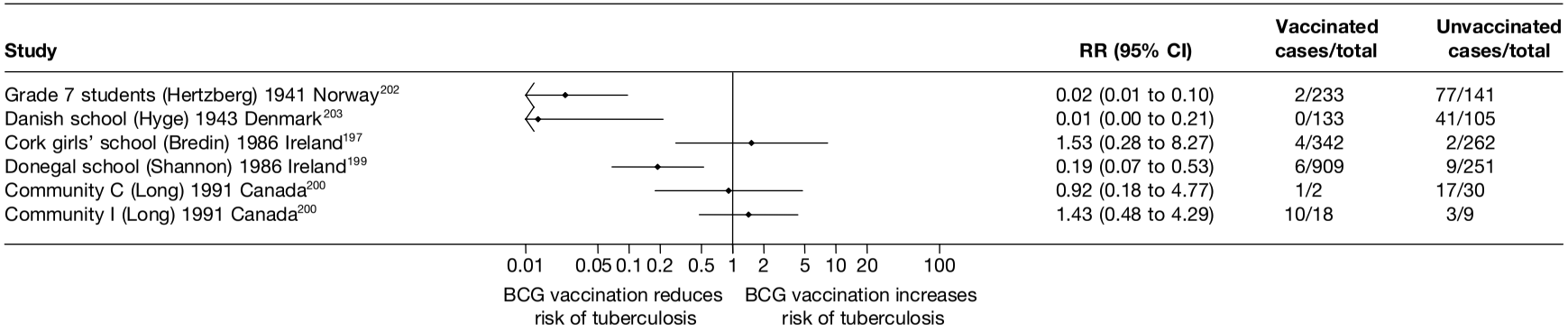

FIGURE 44 Risk ratios (with 95% CI) comparing the incidence of all tuberculosis morbidity outcomes among BCG vaccinated individuals with that in unvaccinated individuals, in cross-sectional studies ordered by year of study start.

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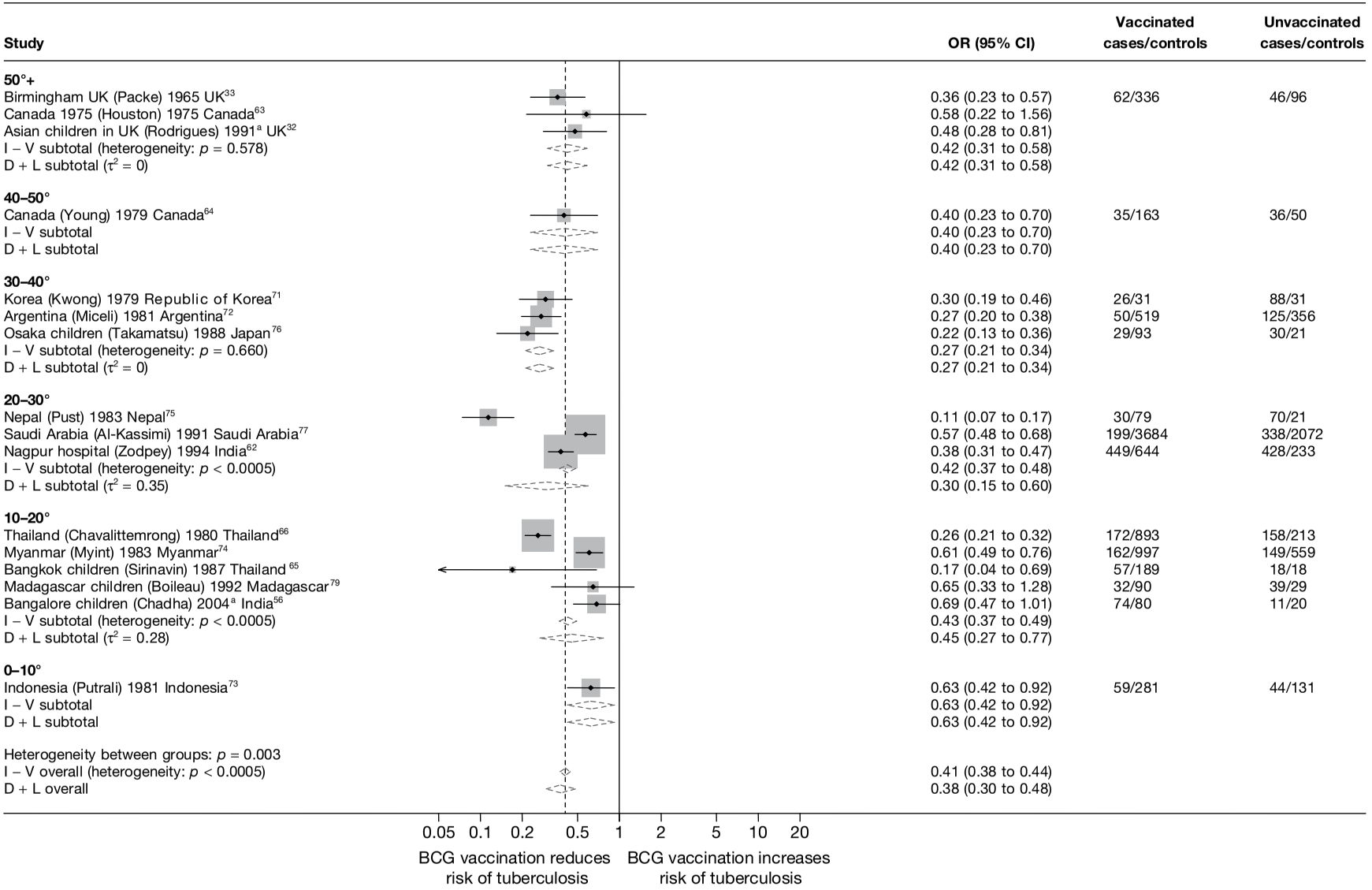

FIGURE 45 Odds ratios (with 95% CI) comparing the BCG vaccination status of all tuberculosis outcome cases and control subjects in case–control studies, stratified by latitude of study location (10° bands), ordered by year of study start. a, Date of study publication was used if study start date was not available. D+L, DerSimonian and Laird method; I–V, inverse variance method.

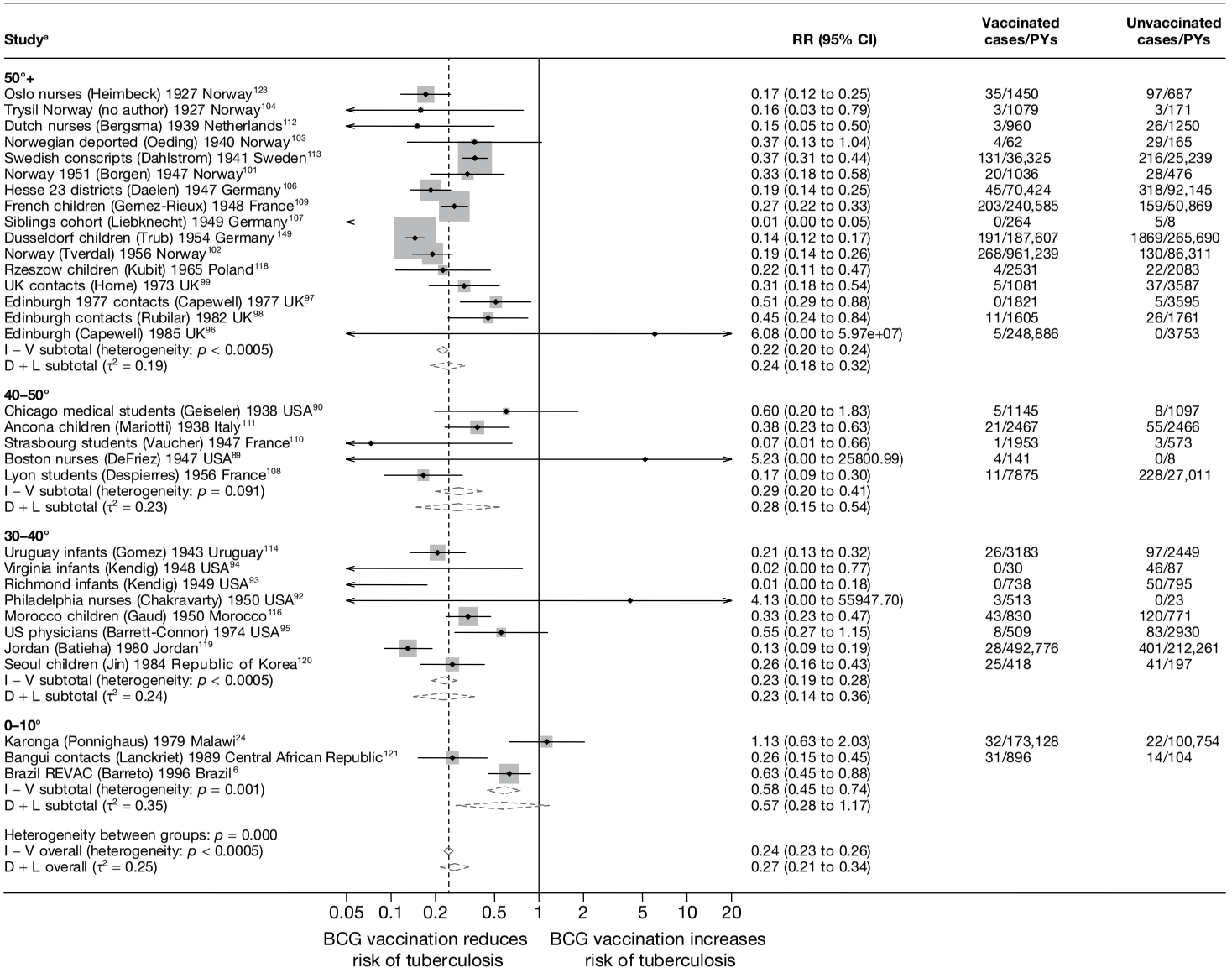

FIGURE 46 Rate ratios (with 95% CI) comparing the incidence of all tuberculosis morbidity outcomes among BCG vaccinated individuals with that in unvaccinated individuals for the longest duration of follow-up (see *Table 4*) in cohort studies, stratified by latitude of study location (10° bands), ordered by year of study start. a, Date of study publication was used if study start date was not available. D+L, DerSimonian and Laird method; I–V, inverse variance method.

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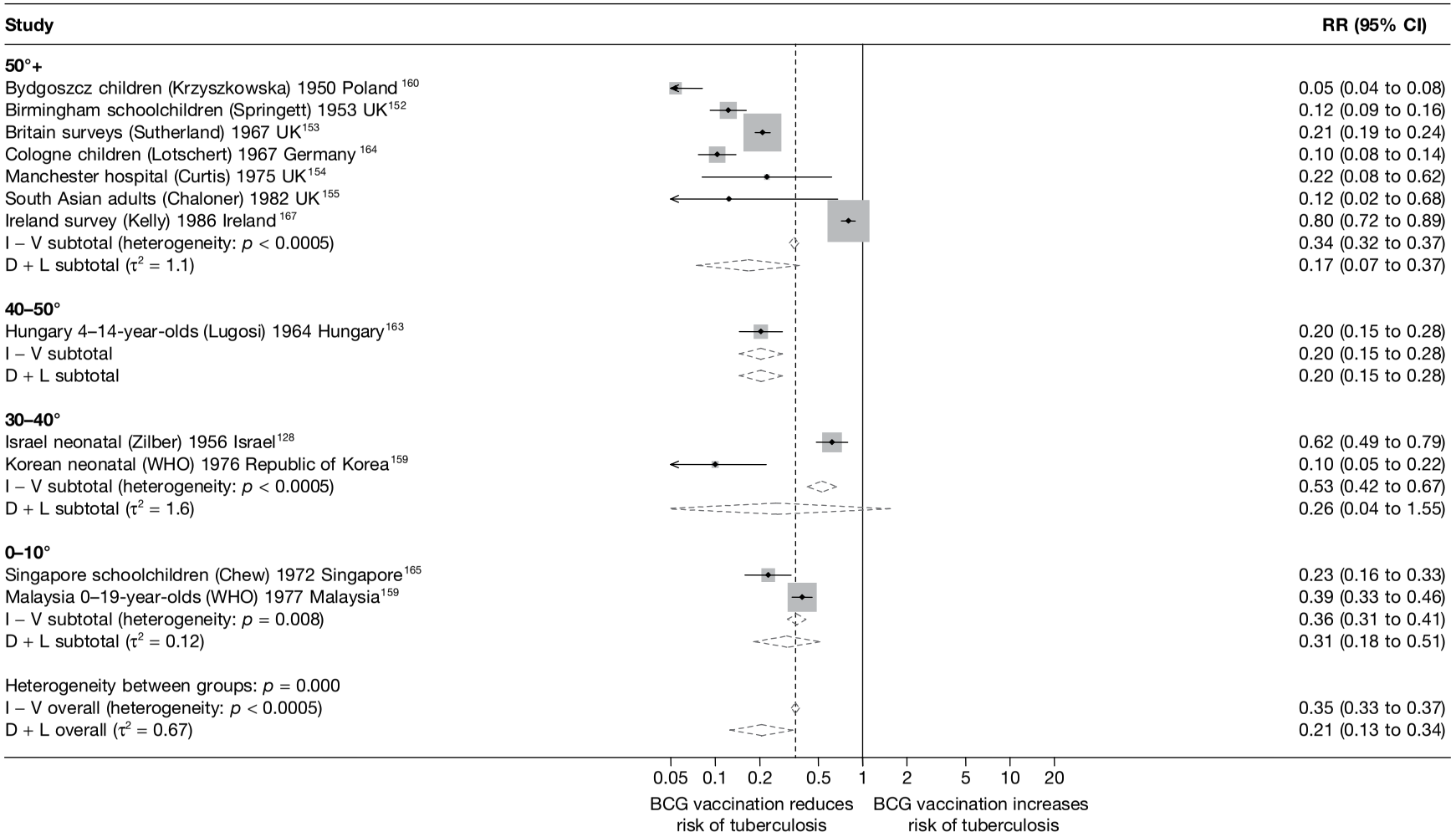

FIGURE 47 Rate ratios (with 95% CI) comparing the prevalence of all tuberculosis morbidity outcomes among BCG vaccinated individuals with that in unvaccinated individuals for the longest duration of follow-up (see *Table 5*) in case population studies, stratified by latitude of study location (10° bands), ordered by year of study start. D+L, DerSimonian and Laird method; I–V, inverse variance method.

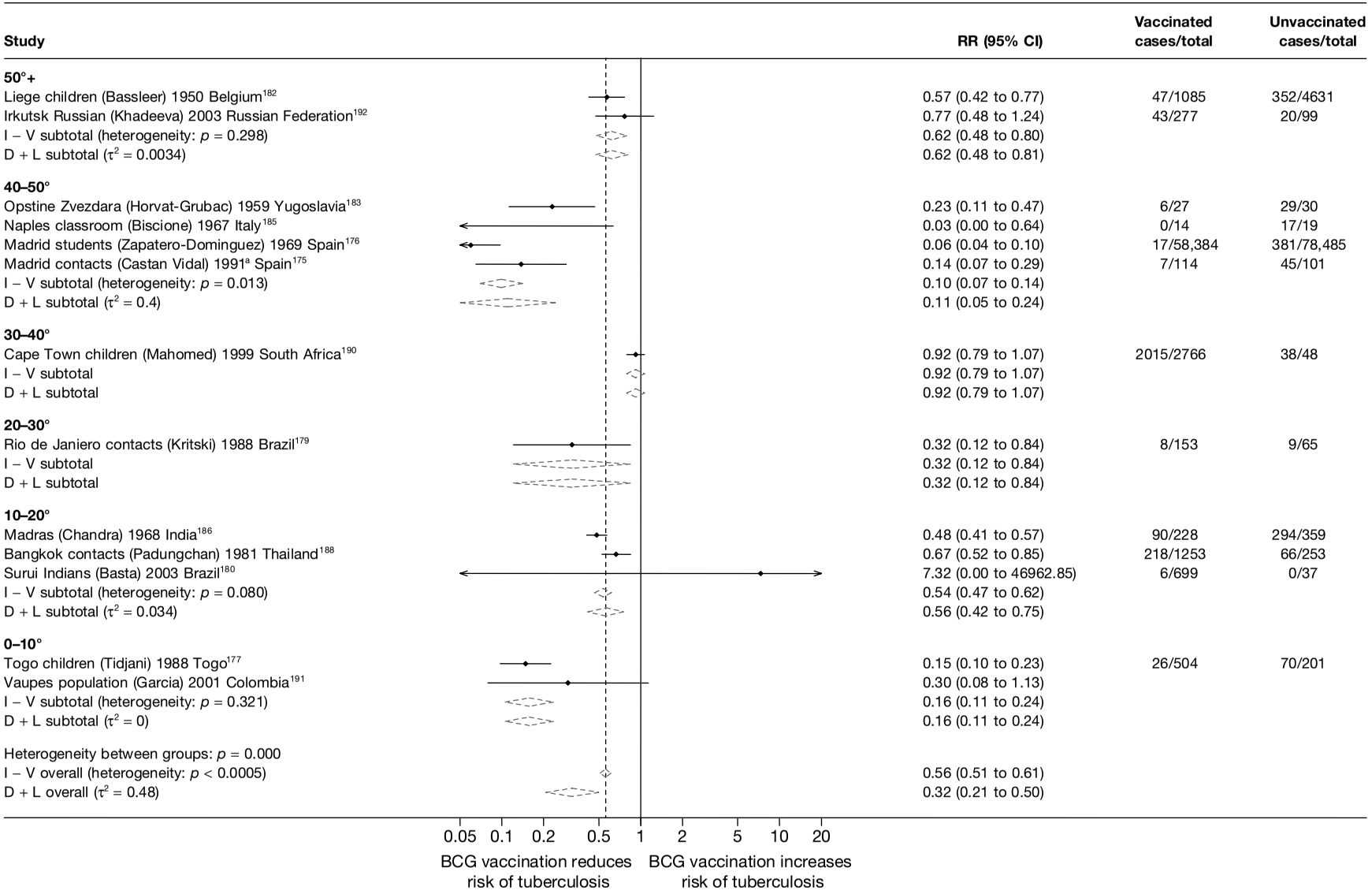

FIGURE 48 Risk ratios (with 95% CI) comparing the incidence of all tuberculosis morbidity outcomes among BCG vaccinated individuals with that in unvaccinated individuals, in cross-sectional studies stratified by latitude of study location (10° bands), ordered by year of study start. a, Date of study publication was used if study start date was not available. D+L, DerSimonian and Laird method; I–V, inverse variance method.

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Meta-regression analysis

Stratification of case–control studies on age at vaccination did not explain the between-study variation ($\tau^2 = 0.215$ after stratification, compared with $\tau^2 = 0.208$ in the null model, as shown in *Table 15*). Age at vaccination did not explain any of the variation between cohort studies [τ^2 values before and after stratification = 0.253 and 0.268, respectively (see *Table 16*)], case population studies [τ^2 values before and after stratification = 0.619 and 0.705, respectively (see *Table 17*)] or cross-sectional studies [τ^2 values before and after stratification = 0.736 and 0.716, respectively (see *Table 18*)]. There was no evidence that effectiveness of BCG vaccination against all forms of tuberculosis varied by age at vaccination for case–control studies, cohort studies or cross-sectional studies (*p*-values = 0.537, 0.487 and 0.398, respectively).

Case–control studies

See *Figure 49*.

Cohort studies

See *Figure 50*.

Case population studies

See *Figure 51*.

Cross-sectional studies

See *Figure 52*.

Outbreak studies

See *Figure 53*.

Stratified analysis by study design, ordered by year study started

Cohort studies

Figure 54 shows the result of cohort studies grouped by retrospective and prospective design and contact studies. As with pulmonary tuberculosis the most consistent protective effect of BCG vaccination against all types of tuberculosis disease was seen in retrospective cohort studies. Stratifying on cohort study design explained a small amount of the heterogeneity seen.

Meta-regression analysis

Based on meta-regression analyses, however, only 7% of the between-study variation was explained by study design [τ^2 values before and after stratification were 0.253 and 0.236, respectively (see *Table 16*)].

Meta-regression analysis

Case–control studies

The univariable meta-regression analysis of case–control studies suggest that latitude and 'were vaccination definitions the same for cases and controls?' explained the largest amount of between-study variation in overall BCG vaccination effectiveness against all types of tuberculosis disease with τ^2 values of 0.180 and 0.139, respectively, compared with the baseline τ^2 value (0.208). There was some evidence (*p*-value = 0.021) that studies with a high risk of bias, due to vaccination definitions not being the same for cases and control subjects, were associated with BCG vaccination efficacy.

Cohort studies

Results from univariable meta-regressions of cohort studies indicate that latitude and 'Were results adjusted for socio-economic status?' each explained the largest amount of between-study variation in overall BCG vaccination effectiveness with τ^2 values 0.185 and 0.130, respectively,

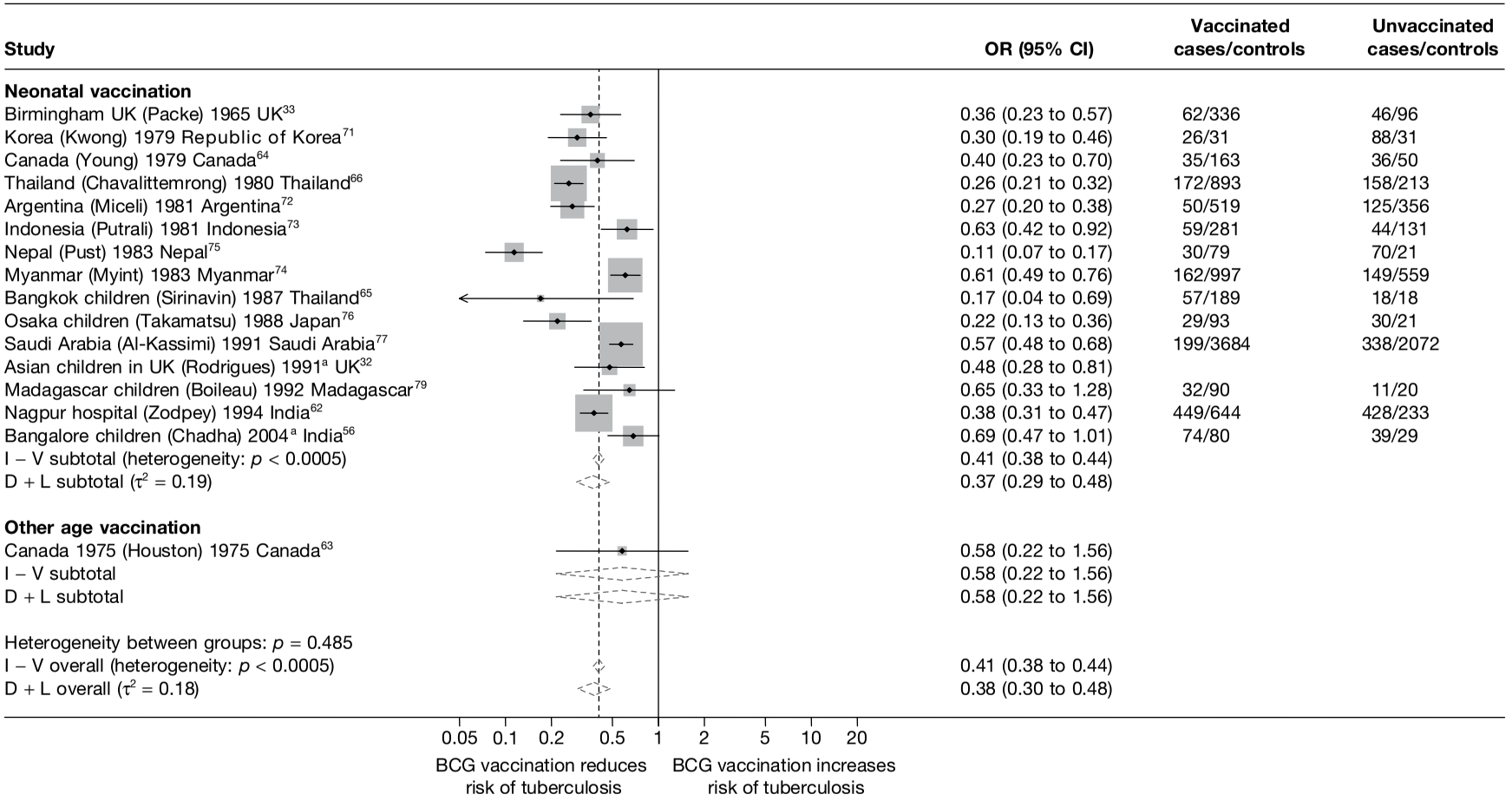

FIGURE 49 Odds ratios (with 95% CI) comparing the BCG vaccination status of all tuberculosis morbidity outcomes cases and control subjects in case–control studies, stratified by age at vaccination, ordered by year of study start. a, Date of study publication was used if study start date was not available. D + L, DerSimonian and Laird method; I – V, inverse variance method.

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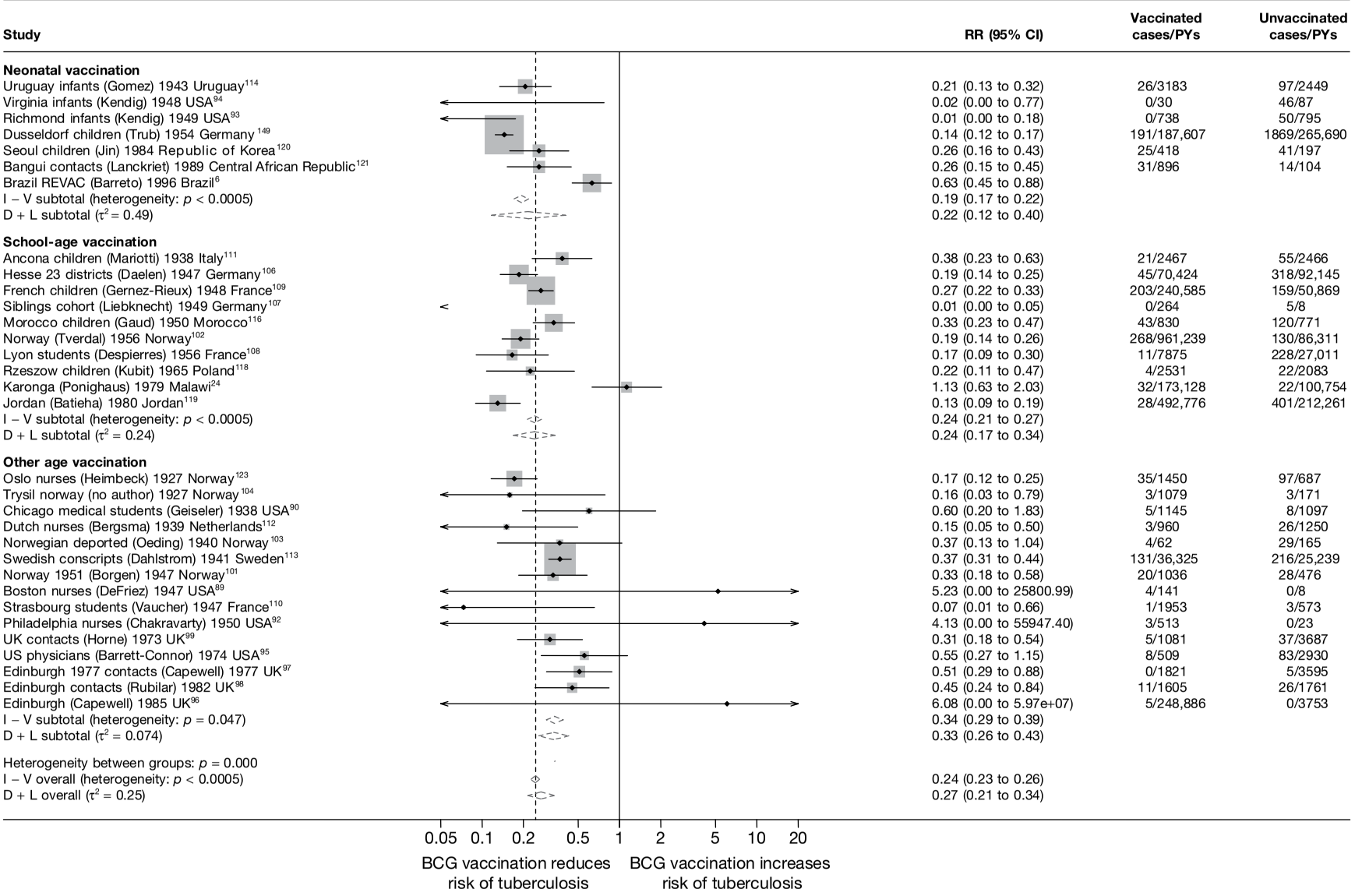

FIGURE 50 Rate ratios (with 95% CI) comparing the incidence of all tuberculosis morbidity outcomes among BCG vaccinated individuals with that in unvaccinated individuals for the longest duration of follow-up (see *Table 4*) in cohort studies, stratified by age at vaccination, ordered by year of study start. D+L, DerSimonian and Laird method; I–V, inverse variance method.

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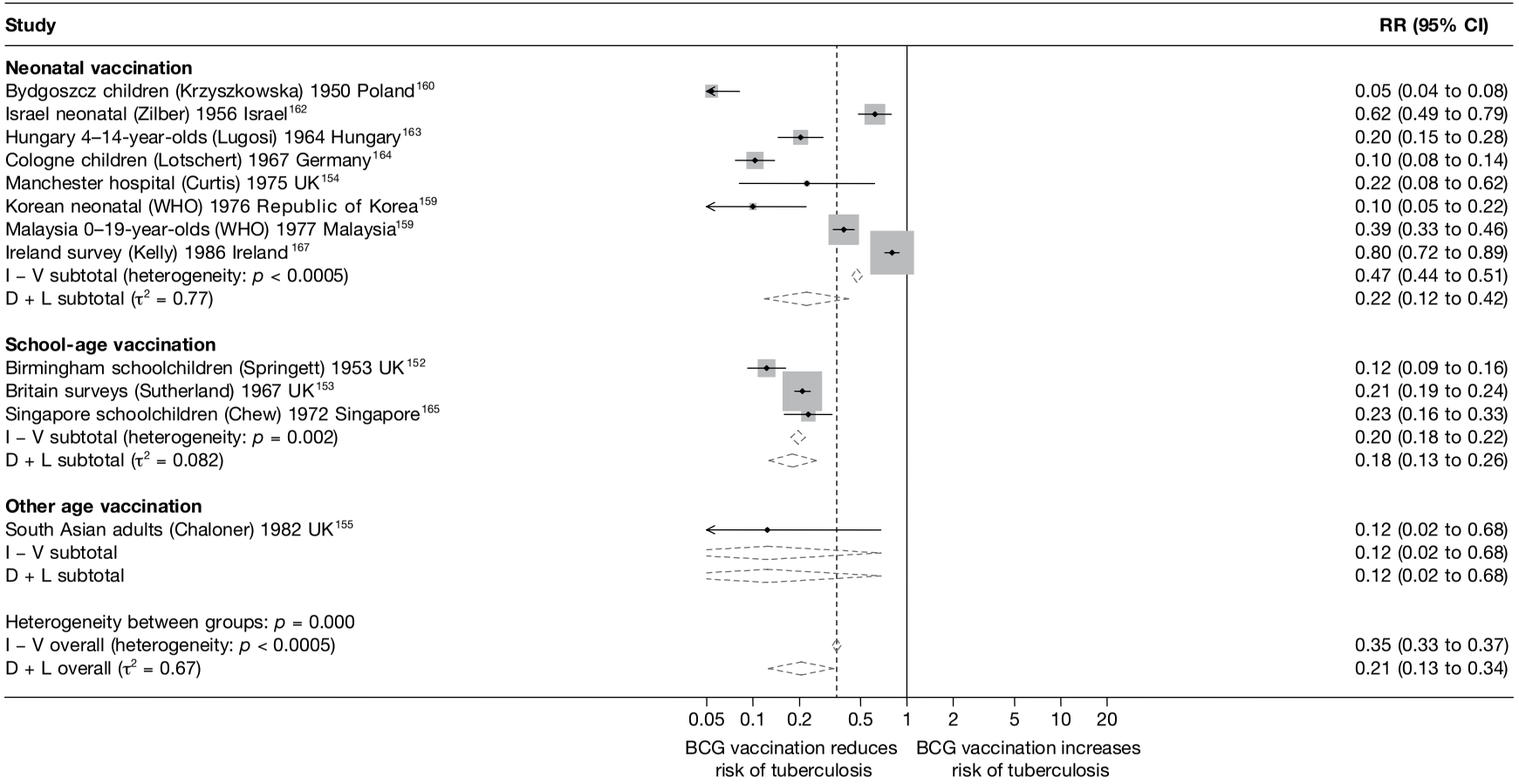

FIGURE 51 Rate ratios (with 95% CI) comparing the incidence of all tuberculosis morbidity outcomes among BCG vaccinated individuals with that in unvaccinated individuals for the longest duration of follow-up (see *Table 5*) in case population studies, stratified by age at vaccination, ordered by year of study start. D+L, DerSimonian and Laird method; I–V, inverse variance method.

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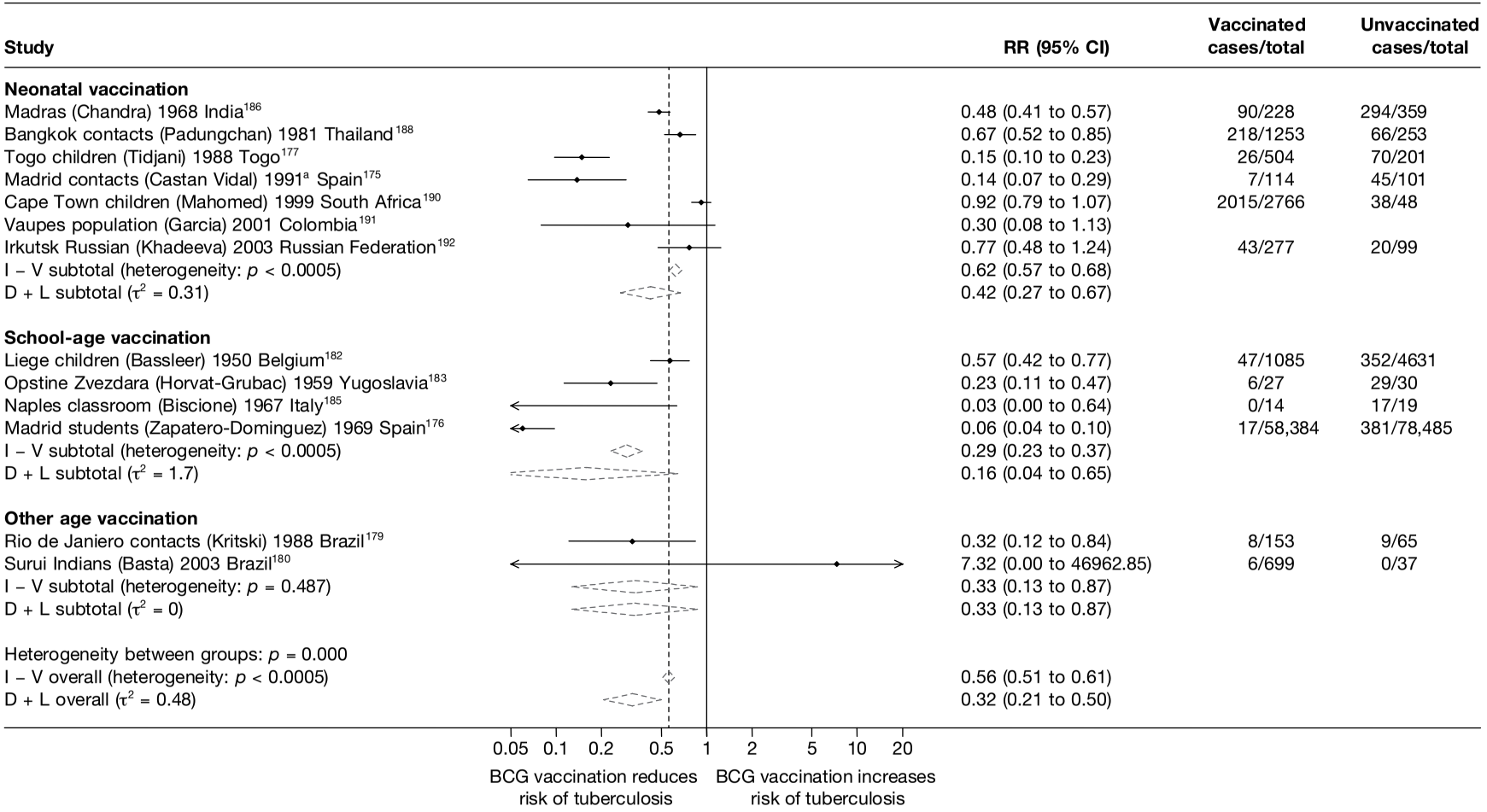

FIGURE 52 Risk ratios (with 95% CI) comparing the prevalence of all tuberculosis morbidity outcomes among BCG vaccinated individuals with that in unvaccinated individuals in cross-sectional studies, stratified by age at vaccination, ordered by year of study start. a, Date of study publication was used if study start date was not available. D+L, DerSimonian and Laird method; I–V, inverse variance method.

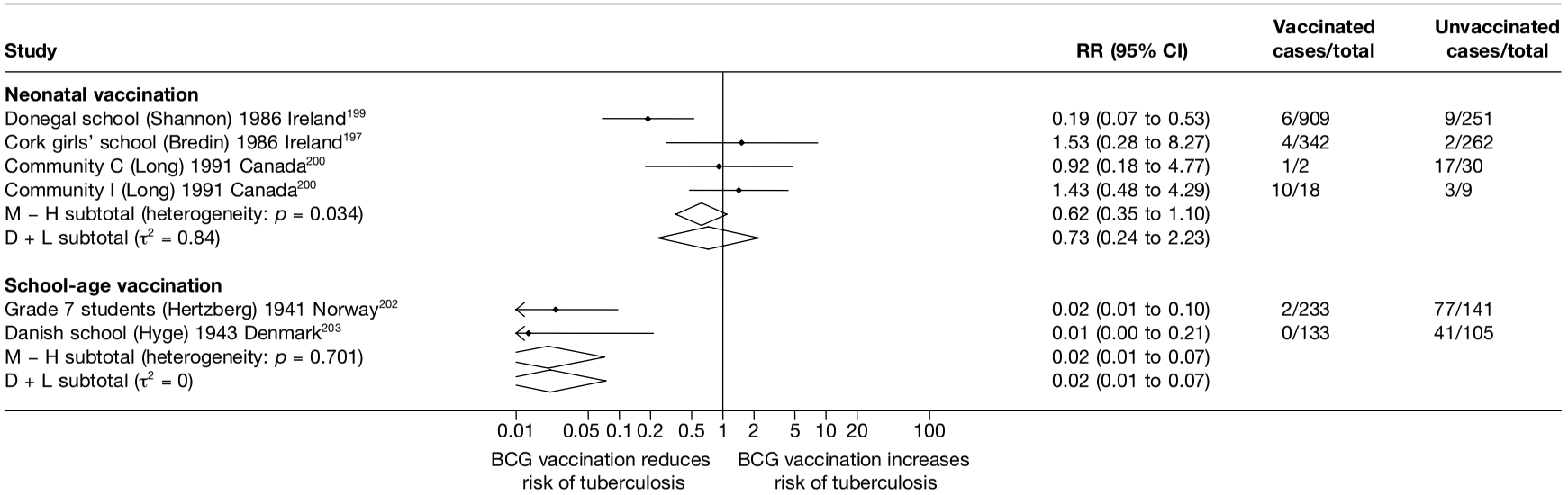

FIGURE 53 Risk ratios (with 95% CI) comparing the incidence of all tuberculosis morbidity outcomes among BCG vaccinated individuals with that in unvaccinated individuals in outbreak studies, stratified by age at vaccination, ordered by year of study start. D+L, DerSimonian and Laird method; I–V, inverse variance method.

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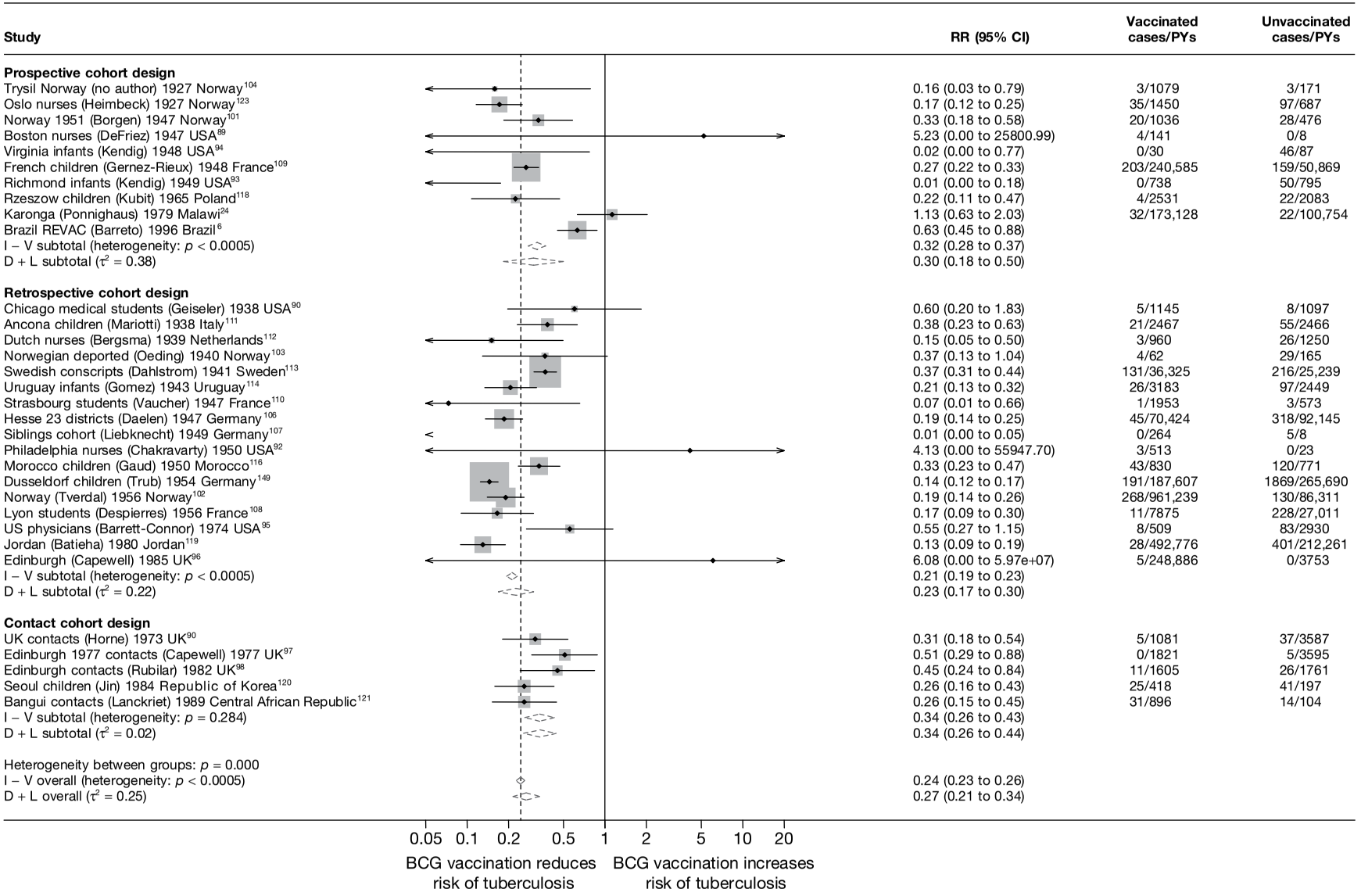

FIGURE 54 Rate ratios (with 95% CI) comparing the incidence of all tuberculosis morbidity outcomes among BCG vaccinated individuals with that in unvaccinated individuals for the longest duration of follow-up (see *Table 4*) in cohort studies, stratified by cohort study design, ordered by year of study start. D+L, DerSimonian and Laird method; I–V, inverse variance method.

TABLE 15 Ratios of odds ratios (with 95% CI) comparing the BCG vaccination status of cases of all tuberculosis morbidity outcomes and control subjects in case–control studies, according to univariable meta-regression

Variable	Number of studies	Univariable ORs (95% CI)	Univariable model		
			Ratio of ORs (95% CI)	*p*-value	τ^2
Null model	16				0.208
Latitude					
>40°	4	0.43 (0.24 to 0.77)	1.00 (ref.)		
20–40°	6	0.29 (0.19 to 0.43)	0.66 (0.33 to 1.33)		
0–20°	6	0.49 (0.31 to 0.76)	1.13 (0.55 to 2.31)	0.174	0.180
Age at vaccination					
Neonatal	15	0.37 (0.28 to 0.50)	1.00 (ref.)		
School age	0				
Other	1	0.58 (0.13 to 2.55)	1.56 (0.35 to 6.96)	0.537	0.215
Was disease status blinded to BCG assessors?					
Lower risk of bias	0				
Higher risk of bias	16				0.208
Were vaccination definitions the same for cases and control subjects?					
Lower risk of bias	12	0.45 (0.34 to 0.60)	1.00 (ref.)		
Higher risk of bias	4	0.24 (0.14 to 0.38)	0.52 (0.31 to 0.89)	0.021	0.139
Were cases and control subjects determined independently of BCG vaccination status?					
Lower risk of bias	11	0.40 (0.28 to 0.56)	1.00 (ref.)		
Higher risk of bias	5	0.35 (0.21 to 0.57)	0.87 (0.48 to 1.60)	0.640	0.221
Were results adjusted for SES?					
Yes	8	0.40 (0.27 to 0.61)	1.00 (ref.)		
No	8	0.36 (0.24 to 0.53)	0.88 (0.50 to 1.56)	0.650	0.221
If a matched design was used, was a matched analysis performed?					
Unmatched design	3	0.39 (0.20 to 0.76)	1.00 (ref.)		
Matched design – matched analysis	5	0.39 (0.21 to 0.70)	1.00 (0.41 to 2.41)		
Matched design – matched analysis	8	0.37 (0.24 to 0.56)	0.94 (0.43 to 2.06)	0.981	0.248

ref., reference category; τ^2, estimated between-study variance.

compared with the baseline τ^2 (0.253). There was evidence (*p*-values = 0.069 and 0.003, respectively) that higher latitude and no adjustment for SES were associated with an increase in BCG vaccination effectiveness.

Case population studies

Results from univariable meta-regressions of case population studies indicate that none of the study level variables explained the between-study variation in overall BCG vaccination effectiveness.

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TABLE 16 Ratios of rate ratios (with 95% CI) comparing the incidence of all tuberculosis morbidity outcomes among vaccinated individuals compared with unvaccinated individuals for the longest duration of follow-up (see *Table 4)* in cohort studies, according to univariable meta-regression analysis

Variable	Number of studies	Univariable rate ratios (95% CI)	Univariable model		
			Ratio of rate ratios (95% CI)	*p*-value	τ^2
Null model	32				0.253
Latitude					
40°+	21	0.25 (0.18 to 0.33)	1.00 (ref.)		
20–40°	8	0.23 (0.14 to 0.38)	0.94 (0.53 to 1.68)		
0–20°	3	0.57 (0.29 to 1.11)	2.30 (1.10 to 4.78)	0.069	0.185
Age at vaccination					
Neonatal	7	0.23 (0.14 to 0.41)	1.00 (ref.)		
School age	10	0.24 (0.15 to 0.37)	1.02 (0.51 to 2.04)		
Other	15	0.33 (0.21 to 0.51)	1.40 (0.69 to 2.84)	0.487	0.268
Was follow-up independent of vaccination status?					
Lower risk of bias	23	0.31 (0.23 to 0.41)	1.00 (ref.)		
Higher risk of bias	9	0.16 (0.10 to 0.28)	0.53 (0.29 to 0.99)	0.047	0.271
Was case ascertainment blinded to vaccination status?					
Lower risk of bias	2	0.27 (0.11 to 0.66)	1.00 (ref.)		
Higher risk of bias	30	0.27 (0.20 to 0.36)	1.01 (0.39 to 2.61)	0.980	0.272
Were methods of case ascertainment identical for vaccinated and unvaccinated group?					
Lower risk of bias	30	0.27 (0.20 to 0.35)	1.00 (ref.)		
Higher risk of bias	2	0.28 (0.11 to 0.70)	1.03 (0.39 to 2.74)	0.954	0.272
Were losses to follow-up similar in each group?					
Lower risk of bias	5	0.31 (0.17 to 0.55)	1.00 (ref.)		
Higher risk of bias	27	0.26 (0.19 to 0.35)	0.85 (0.44 to 1.63)	0.607	0.273
Was diagnostic detection bias present?					
Lower risk of bias	13	0.28 (0.18 to 0.37)	1.00 (ref.)		
Higher risk of bias	19	0.26 (0.19 to 0.43)	0.91 (0.53 to 1.57)	0.737	0.263
Were results adjusted for SES?					
Yes	2	0.80 (0.39 to 1.64)	1.00 (ref.)		
No	30	0.25 (0.20 to 0.31)	0.30 (0.14 to 0.64)	0.003	0.130
Study type					
Prospective	10	0.31 (0.19 to 0.52)	1.00 (ref.)		
Retrospective	17	0.23 (0.16 to 0.32)	0.71 (0.39 to 1.32)		
Contact	5	0.34 (0.19 to 0.60)	1.08 (0.50 to 2.30)	0.353	0.236

ref., reference category; τ^2, estimated between-study variance.

Cross-sectional studies

Only the variable 'Were cases and controls determined independently of BCG vaccination status?' explained some of the between-study heterogeneity in cross-sectional studies reducing the τ^2 value from 0.716 (null model) to 0.646 but with insufficient data to support the suggestion that knowledge of BCG vaccination status was associated with a reduced effectiveness.

TABLE 17 Ratios of rate ratios (with 95% CI) comparing the incidence of all tuberculosis morbidity outcomes among vaccinated individuals compared with unvaccinated individuals for the longest duration of follow-up (see *Table 5*) in case population studies, according to univariable meta-regression analysis

Variable	Number of studies	Univariable rate ratios (95% CI)	Univariable model		
			Ratio of rate ratios (95% CI)	*p*-value	τ^2
Null model	12				0.619
Latitude					
>40°	8	0.17 (0.08 to 0.35)	1.00 (ref.)		
20–40°	2	0.27 (0.07 to 1.13)	1.58 (0.33 to 7.57)		
0–20°	2	0.30 (0.07 to 1.17)	1.74 (0.38 to 7.91)	0.643	0.683
Age at vaccination					
Neonatal	8	0.22 (0.11 to 0.46)	1.00 (ref.)		
School age	3	0.18 (0.06 to 0.56)	0.81 (0.22 to 3.00)		
Other	1	0.12 (0.01 to 2.00)	0.56 (0.03 to 9.30)	0.856	0.705
Were cases and population the same in terms of time?					
Lower risk of bias	12				
Higher risk of bias	0				0.619
Were cases and population the same in terms of geography?					
Lower risk of bias	11	0.12 (0.01 to 1.79)	1.00 (ref.)		
Higher risk of bias	1	0.21 (0.12 to 0.37)	0.59 (0.04 to 8.68)	0.671	0.643
Were cases and population the same in terms of age?					
Lower risk of bias	12				
Higher risk of bias	0				0.619
Was case ascertainment blinded to vaccination status?					
Lower risk of bias	0				
Higher risk of bias	12				0.619
Was disease status blinded to BCG assessors?					
Lower risk of bias	2	0.19 (0.10 to 0.34)	1.00 (ref.)		
Higher risk of bias	10	0.32 (0.09 to 1.15)	0.59 (0.14 to 2.40)	0.421	0.639
Were methods of case ascertainment same for vaccinated and unvaccinated?					
Lower risk of bias	9	0.11 (0.04 to 0.28)	1.00 (ref.)		
Higher risk of bias	3	0.26 (0.15 to 0.47)	0.41 (0.14 to 1.22)	0.101	0.491

ref., reference category; τ^2, estimated between-study variance.

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Combined meningeal and/or miliary tuberculosis

Unstratified analysis ordered by year study started

A total of 31 observational studies provided data on the effect of BCG vaccination against miliary tuberculosis and tuberculosis meningitis. The majority of studies assessed this effect on meningeal tuberculosis (14 case–control studies, six cohorts, six case population studies and six cross-sectional studies), seven studies provided data on the combined outcome of both miliary tuberculosis and meningitis, whereas one cohort and one cross-sectional study provided data on miliary tuberculosis only. *Figures 55–58* present the unstratified results of these studies. Despite variation in the protective effectiveness of BCG vaccination against meningeal and/or miliary tuberculosis between individual studies, the majority (21) of these showed an overall protective effect.

All case–control studies showed evidence of a protective effect of BCG vaccination against the combined outcome of meningeal and miliary tuberculosis, and meningeal tuberculosis only (see

TABLE 18 Ratios of risk ratios (with 95% CI) comparing the prevalence of all tuberculosis morbidity outcomes among vaccinated individuals compared with unvaccinated individuals in cross-sectional studies according to univariable meta-regression analysis

Variable	Number of studies	Univariable RRs (95% CI)	RRRs (95% CI)	*p*-value	τ^2
Null model	13				0.716
Latitude					
40°+	6	0.22 (0.09 to 0.55)	1.00 (ref.)		
20–40°	2	0.58 (0.13 to 2.57)	2.62 (0.47 to 14.50)		
0–20°	5	0.37 (0.13 to 1.03)	1.64 (0.42 to 6.36)	0.448	0.754
Age at vaccination					
Neonatal	7	0.41 (0.19 to 0.88)	1.00 (ref.)		
School age	4	0.17 (0.06 to 0.53)	0.43 (0.11 to 1.63)		
Other	2	0.37 (0.04 to 3.28)	0.90 (0.09 to 8.88)	0.398	0.736
Was disease status blinded to BCG assessors?					
Lower risk of bias	1	0.15 (0.02 to 1.04)	1.00 (ref.)		
Higher risk of bias	12	0.34 (0.18 to 0.64)	2.29 (0.30 to 17.35)	0.386	0.720
Were vaccination definitions the same for cases and control subjects?					
Lower risk of bias	11	0.30 (0.15 to 0.60)	1.00 (ref.)		
Higher risk of bias	2	0.37 (0.09 to 1.62)	1.24 (0.25 to 6.14)	0.775	0.795
Were cases and control subjects determined independently of BCG vaccination status?					
Lower risk of bias	11	0.26 (0.14 to 0.50)	1.00 (ref.)		
Higher risk of bias	2	0.67 (0.19 to 2.38)	1.54 (0.62 to 10.35)	0.172	0.646
Were results adjusted for SES?					
Yes	1	0.32 (0.03 to 3.07)	1.00 (ref.)		
No	12	0.31 (0.16 to 0.60)	0.98 (0.10 to 9.97)	0.982	0.787
Study type					
Non-contact	8	0.30 (0.13 to 0.70)	1.00 (ref.)		
Contact	5	0.33 (0.13 to 0.84)	0.92 (0.27 to 3.20)	0.890	0.780

ref., reference category; τ^2, estimated between-study variance.

Figure 55). Similarly, the effect of BCG vaccination observed in cohort studies was protective, although in three of the six studies the sample sizes were small and CI crossed one. All case population studies showed evidence of a strong protection against meningeal tuberculosis. Only one out of the six cross-sectional studies did not find evidence of a clinical benefit (see *Figure 58*).

Case–control studies
See *Figure 55*.

Cohort studies
See *Figure 56*.

Case population studies
See *Figure 57*.

Cross-sectional studies
See *Figure 58*.

Stratified analysis by latitude (10°), ordered by year study started
Figures 59–62 show the estimated effects of BCG vaccination against meningeal and miliary tuberculosis, stratified by latitude of study location. All case–control studies were conducted at latitudes of < 40°. The most consistent, protective effect was high, and seen in studies conducted between 30° and 40° with an overall OR of 0.19 (95% CI 0.12 to 0.31), corresponding to a VE of 81% (95% CI 69% to 88%). There was evidence of heterogeneity for studies from locations between 20° and 30°, with some studies showing a protective effect similar to that seen at higher latitudes, whereas in others the protective effect was low. Studies at lower latitudes (0° to 20°) showed evidence of a good protective effect. There was consistent evidence of high protection in cohort studies conducted above 50° latitude [rate ratio 0.23 (95% CI 0.12 to 0.44)] equivalent to a good VE of 77% (95% CI 56% to 88%), whereas only one cohort study each was conducted at 30–40° and 40–50° latitude. Results from observational case population and cross-sectional studies showed no evidence that protection by BCG vaccination against meningeal and miliary tuberculosis varied substantially by latitude.

Meta-regression analysis
Stratification by bands of 20° latitude did not explain any of the between-study variance (null model $\tau^2 = 0.275$; after stratification band $\tau^2 = 0.291$) in case–control studies (*Table 19*). There was no clear evidence that BCG vaccination effectiveness in case–control studies varied with latitude (p-value = 0.570). The stratification on 20° latitude group for cohort (*Table 20*) accounted for the between-study heterogeneity (null model $\tau^2 = 0.035$; after stratification by 20° band $\tau^2 = 0.000$), but did not explain the heterogeneity for case population studies: null model $\tau^2 = 0.292$; after stratification by 20° band $\tau^2 = 0.434$, respectively) and no evidence (p-value = 0.839 and 0.723, respectively) indicated that BCG vaccination effectiveness differed according to latitude in cohort and case population studies. Similarly, latitude did not account for any of the between-study heterogeneity seen within cross-sectional studies (*Table 21*), with τ^2 value before and after stratification on latitude = 1.433 and 2.140. There was no evidence (p-value = 0.734) that BCG vaccination effectiveness varied with latitude (*Table 22*).

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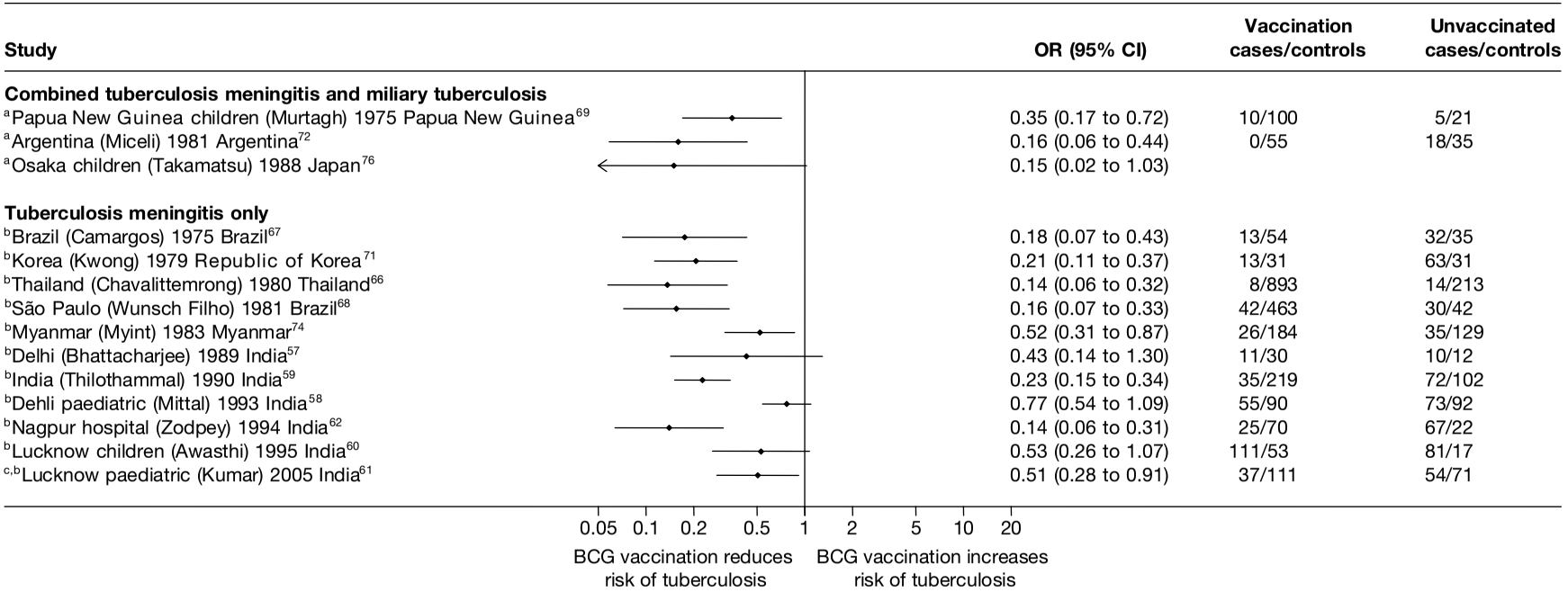

FIGURE 55 Odds ratios (with 95% CI) comparing the BCG vaccination status of meningeal and/or miliary tuberculosis cases and control subjects in case–control studies, ordered by year of study start. D+L, DerSimonian and Laird method; I–V, inverse variance method. a, Combined tuberculosis meningitis and miliary tuberculosis outcomes; b, Tuberculosis meningitis outcome only; c, Date of study publication was used if study start date was not available.

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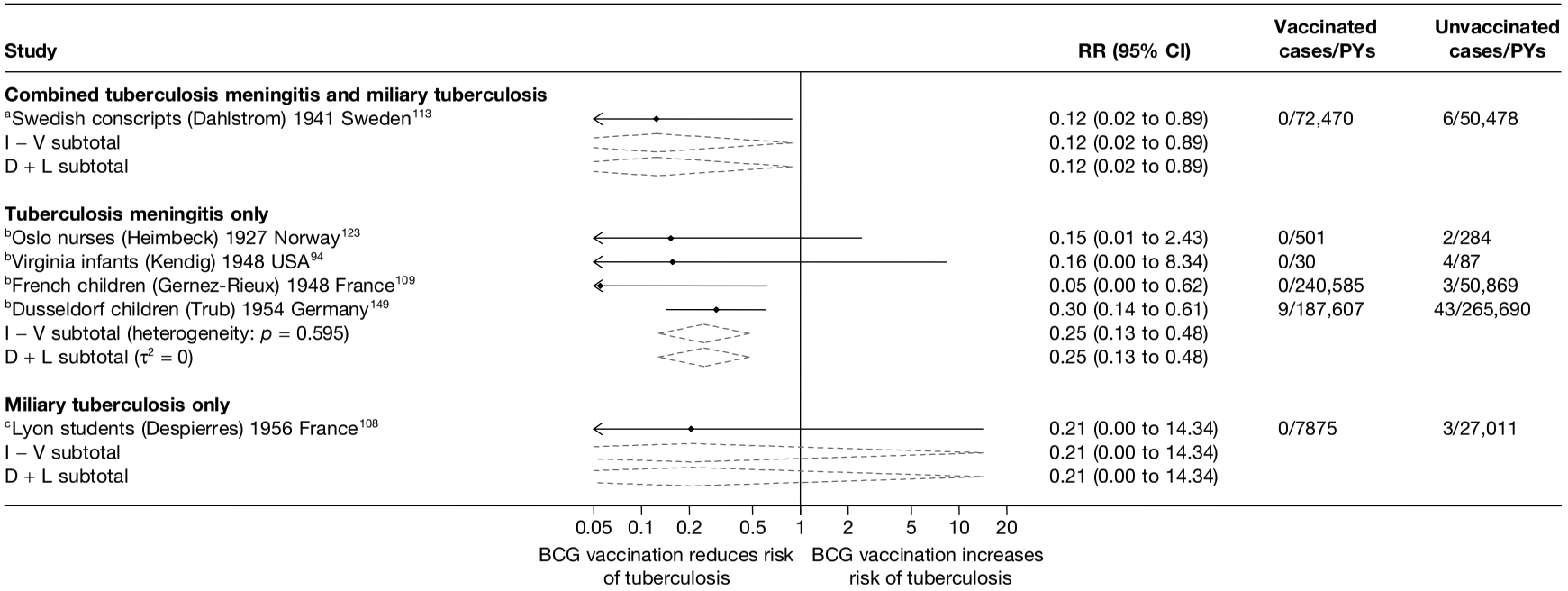

FIGURE 56 Rate ratios (with 95% CI) comparing the incidence of meningeal and/or miliary tuberculosis among cases with that in control subjects for the longest duration of follow-up (see *Table 4*) in cohort studies, ordered by year of study start. a, Combined tuberculosis meningitis and miliary tuberculosis outcomes; b, Tuberculosis meningitis outcome only; c, Miliary tubeculosis outcome only. D+L, DerSimonian and Laird method; I–V, inverse variance method.

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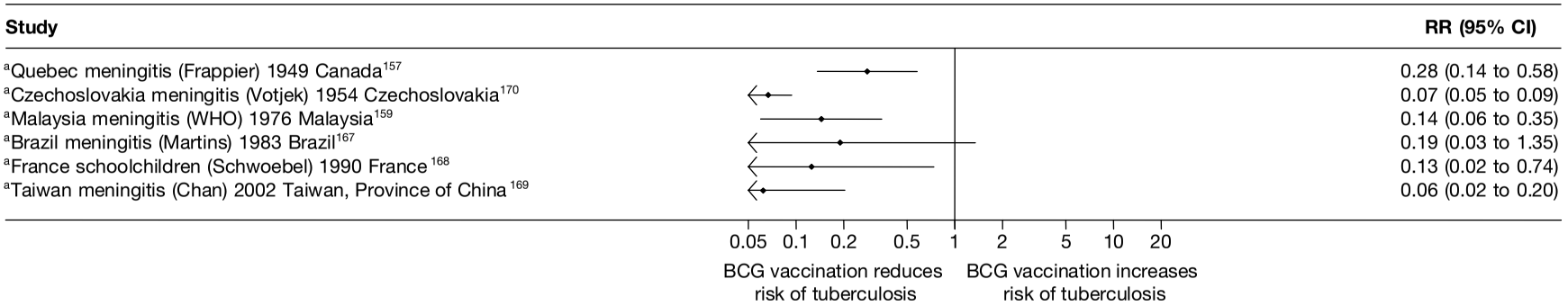

FIGURE 57 Rate ratios (with 95% CI) comparing the incidence of meningeal and/or miliary tuberculosis among vaccinated individuals with that in unvaccinated individuals for the longest duration of follow-up (see *Table 5*) in case population studies, ordered by year of study start. a, Tuberculosis meningitis outcome only.

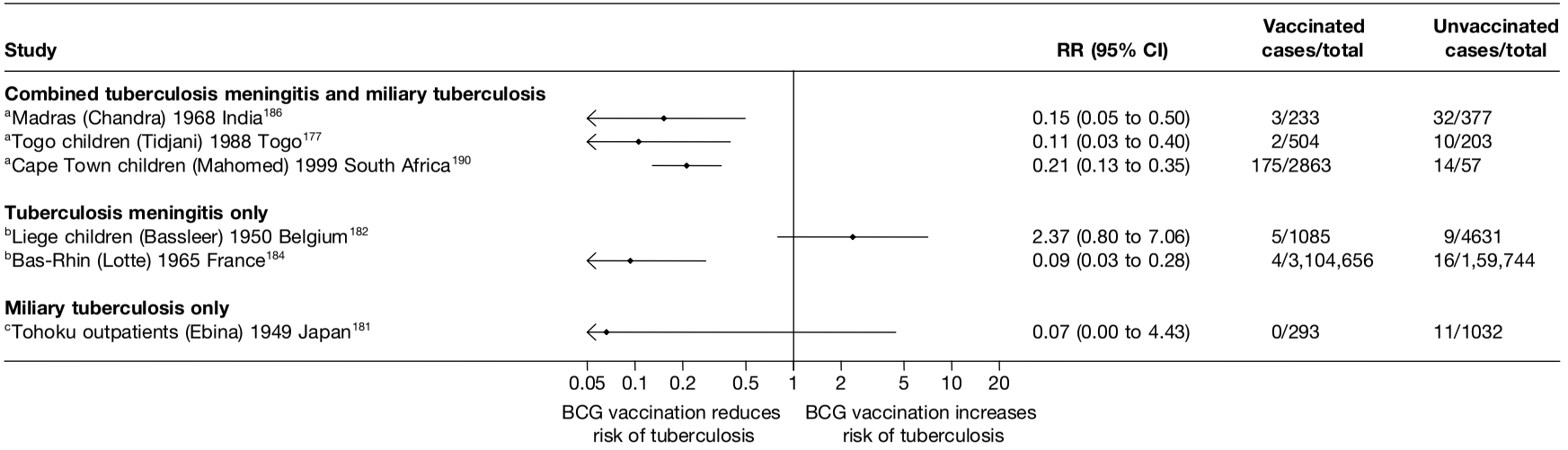

FIGURE 58 Risk ratios (with 95% CI) comparing the prevalence of meningeal and/or miliary tuberculosis among vaccinated individuals with that in unvaccinated individuals in cross-sectional studies, ordered by year of study start. a, Combined tuberculosis meningitis and miliary tuberculosis outcomes; b, Tuberculosis meningitis outcome only; c, Miliary tuberculosis outcome only. D+L, DerSimonian and Laird metod; I–V, inverse variance method.

Case–control studies
See *Figure 59*.

Cohort studies
See *Figure 60*.

Case population studies
See *Figure 61*.

Cross-sectional studies
See *Figure 62*.

Stratified analysis by age at vaccination, ordered by year study started
The estimated effects of BCG vaccination against meningeal and miliary tuberculosis from observational studies were stratified by age at vaccination (*Figures 63–66*). Overall, the protective effect of BCG vaccination from case–control studies of school-age vaccination [OR 0.23 (95% CI 0.16 to 0.33), VE of 77% (95% CI 67% to 84%)] was similarly good, and similar to studies of neonatal vaccination [OR 0.31, 95% CI 0.20 to 0.47, equivalent to VE of 69% (95% CI 53% to 80%)]. The small number of cohort studies in each age at vaccination category makes results difficult to interpret (see *Figure 64*).

All but one case population study evaluated neonatal vaccination, with high overall levels of effectiveness (see *Figure 65*). This study of school-age vaccination showed a substantial high protective effect [rate ratio 0.13 (95% CI 0.02 to 0.74)], similar to the overall effect of neonatal vaccination studies [rate ratio 0.12 (95% CI 0.06 to 0.24) equivalent to VE of 88% (95% CI 76% to 94%)]. Results from cross-sectional studies in *Figure 66* also showed strong evidence of high protection from vaccination at birth [RR 0.19 (95% CI 0.12 to 0.29, VE of 81% (95% CI 71% to 88%)]. The Tohoku outpatients study,[143] which performed vaccination in other age groups, also shows a high estimate of vaccine effectiveness.

Meta-regression analysis
Based on meta-regression analyses, age at vaccination explained very little of the between-study variability (τ^2 before and after stratification = 0.275 and 0.266, respectively): see *Table 19*. Stratification on age at vaccination explained some of between-study heterogeneity within cohorts, in *Table 20* (τ^2 before and after stratification = 0.035 and 0.000, respectively) although heterogeneity was already low prior to stratification. *Table 21* showed that age at vaccination did not account for any of the between-study heterogeneity in case population studies (τ^2 before and after stratification = 0.292 and 0.340, respectively). Age at vaccination was not found to account for any of the heterogeneity seen in cross-sectional studies (τ^2 before and after stratification = 1.433 and 2.140, respectively), as shown in *Table 22*. However, there was insufficient evidence that BCG vaccination protection varied according to age at vaccination in case–control, cohort, case population and cross-sectional studies (p = 0.386, 0.475, 0.969, 0.734, respectively).

Case–control studies
See *Figure 63*.

Cohort studies
See *Figure 64*.

Case population studies
See *Figure 65*.

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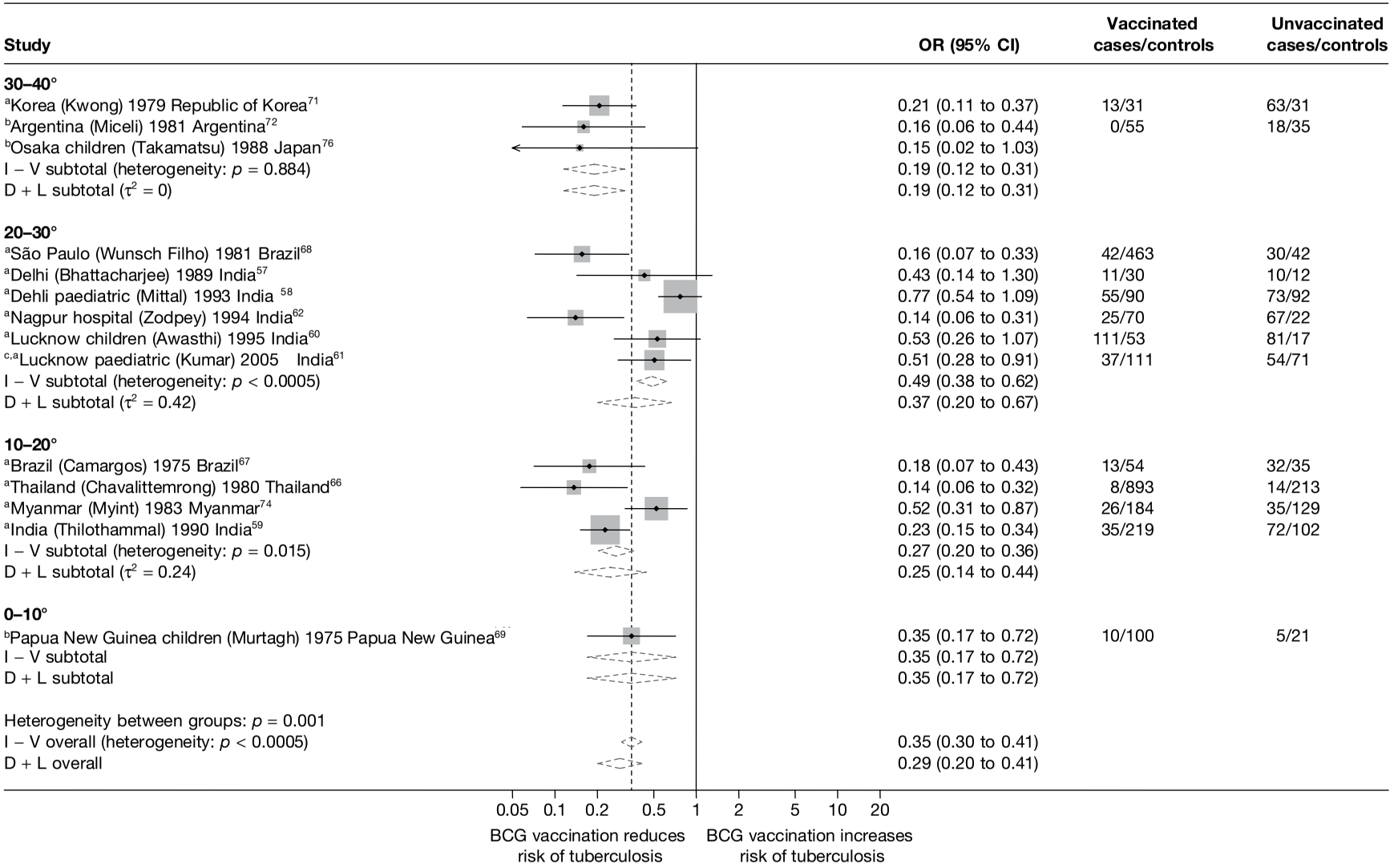

FIGURE 59 Odds ratios (with 95% CI) comparing the BCG vaccination status of meningeal and/or miliary tuberculosis cases and control subjects in case–control studies, stratified by latitude (10°), ordered by year of study start. a, Meningitis only; b, Combined meningitis and miliary; c, Date of study publication was used if study start date was not available. D+L, DerSimonian and Laird method; I–V, inverse variance method.

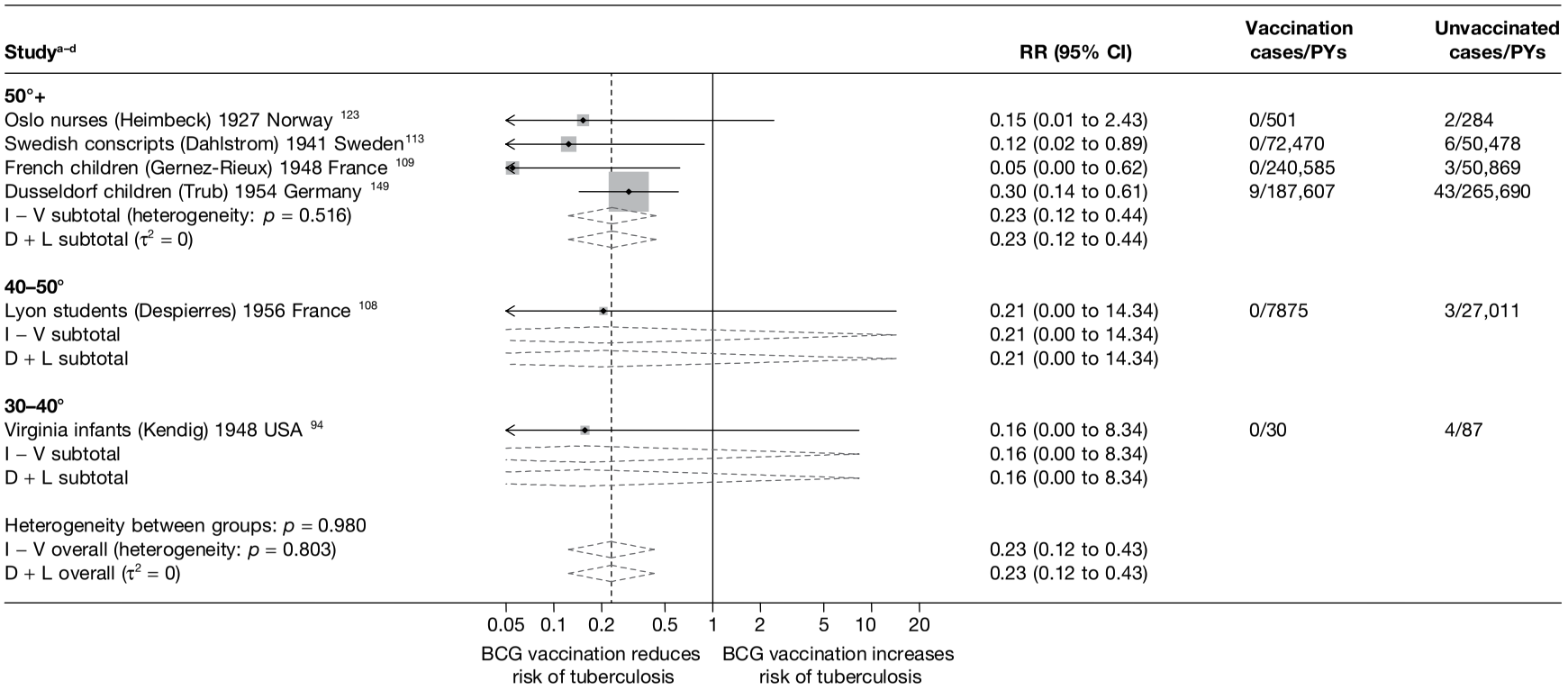

FIGURE 60 Rate ratios (with 95% CI) comparing the incidence of meningeal and/or miliary tuberculosis among BCG vaccinated individuals with that in unvaccinated individuals for the longest duration of follow-up (see *Table 4*) in cohort studies, stratified by latitude (10°), ordered by year of study start. a, Date of study publication was used if study start date was not available; b, Combined tuberculosis meningitis and miliary tuberculosis outcomes; c, Tuberculosis meningitis outcome only; d, Miliary tuberculosis outcome only. D+L, DerSimonian and Laird method; I–V, inverse variance method.

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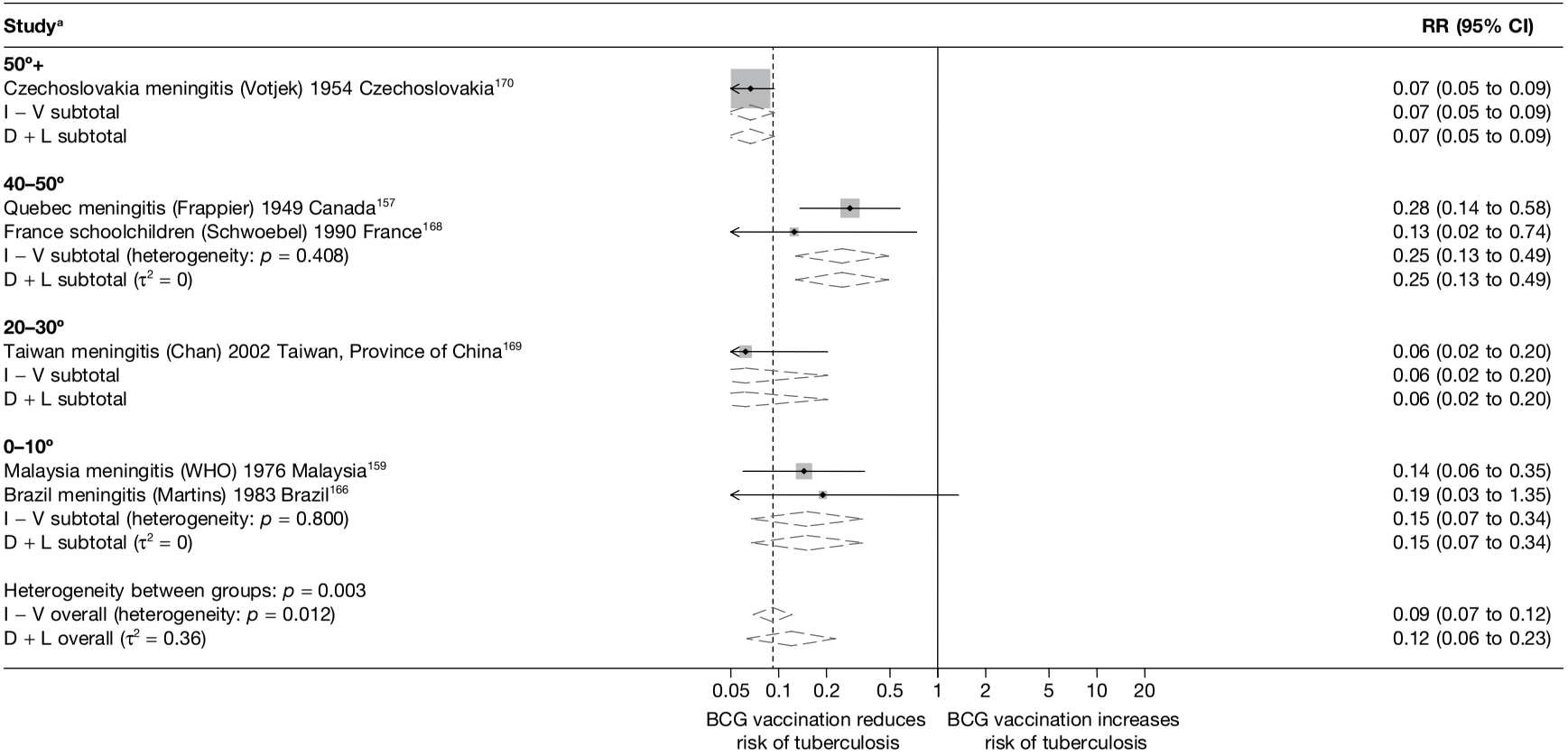

FIGURE 61 Rate ratios (with 95% CI) comparing the incidence of meningeal and/or miliary tuberculosis among BCG vaccinated individuals with that in unvaccinated individuals for the longest duration of follow-up (see *Table 5*) in case population studies, stratified by latitude (10°), ordered by year of study start. a, Tuberculosis meningitis outcome only. D+L, DerSimonian and Laird method; I–V, inverse variance method.

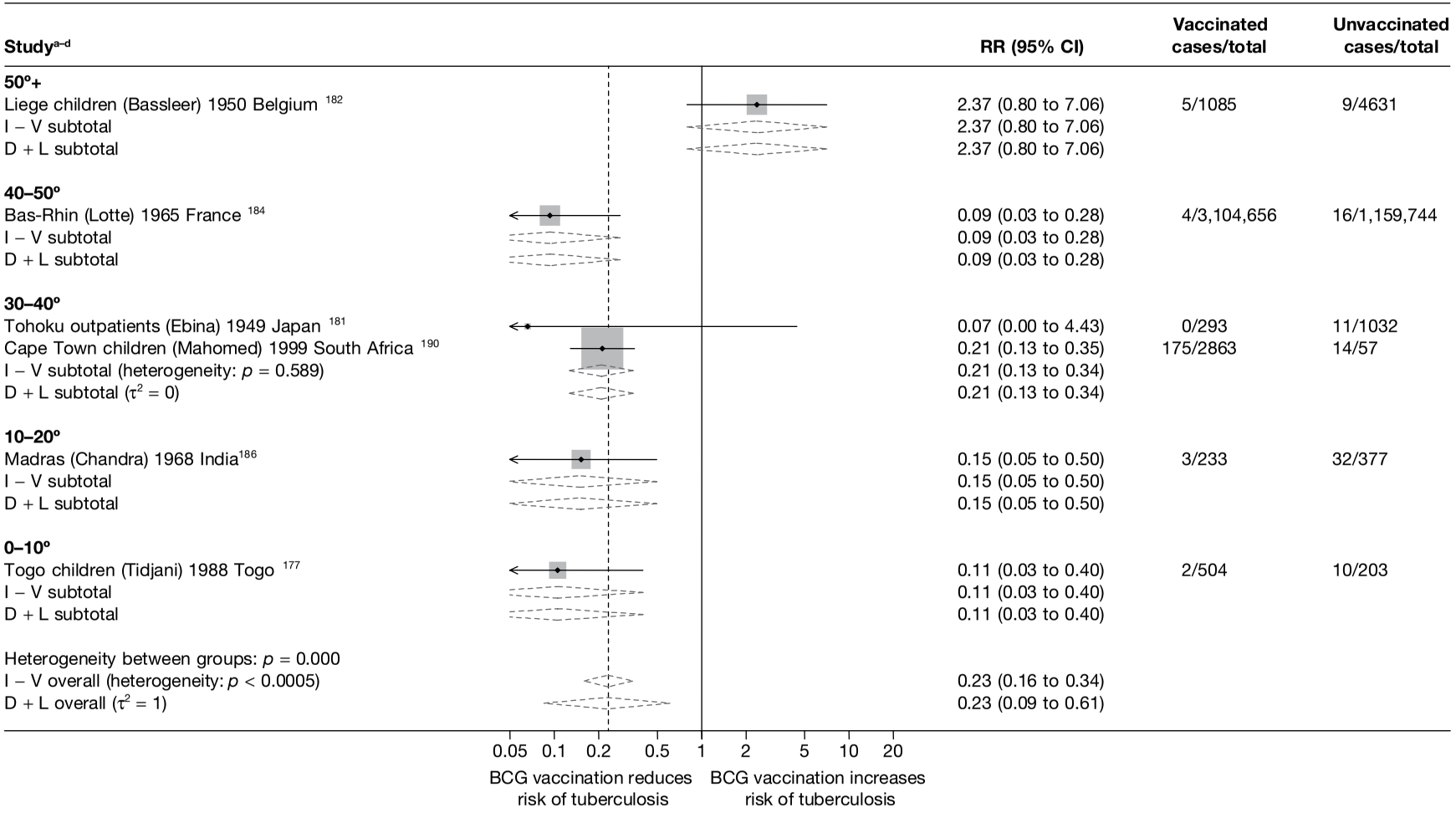

FIGURE 62 Risk ratios (with 95% CI) comparing the prevalence of meningeal and/or miliary tuberculosis among BCG vaccinated individuals with that in unvaccinated individuals in cross-sectional studies, stratified by latitude (10°), ordered by year of study start. a, Date of study publication was used if study start date was not available; b, Combined tuberculosis meningitis and miliary tuberculosis outcomes; c, Tuberculosis meningitis outcome only; d, Miliary tuberculosis outcome only. D+L, DerSimonian and Laird method; I–V, inverse variance method.

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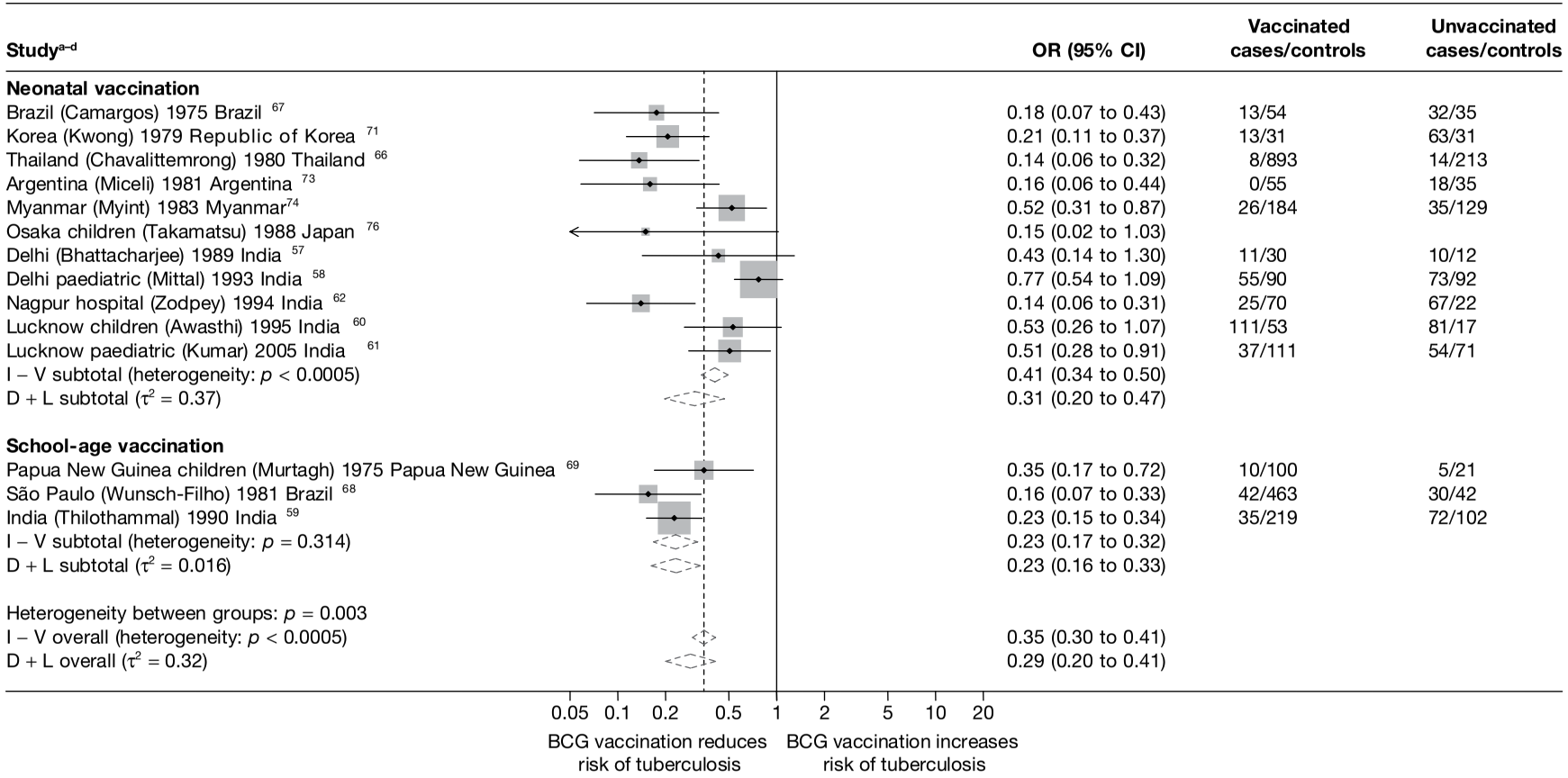

FIGURE 63 Odds ratios (with 95% CI) comparing the BCG vaccination status of meningeal and/or miliary tuberculosis cases and control subjects, stratified by age at vaccination, ordered by year of study start. a, Date of study publication was used if study start date was not available; b, Combined tuberculosis meningitis and miliary tuberculosis outcomes; c, Tuberculosis meningitis outcome only; d, Miliary tuberculosis outcome only. D+L, DerSimonian and Laird method; I–V, inverse variance method.

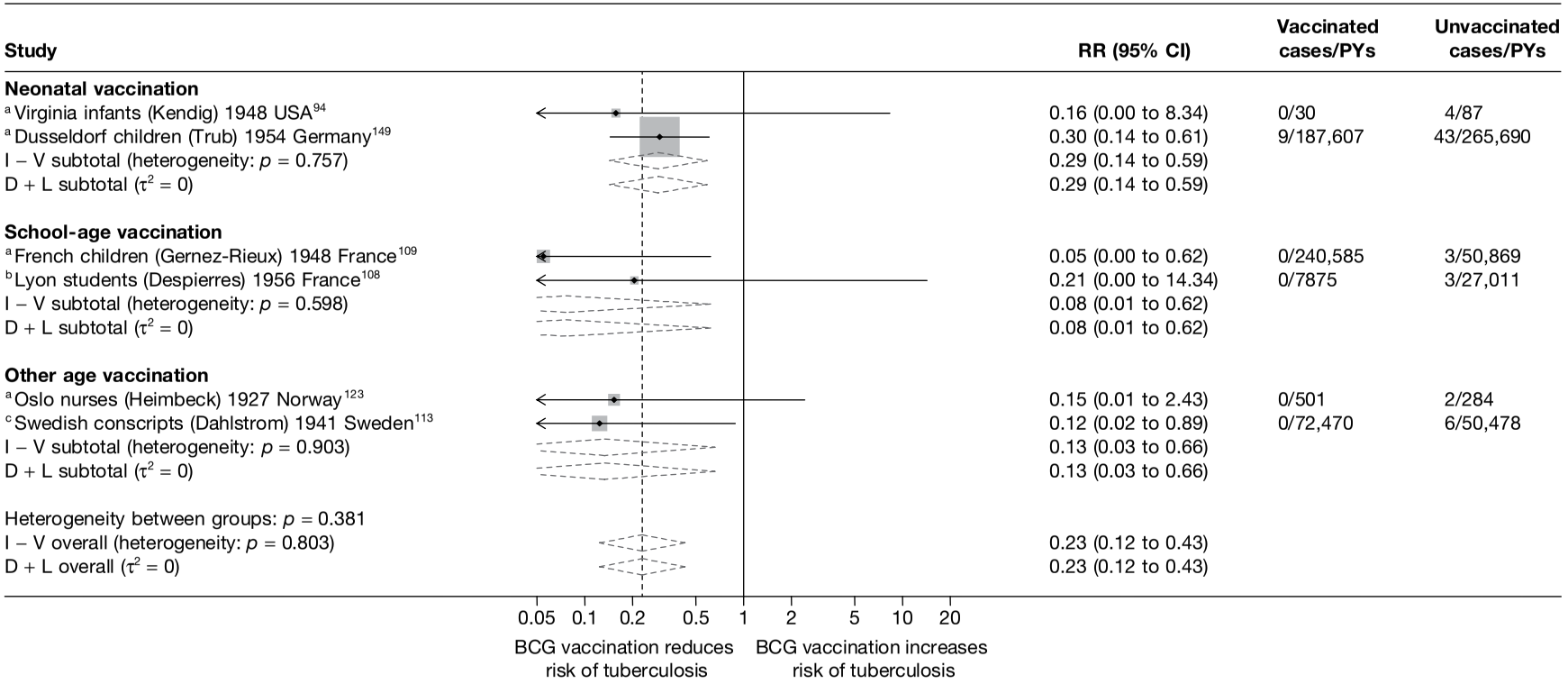

FIGURE 64 Rate ratios (with 95% CI) comparing the incidence of meningeal and/or miliary tuberculosis among BCG vaccinated individuals with that in unvaccinated individuals for the longest duration of follow-up (see *Table 4*) in cohort studies, stratified by age at vaccination, ordered by study start. a, Tuberculosis meningitis outcome only; b, Miliary tuberculosis outcome only; c, Combined tuberculosis meningitis and miliary tuberculosis outcomes. D+L, DerSimonian and Laird method; I–V, inverse variance method.

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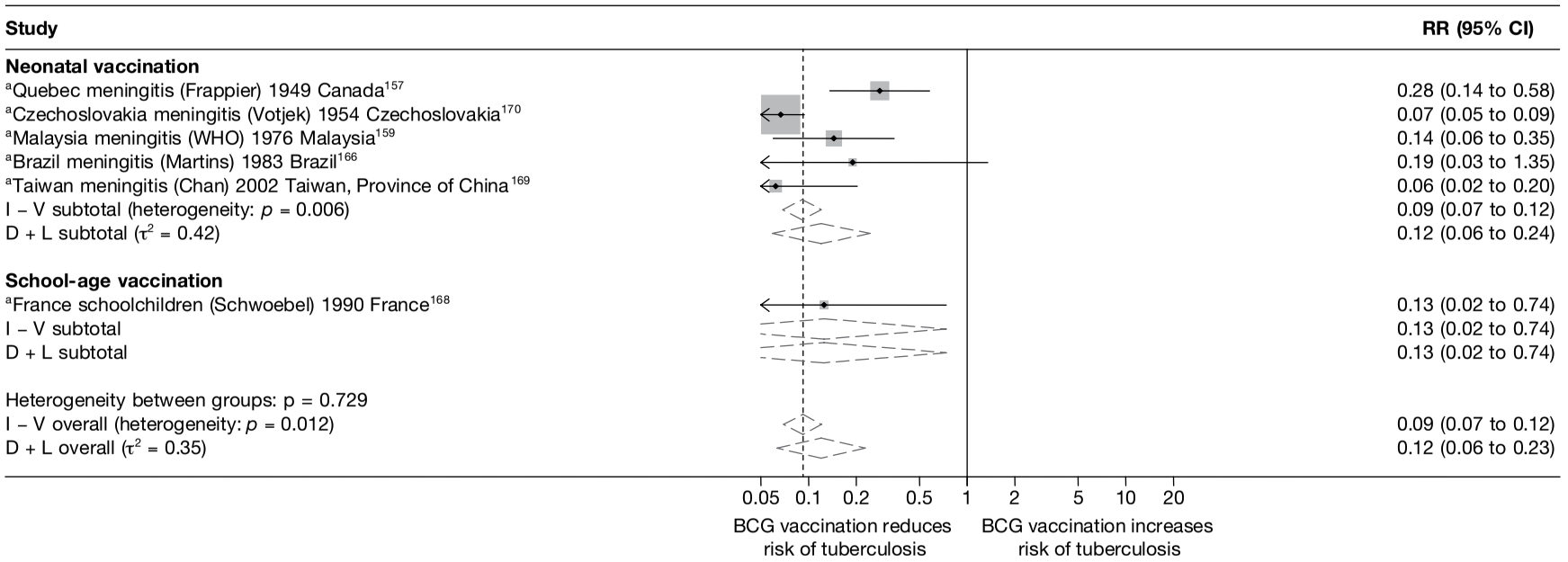

FIGURE 65 Rate ratios (with 95% CI) comparing the incidence of meningeal and/or miliary tuberculosis among BCG vaccinated individuals with that in unvaccinated individuals for the longest duration of follow-up (see *Table 5*) in case population studies, stratified by age at vaccination, ordered by year of study start. a, Tuberculosis meningitis outcome only. D+L, DerSimonian and Laird method; I–V, inverse variance method.

Cross-sectional studies

See *Figure 66*.

Stratified analysis by study design, ordered by year study started

Cohort studies

Figure 67 shows the forest plot for cohort studies stratified by study design. Contrary to results on protection against pulmonary and all types of tuberculosis disease, prospective studies of BCG vaccination against miliary and or meningeal tuberculosis showed evidence of overall higher protection against tuberculosis meningitis with rate ratio 0.10 (95% CI 0.02 to 0.50), corresponding to VE of 90% (95% CI 50% to 98%), compared with retrospective studies (which include a study with data on miliary tuberculosis only), with an overall good protective effect rate ratio 0.27 (95% CI 0.14 to 0.52) which corresponds to VE of 73% (95% CI 48% to 86%) VE. Cohort study design thus appears to explain a substantial amount of between-study variability.

Meta-regression analysis

Stratification of cohort studies by study design accounted for the between-study heterogeneity (τ^2 before and after stratification = 0.035 and 0.000) (see *Table 20*). There was, however, insufficient evidence that BCG vaccination effectiveness varies according to study design in cohort: rate ratio for retrospective cohort studies was 2.79 (95% CI 0.22 to 34.99, *p*-value = 0.323) times the rate ratio of prospective cohort studies.

Meta-regression analyses

Case–control studies

Results from univariable meta-regressions for all study variables for case–control studies are given in *Table 19*. Age at vaccination, 'were vaccination definitions the same for cases and controls?', 'were cases and controls determined independently of BCG vaccination status?' and 'if the study design was matched, was a matched analysis performed?' each explained some of the between-study variation in overall BCG vaccination effectiveness with a τ^2 value of 0.266, 0.229 and 0.244 and 0.178 respectively, compared with the baseline τ^2 (0.275), but there was no evidence consistent with an association between any of the factors and BCG vaccination effectiveness.

Cohort studies

Results from univariable meta-regressions for cohort studies indicate that all variables, apart from 'Was case ascertainment blinded to vaccination status?' and 'were methods of case ascertainment identical for vaccinated and unvaccinated group?' explained all of the between-study variation in overall BCG vaccination effectiveness reducing the null τ^2 (0.035) to 0.000 (see *Table 20*). There was, however, no evidence of association of these variables with BCG vaccine effectiveness.

Case population studies

For case population studies there was little between-study heterogeneity, with overall clear evidence of effectiveness of BCG vaccination against meningeal and/or miliary forms of tuberculosis.

Cross-sectional studies

The results of the univariate meta-regression for the six cross-sectional studies (see *Table 22*) examining all study variables indicate that only stratification on the quality assessment criterion 'Were vaccination definitions the same for cases and controls?' was associated with a reduction in the heterogeneity seen within these studies (null model $\tau^2 = 1.433$ and after stratification by criterion $\tau^2 = 0.061$). There was evidence (*p*-value = 0.022) that this variable was associated with a degree of protection from BCG vaccination against tuberculosis meningitis and/or miliary tuberculosis.

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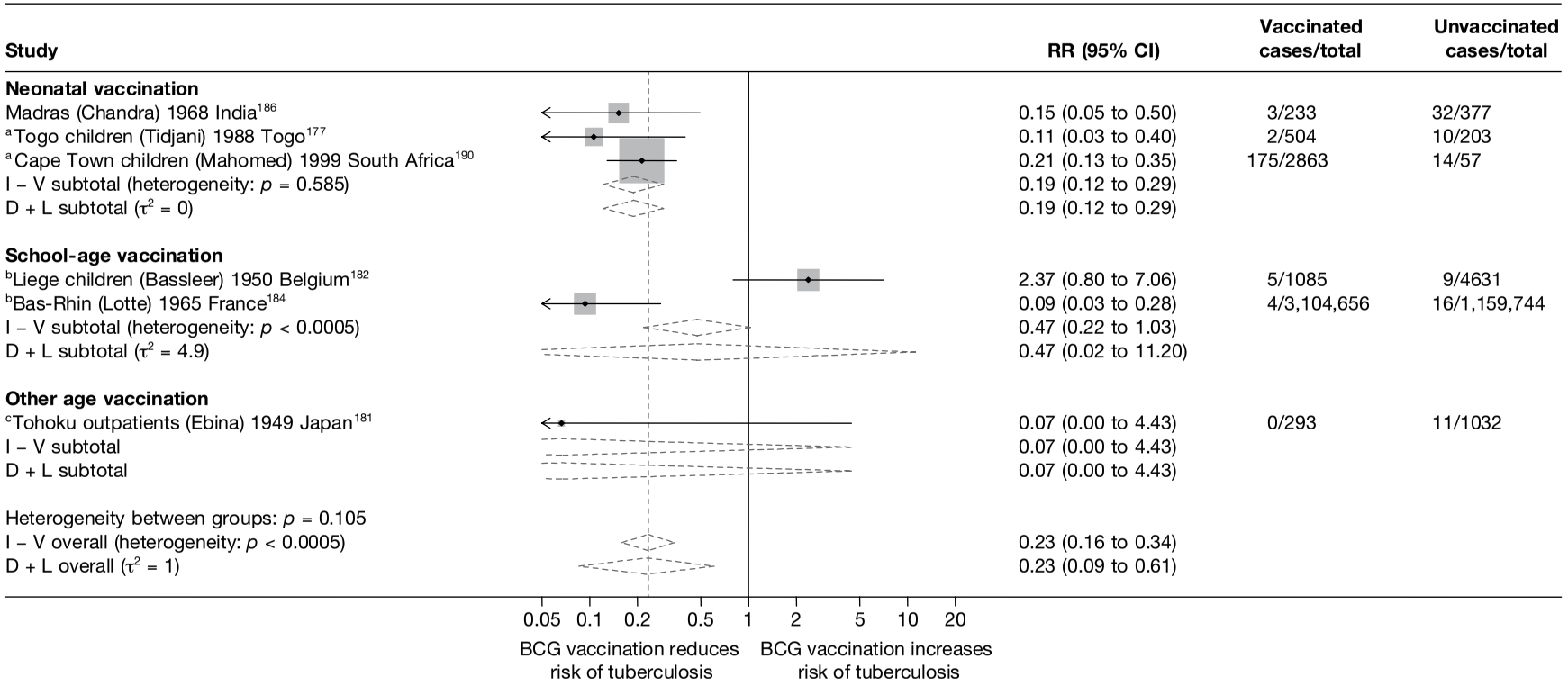

FIGURE 66 Risk ratios (with 95% CI) comparing the prevalence of meningeal and/or miliary tuberculosis among BCG vaccinated individuals with that in unvaccinated individuals in cross-sectional studies, stratified by age at vaccination, ordered by year of study start. a, Combined tuberculosis meningitis and miliary tuberculosis outcomes; b, Tuberculosis meningitis outcome only; c, Miliary tuberculosis outcome only. D+L, DerSimonian and Laird method; I–V, inverse variance method.

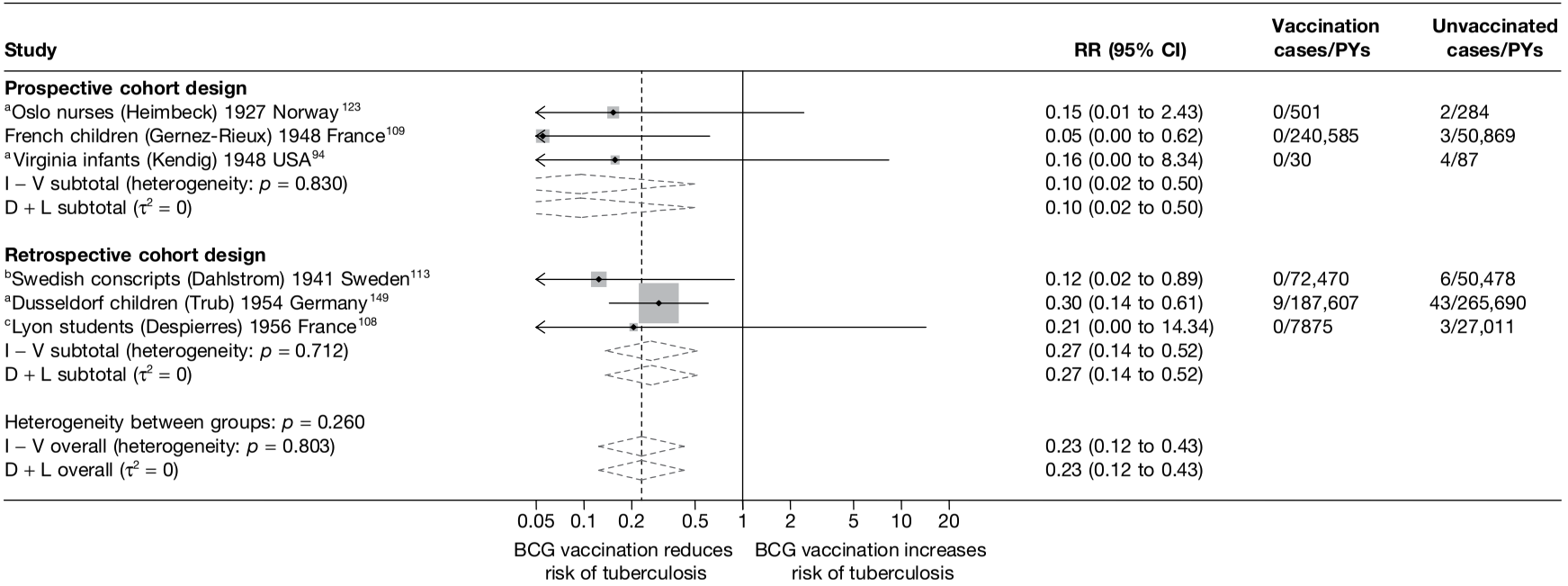

FIGURE 67 Rate ratios (with 95% CI) comparing the incidence of meningeal and/or miliary tuberculosis among BCG vaccinated individuals with that in unvaccinated individuals for the longest duration of follow-up (see *Table 4*) in cohort studies, stratified by cohort study design, ordered by year of study start. a, Tuberculosis meningitis outcome only; b, Combined tuberculosis meningitis and miliary tuberculosis outcomes; c, Miliary tuberculosis outcome only. D+L, DerSimonian and Laird method; I–V, inverse variance method.

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TABLE 19 Ratios of odds ratios (with 95% CI) comparing the BCG vaccination status of meningeal and/or miliary tuberculosis cases and control subjects, according to univariable meta-regression analysis

Variable	Number of studies	Univariable ORs (95% CI)	Univariable model		
			Ratio of ORs (95% CI)	*p*-value	τ^2
Null model	14				0.275
Latitude					
>40°	0				
20–40°	9	0.32 (0.19 to 0.54)	1.00		
0–20°	5	0.26 (0.13 to 0.49)	0.80 (0.35 to 1.82)	0.570	0.291
Age at vaccination					
Neonatal	11	0.32 (0.21 to 0.51)	1.00 (ref.)		
School age	3	0.22 (0.10 to 0.50)	0.68 (0.27 to 1.71)		
Other	0			0.386	0.266
Was disease status blinded to BCG assessors?					
Lower risk of bias	0				
Higher risk of bias	14				0.275
Were vaccination definitions the same for cases and control subjects?					
Lower risk of bias	11	0.33 (0.22 to 0.51)	1.00 (ref.)		
Higher risk of bias	3	0.17 (0.07 to 0.40)	0.50 (0.19 to 1.29)	0.137	0.229
Were cases and control subjects determined independently of BCG vaccination status?					
Lower risk of bias	10	0.34 (0.22 to 0.54)	1.00 (ref.)		
Higher risk of bias	4	0.21 (0.11 to 0.43)	0.63 (0.27 to 1.43)	0.240	0.241
Were results adjusted for SES?					
Yes	8	0.28 (0.16 to 0.50)	1.00 (ref.)		
No	6	0.31 (0.17 to 0.56)	1.08 (0.48 to 2.45)	0.841	0.308
If a matched design was used, was a matched analysis performed?					
Unmatched design	5	0.44 (0.26 to 0.77)	1.00 (ref.)		
Matched design – matched analysis	4	0.19 (0.10 to 0.37)	0.42 (0.18 to 1.01)		
Matched design – matched analysis	5	0.27 (0.15 to 0.50)	0.61 (0.27 to 1.37)	0.130	0.178

ref., reference category; τ^2, estimated between-study variance.

TABLE 20 Ratios of rate ratios (with 95% CI) comparing the incidence of tuberculosis meningitis and miliary tuberculosis among vaccinated individuals compared with unvaccinated individuals for the longest duration of follow-up (see *Table 4*) in cohort studies, according to univariable meta-regression analysis

Variable	Number of studies	Univariable rate ratios (95% CI)	Univariable model		
			Ratio of rate ratios (95% CI)	*p*-value	τ^2
Null model	6				0.035
Latitude					
>40°	5	0.24 (0.01 to 0.70)	1.00 (ref.)		
20–40°	1	0.16 (0.01 to 99.42)	0.64 (0.01 to 191.85)		
0–20°	0			0.839	0.000
Age at vaccination					
Neonatal	2	0.29 (0.06 to 1.37)	1.00 (ref.)		
School age	2	0.08 (0.01 to 7.69)	0.26 (0.01 to 9.60)		
Other	2	0.16 (0.01 to 12.56)	0.56 (0.02 to 16.96)	0.530	0.000
Was follow-up independent of vaccination status?					
Lower risk of bias	3	0.27 (0.09 to 0.83)	1.00 (ref.)		
Higher risk of bias	3	0.09 (0.01 to 1.82)	0.32 (0.02 to 5.31)	0.325	0.000
Was case ascertainment blinded to vaccination status?					
Lower risk of bias	0				
Higher risk of bias	6				0.035
Were methods of case ascertainment identical for vaccinated and unvaccinated group?					
Lower risk of bias	6				
Higher risk of bias	0				0.035
Were losses to follow-up similar in each group?					
Lower risk of bias	2	0.09 (0.01 to 1.77)	1.00 (ref.)		
Higher risk of bias	4	0.28 (0.09 to 0.83)	3.13 (0.19 to 50.73)	0.318	0.000
Was diagnostic detection bias present?					
Lower risk of bias	2	0.08 (0.01 to 2.31)	1.00 (ref.)		
Higher risk of bias	4	0.27 (0.09 to 0.80)	3.58 (0.16 to 81.52)	0.321	0.000
Were results adjusted for SES?					
Yes	0				
No	6				
Study type					
Prospective	3	0.10 (0.01 to 1.40)	1.00 (ref.)		
Retrospective	3	0.28 (0.09 to 0.87)	2.98 (0.24 to 37.84)		
Contact	0			0.298	0.000

ref., reference category; τ^2, estimated between-study variance.

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TABLE 21 Ratios of rate ratios (with 95% CI) comparing the incidence of tuberculosis meningitis and/or miliary tuberculosis among vaccinated individuals compared with unvaccinated individuals for the longest duration of follow-up (see *Table 5*) in case population studies, according to univariable meta-regression analysis

Variable	Number of studies	Univariable rate ratios (95% CI)	Univariable model		
			Ratio of rate ratios (95% CI)	*p*-value	τ^2
Null model	6				0.292
Latitude					
>40°	3	0.13 (0.02 to 0.92)	1.00 (ref.)		
20–40°	1	0.06 (0.01 to 2.91)	0.49 (0.02 to 12.00)		
0–20°	2	0.16 (0.01 to 2.73)	1.24 (0.09 to 16.17)	0.723	0.434
Age at vaccination					
Neonatal	5	0.12 (0.04 to 0.34)	1.00 (ref.)		
School age	1	0.13 (0.01 to 3.86)	1.04 (0.05 to 24.13)		
Other	0			0.969	0.340
Were cases and population the same in terms of time?					
Lower risk of bias	6				
Higher risk of bias	0				0.292
Were cases and population the same in terms of geography?					
Lower risk of bias	6				
Higher risk of bias	0				0.292
Were cases and population the same in terms of age?					
Lower risk of bias	5	0.06 (0.01 to 0.88)	1.00 (ref.)		
Higher risk of bias	1	0.13 (0.05 to 0.40)	0.46 (0.04 to 5.65)	0.440	0.328
Was case ascertainment blinded to vaccination status?					
Lower risk of bias	1		1.00		
Higher risk of bias	5		0.30 (0.07 to 1.21)	0.075	0.063
Was disease status blinded to BCG assessors?					
Lower risk of bias	0				
Higher risk of bias	6				0.292
Were methods of case ascertainment same for vaccinated and unvaccinated?					
Lower risk of bias	1	0.19 (0.01 to 7.39)	1.00 (ref.)		
Higher risk of bias	6	0.12 (0.04 to 0.33)	1.65 (0.06 to 45.73)	0.697	0.323

ref., reference category; τ^2, estimated between-study variance.

Extrapulmonary tuberculosis

Unstratified analysis ordered by year study started

The results presented in forest plots in *Figures 68–71* show estimated effects of BCG vaccination against non-meningeal and non-miliary forms of extrapulmonary tuberculosis from observational studies. Case–control studies showed relatively high protection of BCG vaccination against extrapulmonary tuberculosis, ranging from substantial protection [OR 0.12 (95% CI 0.06 to 0.26)] in Argentina[72] to a lower effect [OR 0.63 (95% CI 0.30 to 1.32)] in Bangalore Children.[56] There was more substantial variation in estimates of BCG vaccination effectiveness

TABLE 22 Ratios of risk ratios (with 95% CI) comparing the prevalence of tuberculosis meningitis and/or miliary tuberculosis among vaccinated individuals compared with unvaccinated individuals in cross-sectional studies, according to univariable meta-regression analysis

Variable	Number of studies	Univariable RRs (95% CI)	RRRs (95% CI)	*p*-value	τ^2
Null model	6				1.433
Latitude					
>40°	2	0.47 (0.01 to 55.16)	1.00 (ref.)		
20–40°	2	0.16 (0.00 to 42.04)	0.34 (0.01 to 76.59)		
0–20°	2	0.13 (0.00 to 39.65)	0.27 (0.01 to 67.74)	0.734	2.140
Age at vaccination					
Neonatal	3	0.16 (0.01 to 8.90)	1.00 (ref.)		
School age	2	0.47 (0.01 to 38.89)	2.90 (0.04 to 238.16)		
Other	1	0.07 (0.00 to 3516)	0.41 (0.01 to 2160)	0.683	1.793
Was disease status blinded to BCG assessors?					
Lower risk of bias	1	0.11 (0.00 to 39.63)	1.00 (ref.)		
Higher risk of bias	5	0.27 (0.03 to 2.38)	2.55 (0.01 to 631.35)	0.662	1.641
Were vaccination definitions the same for cases and control subjects?					
Lower risk of bias	4	0.16 (0.06 to 0.43)	1.00 (ref.)		
Higher risk of bias	2	1.82 (0.28 to 11.76)	11.33(1.79 to 71.53)	0.022	0.061
Were cases and control subjects determined independently of BCG vaccination status?					
Lower risk of bias	4	0.28 (0.02 to 4.28)	1.00 (ref.)		
Higher risk of bias	2	0.19 (0.01 to 5.74)	0.66 (0.01 to 30.55)	0.783	1.839
Were results adjusted for SES?					
Yes	0				
No	6				1.433
Study type					
Non Contact	5	0.11 (0.00 to 39.63)	1.00 (ref.)		
Contact	1	0.27 (0.03 to 2.38)	2.55(0.01 to 631.35)	0.662	1.641

ref., reference category; τ^2, estimated between-study variance.

in cohort studies (see *Figure 68*), ranging from high levels of protection [rate ratio 0.14 (95% CI 0.10 to 0.19)] in Dusseldorf children,[149] to no evidence of clinical benefit in the Lyon students study[108] [rate ratio 1.71 (95% CI 0.31 to 9.36)]. High levels of protection against extrapulmonary tuberculosis were seen in all case population (see *Figure 70*) and cross-sectional studies (see *Figure 71*).

Case–control studies

See *Figure 68*.

Cohort studies

See *Figure 69*.

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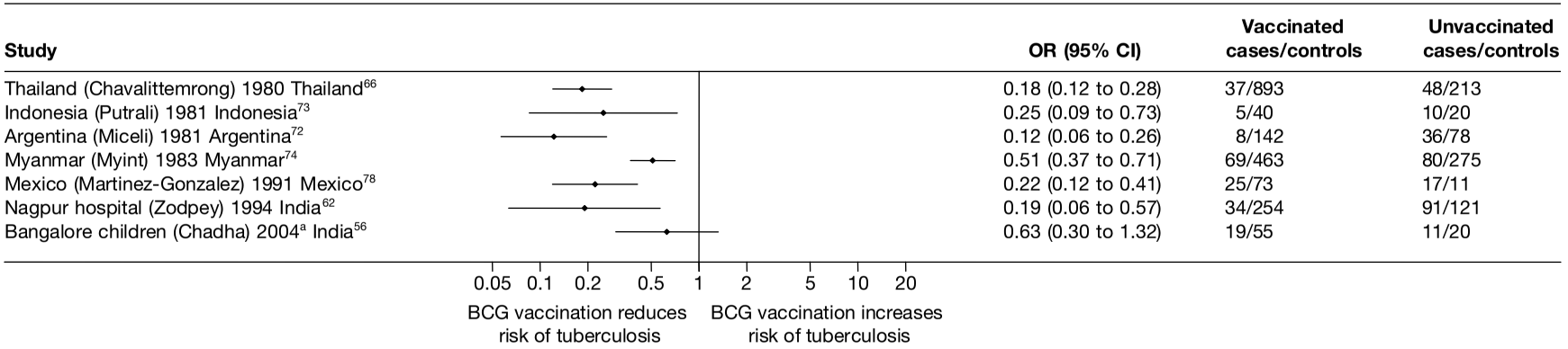

FIGURE 68 Odds ratios (with 95% CI) comparing the BCG vaccination status of extrapulmonary tuberculosis cases and control subjects in case–control studies, ordered by year of study start. a, Date of study publication was used if study start date was not available.

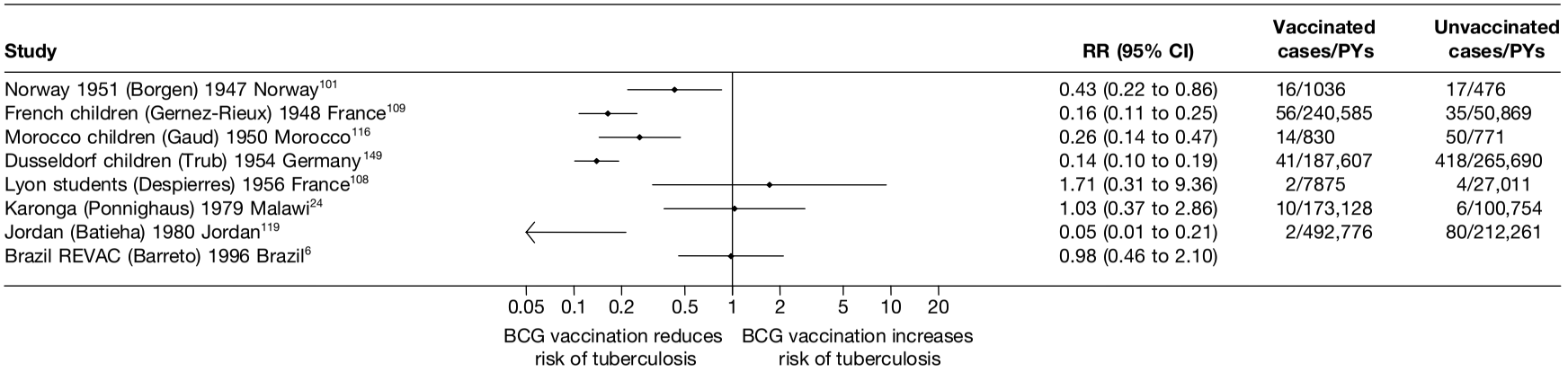

FIGURE 69 Rate ratios (with 95% CI) comparing the incidence of extrapulmonary tuberculosis among BCG vaccinated individuals with that in unvaccinated individuals for the longest duration of follow-up (see *Table 4*) in cohort studies, ordered by year of study start.

Case population studies
See *Figure 70*.

Cross-sectional studies
See *Figure 71*.

Stratified analysis by latitude (10°), ordered by year study started
Forest plots showing stratifications of observational studies assessing the protective effect of BCG vaccination on extrapulmonary tuberculosis according to latitude are provided in *Figures 72* and *73*. Only a few studies fell into each latitude category and the findings should therefore be treated with caution. The overall protective effect of BCG vaccination in case–control studies was lower in the four studies conducted close to the equator, whereas there was reasonably consistent evidence of higher protection observed in three studies conducted at latitudes above 20°. There is also evidence from cohort studies of relatively higher protection observed in studies conducted above 50° with substantial variation between cohort studies conducted at high latitudes. Estimated effects from the one case population study (above 50° latitude) showed a higher protection effect compared with one located between 30° and 40° while there was little variation in the effect of BCG vaccination effectiveness according to latitude in the two cross-sectional studies, one at 30–40° latitude and the other above 50° latitude.

Meta-regression analysis
Only case–control and cohort studies had a sufficient number of studies of the protection by BCG vaccination against extrapulmonary tuberculosis to perform meta-regression analyses. Based on these results, latitude was found to explain respectively 26% and 42% of the between-study variation (τ^2 value before and after stratification = 0.262 and 0.193, respectively for case–control studies and τ^2 values before and after stratification = 0.895 and 0.520, respectively, for cohort studies, *Tables 23* and *24*). However, there was insufficient evidence, from either study design, that BCG vaccination effectiveness was higher at higher latitudes (estimates of protective effect from case–control studies conducted between 0° and 20° latitude were 2.04 (95% CI 0.66 to 6.31; *p*-value = 0.168) times that of studies conducted at higher latitudes (20–40°). Similarly, rate ratios from cohort studies of 0–20° latitudes were 3.65 (95% CI 0.48 to 28.03; *p*-value = 0.2) times the rate ratio for studies of latitudes > 40°.

Case–control studies
See *Figure 72*.

Cohort studies
See *Figure 73*.

Stratified analysis by age at vaccination, ordered by year study started
There were insufficient data from observational studies to investigate the difference in effectiveness of BCG vaccination protection against extrapulmonary tuberculosis according to age at vaccination. All case–control subjects and case population studies assessed neonatal BCG vaccination, and only one cross-sectional study provided data on school-age vaccination (Liege children[182]) and on vaccination in an 'other' age group (Tohoku Outpatients study[181]), respectively. *Figure 74* shows the estimated effects of BCG vaccination on extrapulmonary tuberculosis from cohorts stratified by age at vaccination. There was substantial variation in estimates of effect for neonatal and school-age vaccination. Stratification did not appear to explain the between-study variation.

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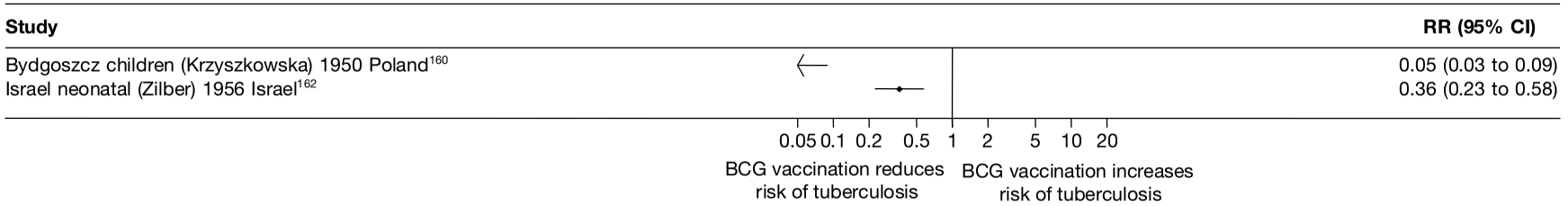

FIGURE 70 Rate ratios (with 95% CI) comparing the incidence of extrapulmonary tuberculosis among BCG vaccinated individuals with that in unvaccinated individuals for the longest duration of follow-up (see *Table 5*) in case population studies, ordered by year of study start.

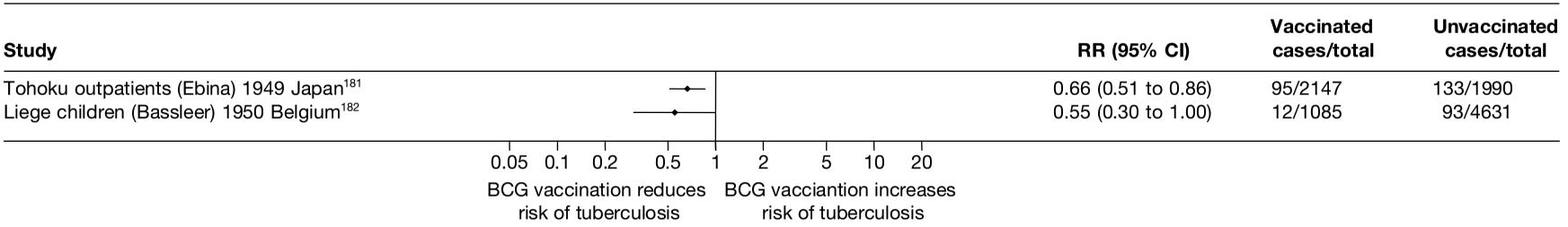

FIGURE 71 Risk ratios (with 95% CI) comparing the prevalence of extrapulmonary tuberculosis among BCG vaccinated individuals with that in unvaccinated individuals in cross-sectional studies, ordered by year of study start.

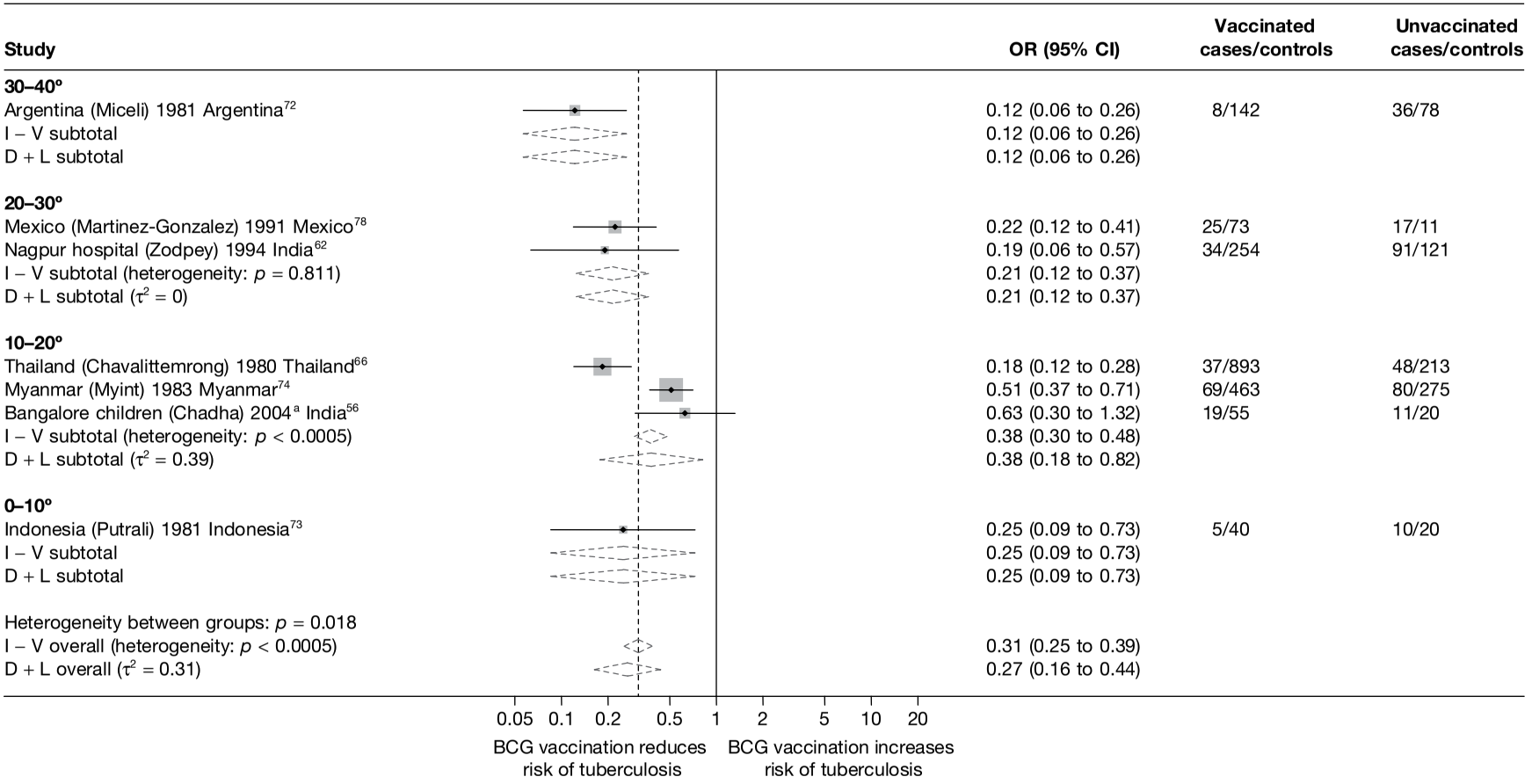

FIGURE 72 Odds ratios (with 95% CI) comparing the BCG vaccination status of extrapulmonary tuberculosis cases and control subjects in case–control studies, stratified by latitude of study location (10° bands), ordered by year of study start. a, Date of study publication was used if study start date was not available. D+L, DerSimonian and Laird method; I–V, inverse variance method.

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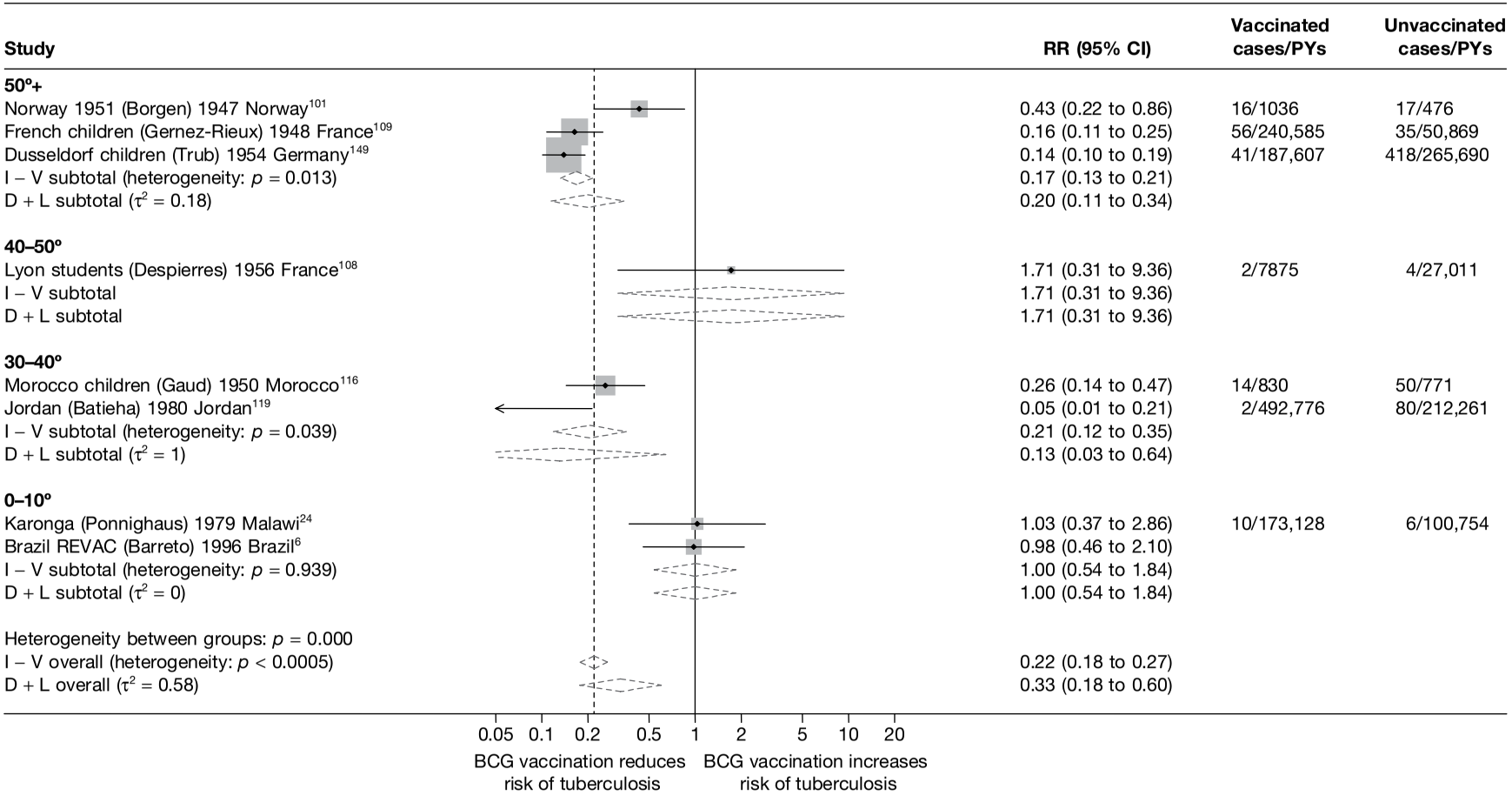

FIGURE 73 Rate ratios (with 95% CI) comparing the incidence of extrapulmonary tuberculosis among BCG vaccinated individuals with that in unvaccinated individuals for the longest duration of follow-up (see *Table 4*) in cohort studies, stratified by latitude of study location (10° bands), ordered by year of study start. D+L, DerSimonian and Laird method; I–V, inverse variance method.

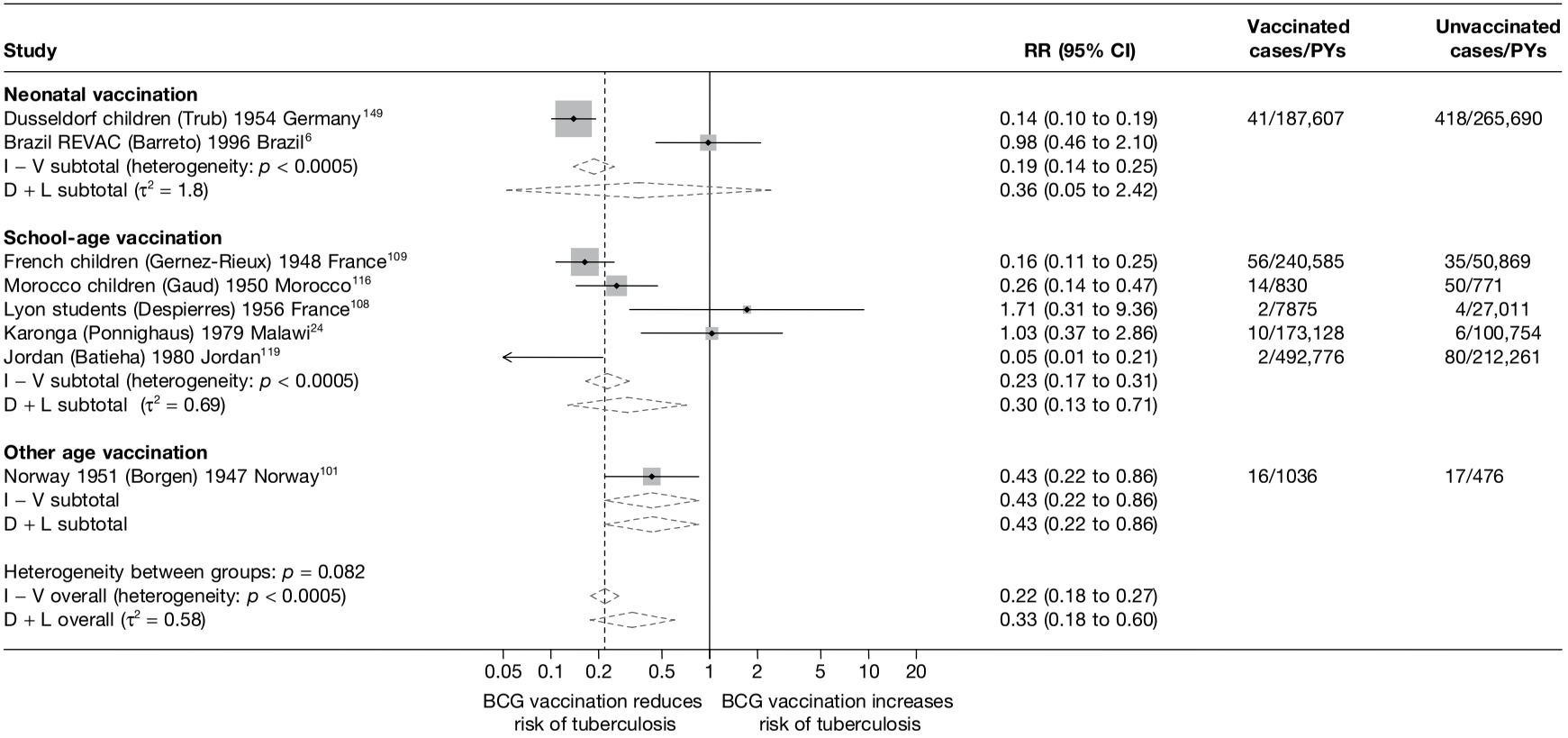

FIGURE 74 Rate ratios (with 95% CI) comparing the incidence of extrapulmonary tuberculosis among BCG vaccinated individuals with that in unvaccinated individuals for the longest duration of follow-up (see *Table 4*) in cohort studies, stratified by age at vaccination, ordered by year of study start. D+L, DerSimonian and Laird method; I–V, inverse variance method.

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DOI: 10.3310/hta17370

Meta-regression analysis

Based on meta-regression analyses, stratification by age at vaccination does not account for any of the heterogeneity in cohort studies (τ^2 before and after stratification, respectively = 0.895 and 1.455). There was therefore no evidence that the effect of BCG vaccination varied according to age at vaccination (p-value = 0.973) (see *Table 24*).

Cohort studies

Stratified analysis by study design, ordered by year study started

Cohort studies

Figure 75 presents estimated effect of BCG vaccination against extrapulmonary tuberculosis excluding meningeal and miliary tuberculosis, stratified by study design. The highest protective effect of BCG vaccination was seen in the pooled estimate for retrospective study design. Study design appears to explain a small amount of the between-study variation, with a substantial amount of variation remaining after stratification.

Meta-regression analysis

Stratification on study design accounted for 9% of the heterogeneity: τ^2 values = 0.895 and 0.817 before and after stratification, respectively. There was no evidence (p-value = 0.320) that the protective effect of BCG vaccination varied according to cohort study design, as shown in *Table 24*.

Meta-regression analysis

Case–control studies

Results from univariable meta-regressions for all study variables for case–control studies indicate that latitude explained some of between-study variation in overall BCG vaccination effectiveness with a τ^2 value of 0.193, compared with the baseline τ^2 (0.262). Nevertheless, there was little evidence (p-value = 0.168) of association between latitude and a degree of protection from BCG.

Cohort studies

For cohort studies, results from univariable meta-regressions indicate that latitude and 'Were results adjusted for socio-economic status?' explained some of between-study variation in overall BCG vaccination effectiveness with a τ^2 value of 0.520 and 0.291, respectively, compared with the baseline τ^2 value (0.895) but little evidence that any factors were associated with the size of the protective effect.

Tuberculosis mortality

Unstratified analysis by year study started

Figures 76 and *77* show the results of cohort and cross-sectional studies, respectively, which presented data on the effect of BCG vaccination on mortality. No case–control or case population studies provided data on tuberculosis mortality.

Despite the small number of events in each cohort study, all estimates were consistent with a good to high protective effect of BCG vaccination against tuberculosis mortality. Both cross-sectional studies provided strong evidence of high BCG vaccination effectiveness.

Cohort studies

See *Figure 76*.

Cross-sectional studies

See *Figure 77*.

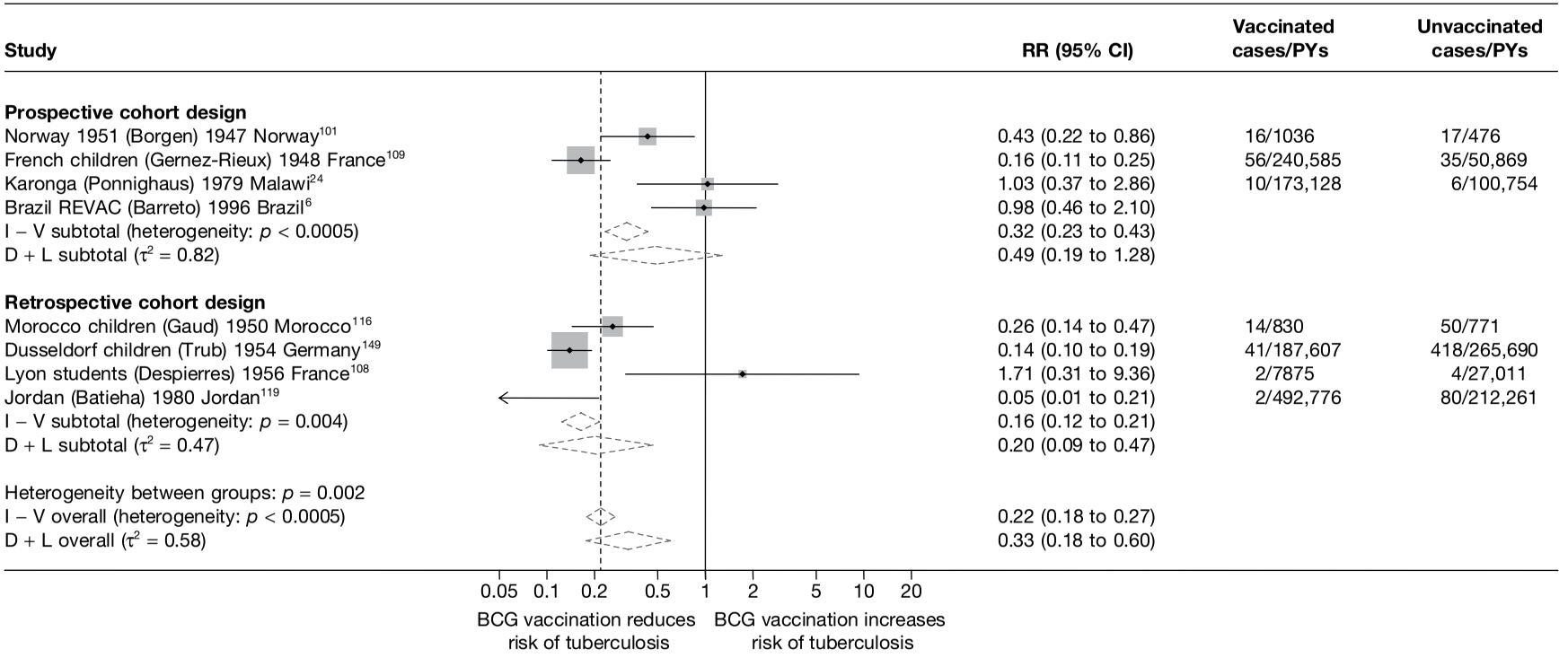

FIGURE 75 Rate ratios (with 95% CI) comparing the incidence of extrapulmonary tuberculosis among BCG vaccinated individuals with that in unvaccinated individuals for the longest duration of follow-up (see *Table 4*) in cohort studies, stratified by cohort study design, ordered by year of study start. D+L, DerSimonian and Laird method; I–V, inverse variance method.

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DOI: 10.3310/hta17370

TABLE 23 Ratios of odds ratios (with 95% CI) comparing the BCG vaccination status of extrapulmonary tuberculosis cases and control subjects in case–control studies, according to univariable and meta-regression analysis

Variable	Number of studies	Univariable ORs (95% CI)	Univariable model		
			Ratio of ORs (95% CI)	*p*-value	τ^2
Null model	7				0.262
Latitude					
40°+	0				
20–40°	3	0.17 (0.07 to 0.46)	1.00 (ref.)		
0–20°	4	0.35 (0.17 to 0.75)	2.04 (0.66 to 6.31)	0.168	0.193
Age at vaccination					
Neonatal	7				
School age	0				
Other	0				0.262
Was disease status blinded to BCG assessors?					
Lower risk of bias	0				
Higher risk of bias	7				0.262
Were vaccination definitions the same for cases and control subjects?					
Lower risk of bias	6	0.28 (0.13 to 0.57)	1.00 (ref.)		
Higher risk of bias	1	0.19 (0.02 to 1.66)	0.69 (0.08 to 5.70)	0.666	0.297
Were cases and control subjects determined independently of BCG vaccination status?					
Lower risk of bias	4	0.24 (0.10 to 0.63)	1.00 (ref.)		
Higher risk of bias	3	0.30 (0.10 to 0.91)	1.22 (0.32 to 4.70)	0.718	0.335
Were results adjusted for SES?					
Yes	5	0.30 (0.13 to 0.65)	1.00 (ref.)		
No	2	0.21 (0.06 to 0.73)	0.69 (0.17 to 2.78)	0.528	0.280
If a matched design was used, was a matched analysis performed?					
Unmatched design	1	0.18 (0.03 to 1.31)	1.00 (ref.)		
Matched design – matched analysis	1	0.19 (0.14 to 2.45)	1.04 (0.06 to 17.19)		
Matched design – matched analysis	5	0.31 (0.12 to 0.80)	1.66 (0.25 to 11.19)	0.711	0.332

ref., reference category; τ^2, estimated between-study variance.
a The τ^2 for this null model is 0.291.

Stratified analysis by latitude (10°), ordered by year study started

Figure 78 shows the estimates of effect of BCG vaccination against tuberculosis mortality from all nine cohort studies stratified by 10° bands of latitude. None were conducted close to the equator. The highest pooled estimate of protection was seen in cohort studies conducted between 30° and 40° latitude [rate ratio 0.11 (95% CI 0.05 to 0.24; VE 88%)], while there was reasonably consistent evidence of lower, albeit still good protection from cohort studies at latitudes further from the equator: rate ratio 0.29 (95% CI 0.11 to 0.77; VE 71%) for studies conducted between 40° and 50° latitude, and rate ratio 0.28 (95% CI 0.17 to 0.46; VE 72%) for studies conducted above 50° latitude.

TABLE 24 Ratios of rate ratios (with 95% CI) comparing the incidence of extrapulmonary tuberculosis among vaccinated individuals compared with unvaccinated individuals for the longest duration of follow-up (see *Table 4*) in cohort studies, according to univariable meta-regression analysis

Variable	Number of studies	Univariable rate ratios (95% CI)	Univariable model		
			Ratio of rate ratios (95% CI)	*p*-value	τ^2
Null model	8				0. 895
Latitude					
>40°	2	0.27 (0.08 to 0.94)	1.00 (ref.)		
20–40°	2	0.14 (0.02 to 0.93)	0.52 (0.06 to 4.18)		
0–20°	4	1.00 (0.16 to 6.18)	3.65 (0.48 to 28.03)	0.200	0.520
Age at vaccination					
Neonatal	2	0.35 (0.03 to 4.41)	1.00 (ref.)		
School age	5	0.31 (0.06 to 1.71)	0.88 (0.05 to 14.73)		
Other	1	0.43 (0.01 to 15.94)	1.22 (0.02 to 71.74)	0.973	1.455
Was follow-up independent of vaccination status?					
Lower risk of bias	3	0.30 (0.08 to 1.16)	1.00 (ref.)		
Higher risk of bias	5	0.41 (0.07 to 2.51)	1.40 (0.16 to 12.07)	0.716	1.126
Was case ascertainment blinded to vaccination status?					
Lower risk of bias	0				
Higher risk of bias	8				0.895
Were methods of case ascertainment identical for vaccinated and unvaccinated group?					
Lower risk of bias	8				
Higher risk of bias	0				0.895
Were losses to follow-up similar in each group?					
Lower risk of bias	2	0.21 (0.03 to 1.47)	1.00 (ref.)		
Higher risk of bias	6	0.40 (0.12 to 1.39)	1.96 (0.21 to 17.99)	0.484	0.990
Was diagnostic detection bias present?					
Lower risk of bias	3	0.44 (0.12 to 1.59)	1.00 (ref.)		
Higher risk of bias	5	0.20 (0.04 to 1.10)	0.46 (0.06 to 3.47)	0.383	0.967
Were results adjusted for SES?					
Yes	2	1.00 (0.21 to 4.71)	1.00 (ref.)		
No	6	0.22 (0.09 to 0.51)	0.22 (0.04 to 1.18)	0.069	0.291
Study type					
Prospective	4	0.49 (0.13 to 1.90)	1.00 (ref.)		
Retrospective	4	0.21 (0.05 to 0.90)	0.43 (0.07 to 2.87)		
Contact	0			0.320	0.817

ref., reference category; τ^2, estimated between-study variance.

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Study	RR (95% CI)	Vaccinated cases/PYs	Unvaccinated cases/PYs
New York infants (Kereszturi) 1927 USA[91]	0.05 (0.00 to 2.21)	0/157	14/422
Oslo nurses (Heimbeck) 1927 Norway[123]	0.14 (0.04 to 0.52)	3/1450	10/687
Bornholm (Olsen) 1936 Denmark[122]	0.23 (0.03 to 1.76)	1/19,376	10/43,634
Ancona children (Mariotti) 1938 Italy[111]	0.33 (0.12 to 0.91)	5/2467	16/2622
Swedish conscripts (Dahlstrom) 1941 Sweden[113]	0.33 (0.19 to 0.58)	2/36,235	9/25,239
Uruguay infants (Gomez) 1943 Uruguay[114]	0.11 (0.05 to 0.25)	6/3183	43/2449
Virginia infants (Kendig) 1948 USA[94]	0.20 (0.00 to 10.86)	0/30	3/87
French children (Gernez-Rieux) 1948 France[109]	0.15 (0.01 to 2.48)	0/240,585	1/50,869
Morocco children (Gaud) 1950 Morocco[116]	0.10 (0.01 to 0.81)	1/830	9/771

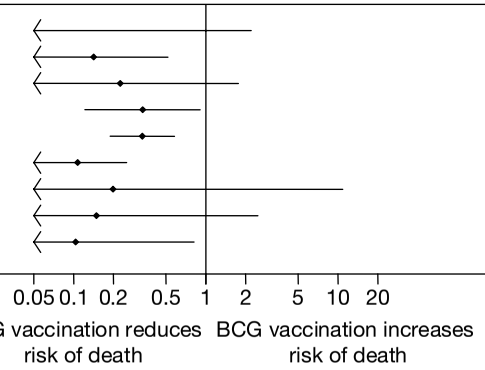

FIGURE 76 Rate ratios (with 95% CI) comparing the incidence of tuberculosis mortality among BCG vaccinated individuals with that in unvaccinated individuals for the longest duration of follow-up (see *Table 4*) in cohort studies, ordered by year of study start.

Study	RR (95% CI)	Vaccinated cases/total	Unvaccinated cases/total
Madras (Chandra) 1968 India[186]	0.17 (0.04 to 0.74)	2/232	18/362
Togo children (Tidjani) 1988 Togo[177]	0.22 (0.01 to 3.98)	0/504	1/201

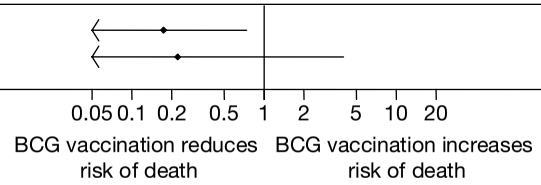

FIGURE 77 Risk ratios (with 95% CI) comparing the prevalence of tuberculosis mortality among BCG vaccinated individuals with that in unvaccinated individuals in cross-sectional studies, ordered by year of study start.

Meta-regression analysis

Stratifying cohort studies by latitude (20° bands) accounted for a very substantial amount of the heterogeneity between-studies (τ^2 values before and after stratification 0.128 and 0.000, respectively) (*Table 25*). There was some evidence (p-value = 0.075) that effectiveness of BCG vaccination against tuberculosis mortality varies with latitude.

Cohort studies

See *Figure 78*.

Stratified analysis by age at vaccination, ordered by year study started

Figure 79 presents the estimated effects of BCG vaccination, stratified by age at vaccination, for cohort studies. Studies of the effect of BCG vaccination given at school and other ages showed slightly lower but still good overall protective effect of BCG vaccination against mortality, compared with neonatal vaccination studies which showed high levels of protection. Age at vaccination appears to explain a substantial amount of between-study variation. Both cross-sectional studies conducted vaccination in neonates.

Meta-regression analysis

Among cohort studies, stratification on age at vaccination explained 98% the heterogeneity seen within studies (null model $\tau^2 = 0.128$, τ^2 value after stratification = 0.003) (see *Table 25*). However, there was no evidence that BCG vaccination effectiveness varied with age at vaccination (p-value = 0.248).

Cohort studies

Stratified analysis by study design, ordered by year study started

Figure 80 presents the estimated effects of BCG vaccination against tuberculosis mortality, stratified by study design. In general, there was no difference in the effectiveness of BCG vaccination between prospective and retrospective cohort studies. Study design did not explain the between-study heterogeneity of cohorts' estimates of BCG vaccination effectiveness against tuberculosis mortality.

Meta-regression analysis

Stratification by cohort study design did not explain any of the between-study heterogeneity (null model $\tau^2 = 0.128$, τ^2 value after stratification = 0.135) (see *Table 25*).

Cohort studies

See *Figure 80*.

Meta-regression analysis

Cohort studies

The results of univariable meta-regressions for all cohort study variables indicate that latitude, age at vaccination and 'Was follow-up independent of vaccination status?' each explained the largest amount of between-study variation in overall BCG vaccination effectiveness with τ^2 values of 0.000, 0.003 and 0.000, respectively, compared with the baseline τ^2 value (0.128). Only latitude showed some weak evidence (p-value = 0.075) that BCG vaccination effectiveness changed with latitude.

Results by gender for all outcomes

Four trials[5,15,28,53] provided data on protective effect of BCG vaccination and gender of participants. Three out of four studies had an estimated ratio of rate ratios indicating that BCG vaccination is more protective in females than in males. Estimates of BCG vaccination

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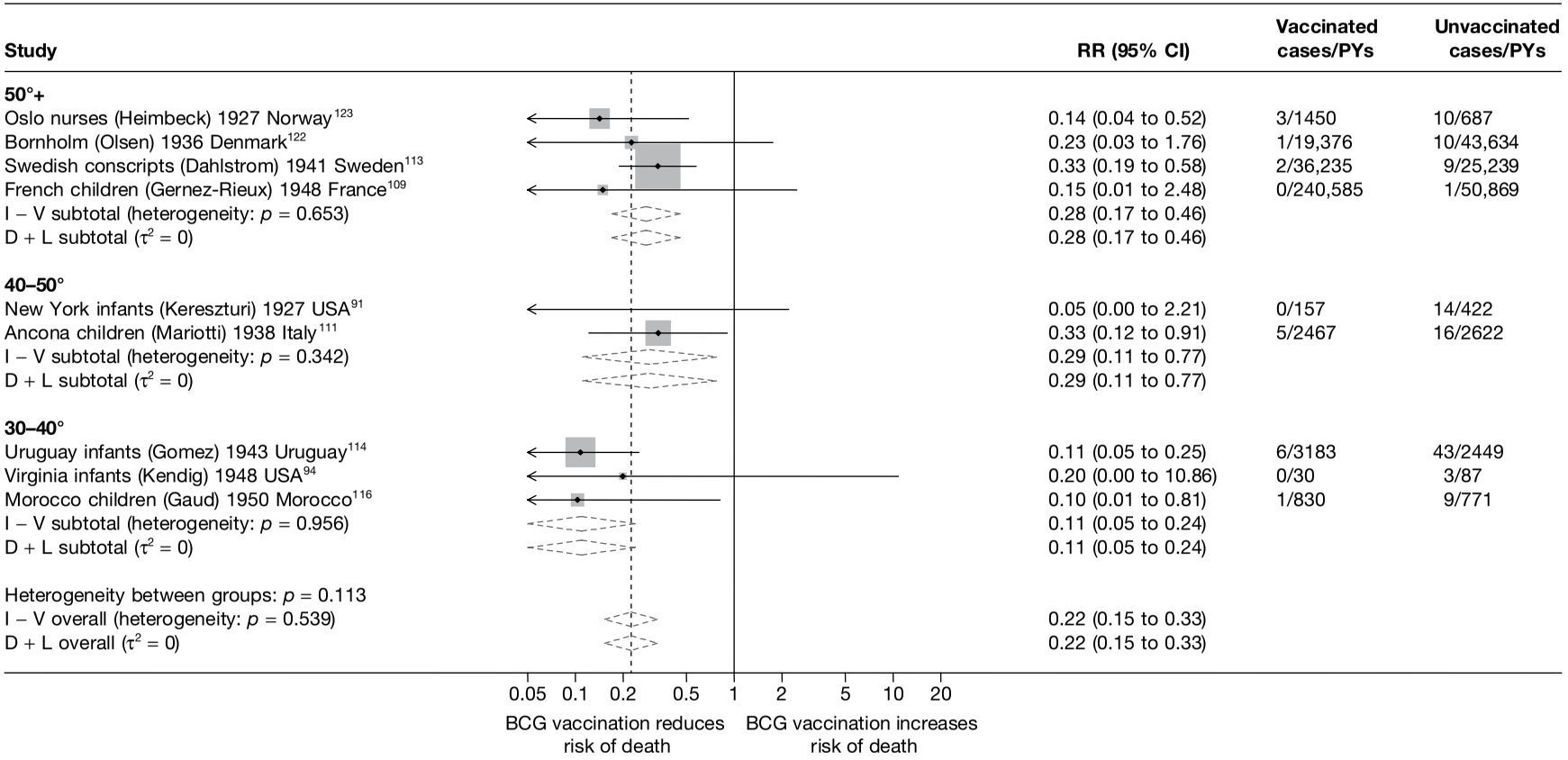

FIGURE 78 Rate ratios (with 95% CI) comparing the incidence of tuberculosis mortality among BCG vaccinated individuals with that in unvaccinated individuals for the longest duration of follow-up (see *Table 6*) in cohort studies, stratified by latitude of study location (10° bands), ordered by year of study start. D+L, DerSimonian and Laird method; I–V, inverse variance method.

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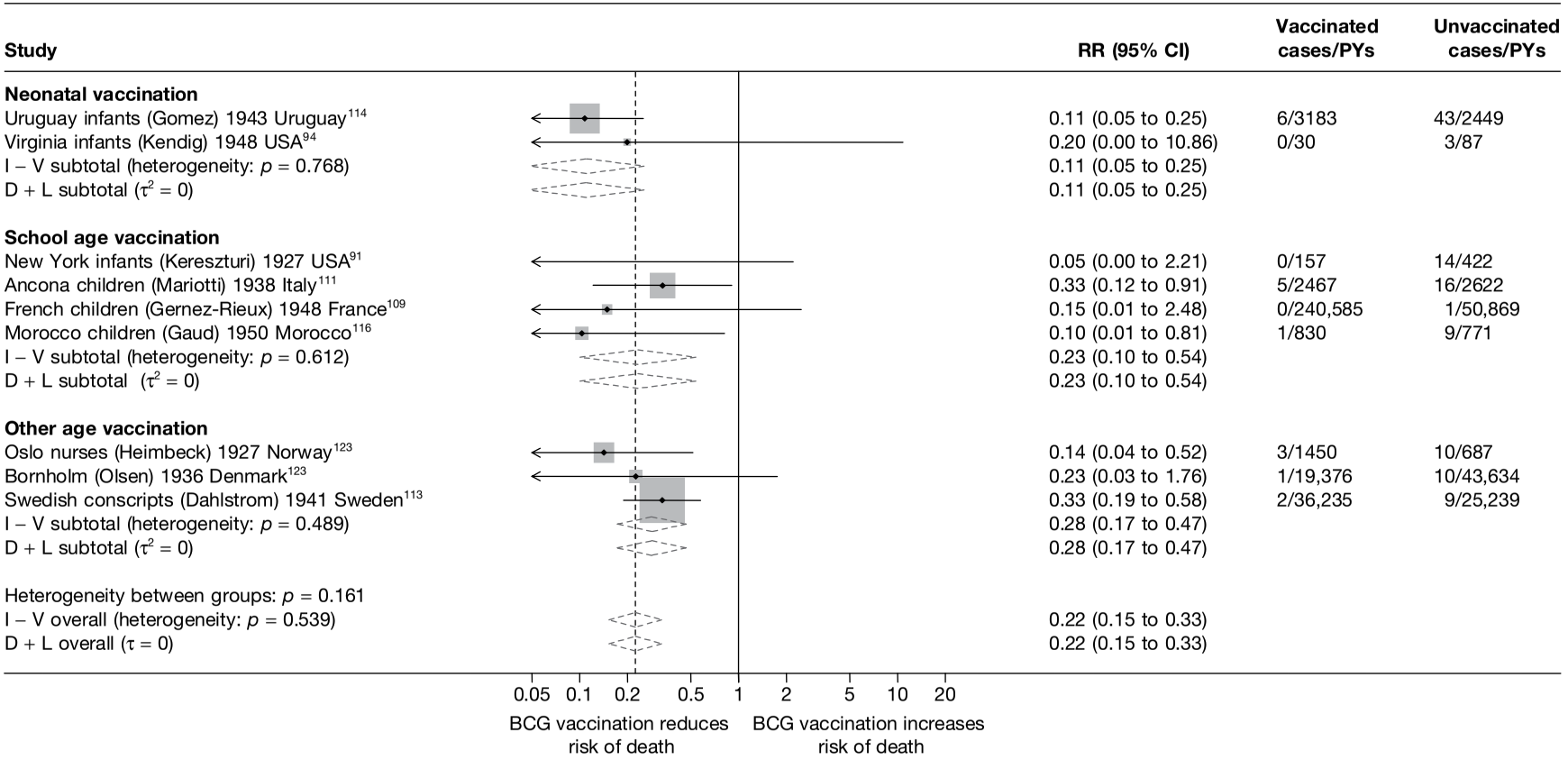

FIGURE 79 Rate ratios (with 95% CI) comparing the incidence of tuberculosis mortality among BCG vaccinated individuals with that in unvaccinated individuals for the longest duration of follow-up (see *Table 4*) in cohort studies, stratified by age at vaccination, ordered by year of study start. D+L, DerSimonian and Laird method; I–V, inverse variance method.

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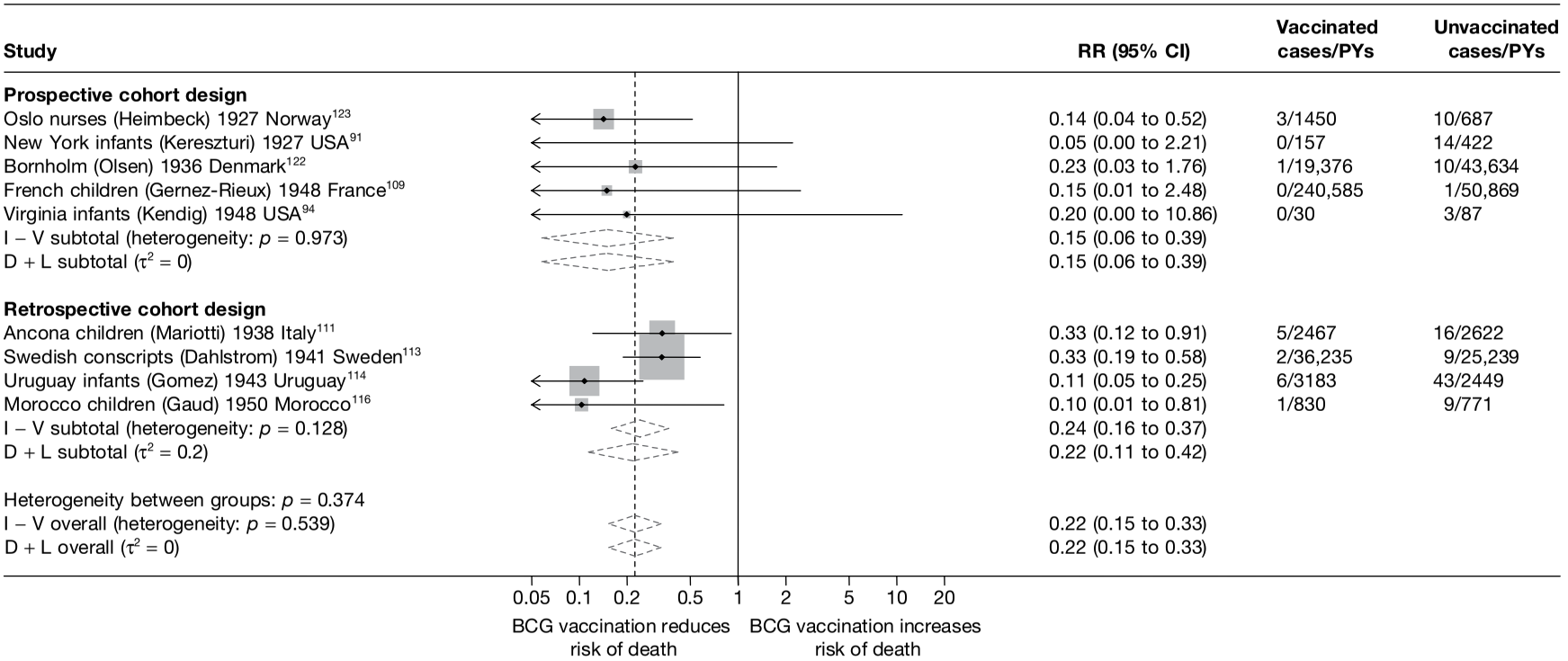

FIGURE 80 Rate ratios (with 95% CI) comparing the incidence of tuberculosis mortality among BCG vaccinated individuals with that in unvaccinated individuals for the longest duration of follow-up (see *Table 4*) in cohort studies, stratified by cohort study design, ordered by year of study start. D+L, DerSimonian and Laird method; I–V, inverse variance method.

TABLE 25 Ratios of rate ratios (with 95% CI) comparing the incidence of tuberculosis mortality among vaccinated individuals compared with unvaccinated individuals for the longest duration of follow-up (see *Table 4*) in cohort studies, according to univariable meta-regression analysis

Variable	Number of studies	Univariable rate ratios (95% CI)	Univariable model		
			Ratio of rate ratios (95% CI)	*p*-value	τ^2
Null model	9				0.128
Latitude					
40°+	6	0.28 (0.16 to 0.49)	1.00 (ref.)		
20–40°	3	0.11 (0.04 to 0.29)	0.39 (0.13 to 1.13)		
0–20°	0			0.075	0.000
Age at vaccination					
Neonatal	2	0.11 (0.04 to 0.33)	1.00 (ref.)		
School age	4	0.23 (0.08 to 0.70)	2.10 (0.47 to 9.30)		
Other	3	0.28 (0.15 to 0.55)	2.57 (0.75 to 8.76)	0.248	0.003
Was follow-up independent of vaccination status?					
Lower risk of bias	5	0.28 (0.16 to 0.48)	1.00 (ref.)		
Higher risk of bias	4	0.12 (0.05 to 0.31)	0.45 (0.16 to 1.28)	0.113	0.000
Was case ascertainment blinded to vaccination status?					
Lower risk of bias	0				
Higher risk of bias	9				0.128
Were methods of case ascertainment identical for vaccinated and unvaccinated group?					
Lower risk of bias	9				
Higher risk of bias	0				0.128
Were losses to follow-up similar in each group?					
Lower risk of bias	3	0.28 (0.12 to 0.66)	1.00 (ref.)		
Higher risk of bias	6	0.17 (0.08 to 0.36)	0.60 (0.20 to 1.81)	0.312	0.065
Was diagnostic detection bias present?					
Lower risk of bias	2	0.12 (0.01 to 1.04)	1.00 (ref.)		
Higher risk of bias	7	0.21 (0.11 to 0.41)	1.81 (0.20 to 16.32)	0.544	0.128
Were results adjusted for SES?					
Yes	0				
No	9				
Study type					
Prospective	5	0.15 (0.04 to 0.56)	1.00 (ref.)		
Retrospective	4	0.22 (0.11 to 0.46)	1.47 (0.35 to 6.28)		
Contact	0			0.547	0.135

ref., reference category; τ^2, estimated between-study variance.

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effectiveness were presented by gender for six case–control studies, one cohort, one case population and two cross-sectional studies in *Appendix 6*. There was no evidence of a difference in protective effect in females compared with males: for any tuberculosis outcome, eight estimates of effect were higher in females than in males, whereas seven showed higher effectiveness in males.

Results by human immunodeficiency virus status for all outcomes

No trials reported results by HIV status of participants.

Only one cross-sectional study (Cape Town Children[190]) commented that the prevalence of HIV+ children in the vaccinated compared with unvaccinated groups was not significantly different. No breakdown of effectiveness by HIV status of the study population was provided. It was not possible to calculate the proportion HIV infected, as not all participants received an HIV test, although it is likely that the BCG group were all HIV tested.

Duration of protection by bacillus Calmette–Guérin vaccination

Randomised controlled trials

Pulmonary tuberculosis

Ten trials provided sufficient data to investigate the duration of protection afforded by BCG vaccination against pulmonary tuberculosis (*Figure 81*). In the majority of studies there was evidence of protection during the first 5 years of follow-up, while one study (Chingleput[28]) found an adverse effect of vaccination during this period. In the majority of studies, the protection afforded by BCG vaccination appeared to decline after the first 5 years. The study with the longest follow-up period (Native American trial[5]) found evidence of protection up to 20 years. By contrast with the trend in the majority of trials, the negative effect of BCG vaccination in the early years of follow-up in the Chingleput study[28] was attenuated, with rate ratios close to 1, in subsequent years. Possible explanations for this result are explored further in the discussion (see *Chapter 5*).

We examined changes in efficacy over time in each study by estimating the ratio of rate ratios per 5 years of follow-up. Such estimates are based on the assumption that, within each study, there is a linear trend in the log-rate ratio over time, and correspond to the assumption of a straight-line relationship for each study in *Figure 81*. The forest plots in *Figures 82* and *83* display these estimated ratios of rate ratios, before and after excluding the first 5 years of follow-up (during which tuberculosis rates may be influenced by prior infection in studies that did not exclude tuberculin skin test positive individuals at enrolment). *Figure 82* shows that, on average, the protective effect of BCG vaccination declined over time (summary ratio of rate ratios = 1.14 per 5 years' follow-up; 95% CI 1.03 to 1.27), with little evidence of between-study heterogeneity ($\tau^2 = 0.00$). *Figure 83* shows that excluding data from the first 5 years of follow-up for each study resulted in a more pronounced decline in the protective effect of BCG vaccination (summary ratio of rate ratios 1.47; 95% CI 1.03 to 1.24), and this effect was also more consistent across studies. Again there was little evidence of between-study heterogeneity ($\tau^2 = 0$).

Temporal changes in efficacy

Figures 84 and *85* are scatterplots of the ratio of rate ratios per 5 years of follow-up compared with the overall rate ratio for each study, including and excluding the first 5 years' follow-up. There was little evidence of an association between change in efficacy over time and overall efficacy across studies.

Temporal changes in efficacy in relation to overall efficacy

See *Figures 84 and 85*.

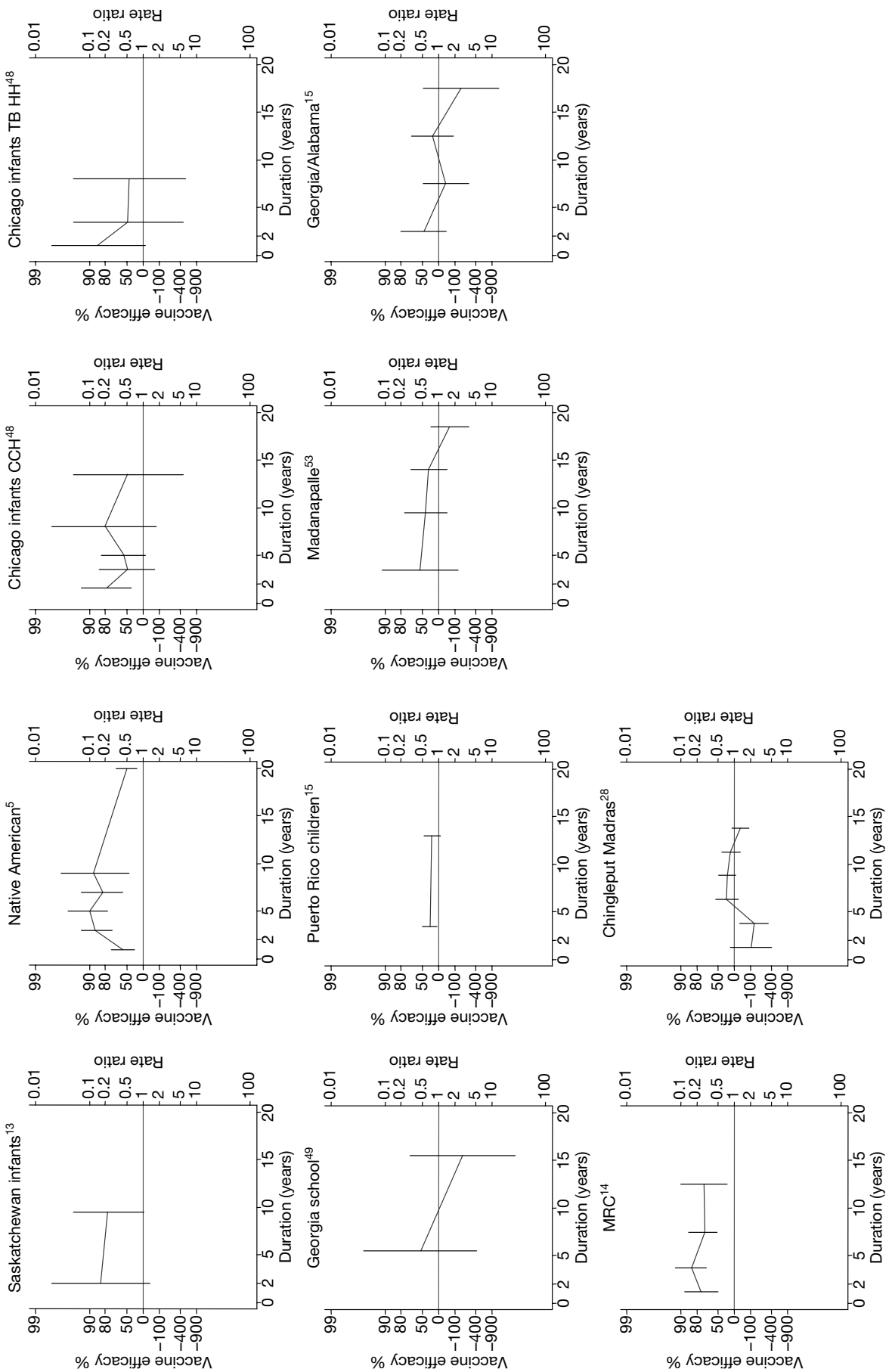

FIGURE 81 Vaccine efficacy and rate ratios (with 95% CI) comparing the incidence of pulmonary tuberculosis among BCG vaccinated individuals with that in unvaccinated individuals, in RCTs, over time. CCH, Cook County Hospital; TB HH, tuberculosis households.

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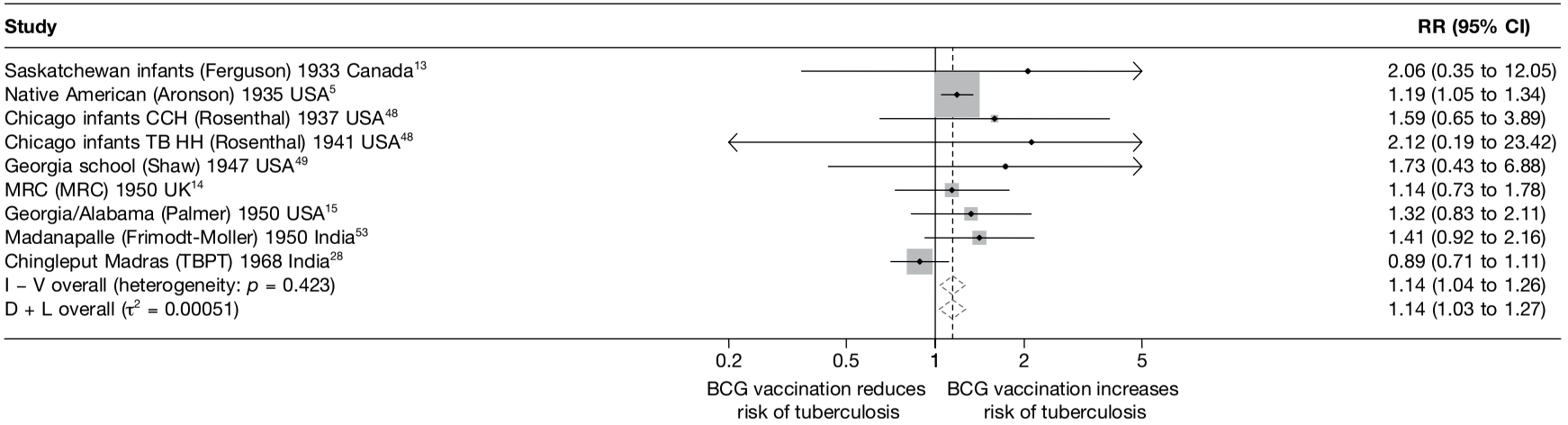

FIGURE 82 Change per 5 years (with 95% CI) in the rate ratio comparing the incidence of pulmonary tuberculosis among BCG vaccinated individuals with that in unvaccinated individuals in RCTs for the longest follow-up period (see *Table 3*), including the first 5 years of data for each study. CCH, Cook County Hospital; D+L, DerSimonian and Laird method; I–V, inverse variance method; TB HH, tuberculosis households; TBPT, Tuberculosis Prevention Trial.

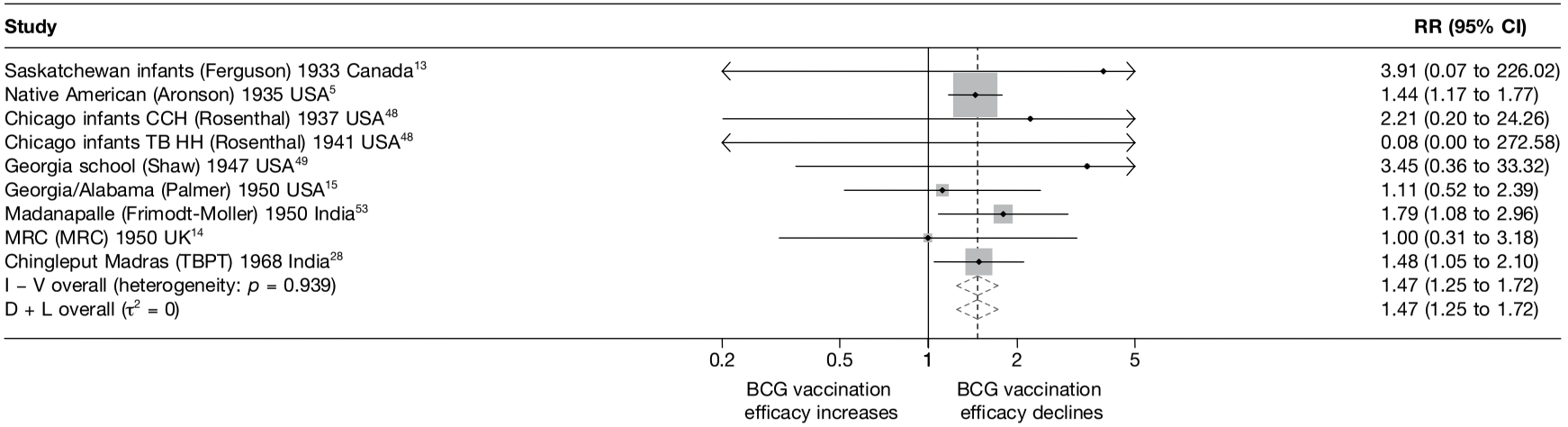

FIGURE 83 Change per 5 years (with 95% CI) in the rate ratio comparing the incidence of pulmonary tuberculosis among BCG vaccinated individuals with that in unvaccinated individuals in RCTs for the longest follow-up period (see *Table 3*), excluding the first 5 years of data for each study. CCH, Cook County Hospital; D+L, DerSimonian and Laird method; I–V, inverse variance method; TB HH, tuberculosis households; TBPT, Tuberculosis Prevention Trial.

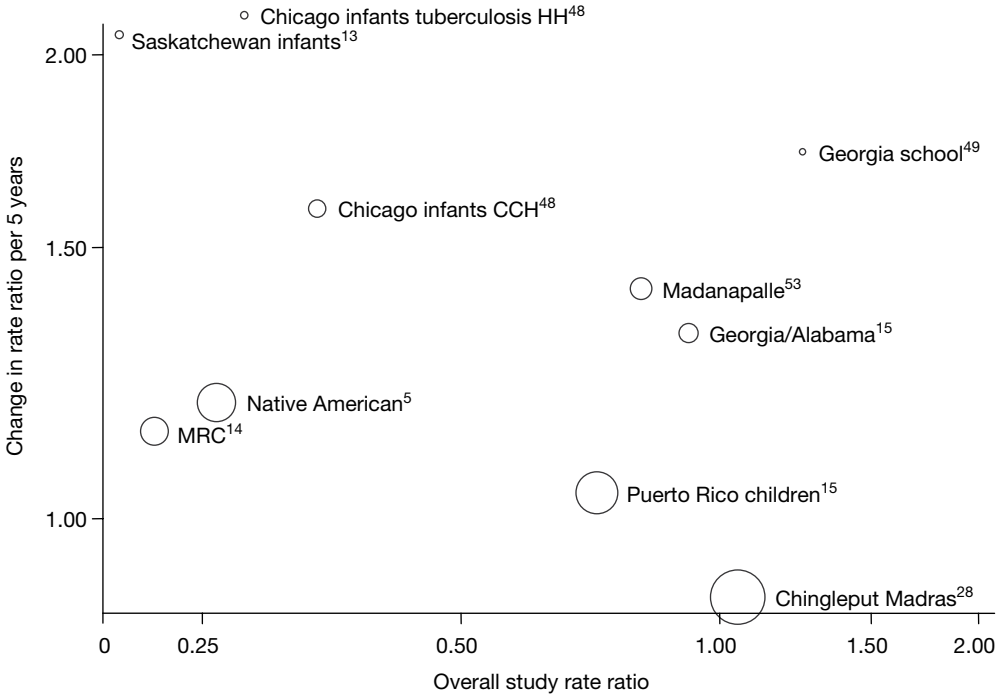

FIGURE 84 Scatterplot of change per 5 years in rate ratio compared with overall rate ratio, comparing incidence of pulmonary tuberculosis among BCG vaccinated individuals with that in unvaccinated individuals, in RCTs, including the first 5 years of data for each study. The area of the circles is proportional to the inverse of the variance of the log-rate ratio comparing vaccinated with unvaccinated individuals. CCH, Cook County Hospital; TB HH, tuberculosis households.

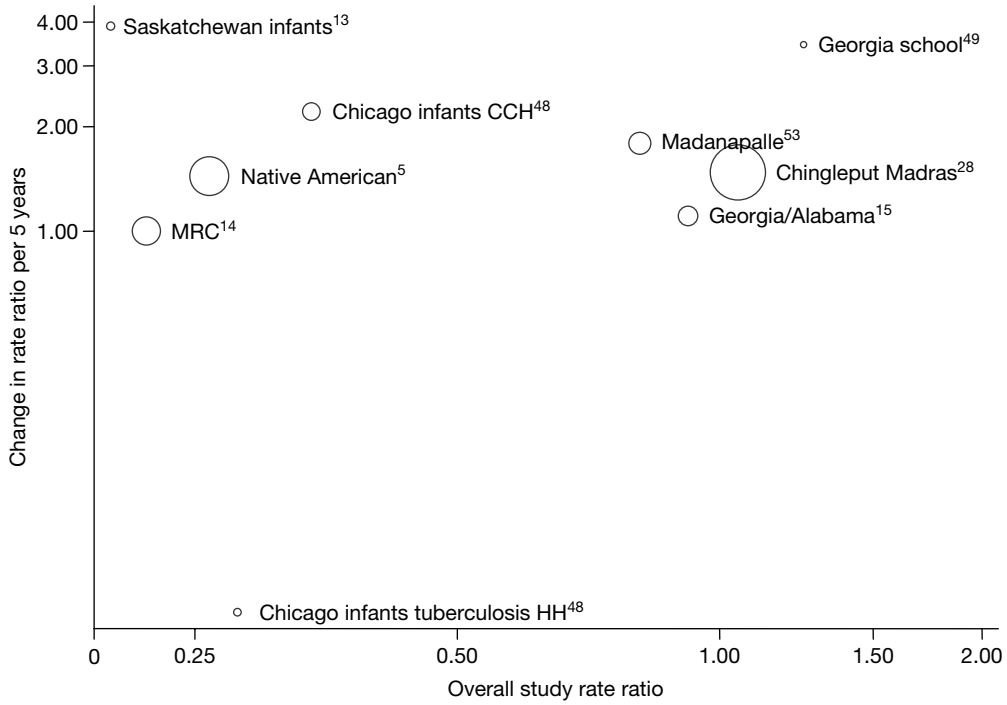

FIGURE 85 Scatterplot of change per 5 years in rate ratio compared with overall rate ratio, comparing incidence of pulmonary tuberculosis among BCG vaccinated individuals with that in unvaccinated individuals, in RCTs, excluding the first 5 years of data for each study. The area of the circles is proportional to the inverse of the variance of the log-rate ratio comparing vaccinated with unvaccinated individuals. CCH, Cook County Hospital; TB HH, tuberculosis households.

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Study efficacy by follow-up period

Figures 86–89 are forest plots of the effect of BCG vaccination in each trial, within the successive follow-up periods 0–5 years, 5–10 years, 10–15 years and > 15 years after vaccination. During the first 5 years after vaccination (see *Figure 86*), there was substantial between-study heterogeneity in the effect of BCG vaccination ($\tau^2 = 0.49$). Although there was evidence of protection in most studies (ranging from low VE of 31% in the Puerto Rico trial[15] to high efficacy of 89% in the Haiti trial[55]), the Chingleput trial[28] found evidence of increased rates of pulmonary tuberculosis in vaccinated individuals (rate ratio 2.07, 95% CI 1.10 to 3.88) (see *Chapter 5*, *Discussion*, for explanations).

Among the seven trials that reported relevant outcome data for the period 5–10 years after vaccination, there was substantial between-study heterogeneity ($\tau^2 = 0.57$) (see *Figure 87*). Although there was little evidence of protection in the Chicago infants,[48] Georgia/Alabama[15] and Chingleput trials,[28] estimated vaccine efficacy was 72% in the MRC trial[14] and 86% in the Native American trial.[5]

Figure 88 displays results from the seven trials that reported relevant data for the period 10–15 years after vaccination. The number of events in the intervention and control arms of most studies was small. There was clear between-study heterogeneity, but this was less marked than for earlier time periods ($\tau^2 = 0.19$).

Relatively few events were reported for the period after 15 years of study follow-up (see *Figure 89*). Although there was some evidence of between-study heterogeneity, this was less than for earlier time periods ($\tau^2 = 0.13$). Only the Native American trial[5] found evidence of protection.

Measure of waning efficacy

Table 26 shows rate ratios for the effect of BCG vaccination during the first 10 years and after 10 years, together with the ratio of these rate ratios (i.e. the change in effect of BCG vaccination after compared with before 10 years described here as a 'measure of waning efficacy'), for the seven trials that reported sufficient data. In general, most cases of tuberculosis were found during the first 10 years' follow-up and so the estimated rate ratios are similar to the overall rate ratios displayed in *Figure 3*. For each of the seven trials, the effect of BCG vaccination was less after than before 10 years (ratio of rate ratios > 1).

Meta-regression analysis

Univariable analysis results on the waning efficacy measure (comparing the rate ratio after 10 years of follow-up with the rate ratio in the first 10 years) found little evidence of associations between any of the study characteristics and the measure of waning efficacy. There was considerable between-study heterogeneity ($\tau^2 = 0.182$), which appeared to be explained either by latitude or by age at vaccination/tuberculin testing (*Table 27*).

All tuberculosis disease outcomes

Ten trials provided data to investigate duration of protection by BCG vaccination against all forms of tuberculosis (*Figure 90*). In the majority of studies, there was evidence of protection during the first 5 years of follow-up except in the Chingleput trial,[28] with protective efficacy appearing to decrease over time. Trials including the Saskatchewan infants[13] and the two Chicago studies[48] showed an initially high protective effect which decreased within 5 to 10 years. The Chingleput trial[28] showed BCG vaccination to be potentially harmful in the first 5 years of study, which attenuated to rate ratios close to 1 in subsequent years [further discussion in the *Discussion* (see *Chapter 5*) provides an explanation for this observation]. The remaining four studies showed low initial protective effects with a rapid decline in efficacy over the MRC and Native American studies[5,14] showed a highly protective effect of BCG vaccination beyond 10 and 15 years, respectively.

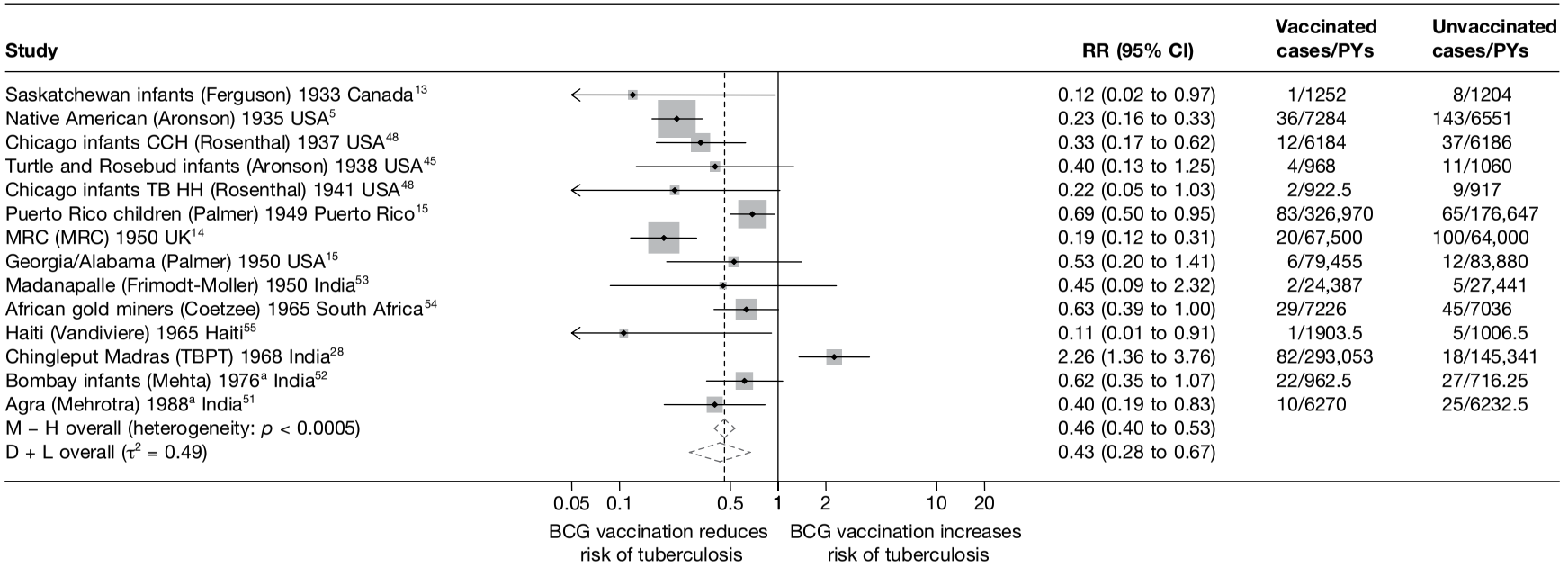

FIGURE 86 Rate ratios (with 95% CI) comparing incidence of pulmonary tuberculosis among BCG vaccinated individuals with that in unvaccinated individuals, in RCTs, in the first 5 years of follow-up. a, Date of study publication was used if study start date was not available. CCH, Cook County Hospital; D+L, DerSimonian and Laird method; M–H, Mantel–Haenszel method; TB HH, tuberculosis households; TBPT, Tuberculosis Prevention Trial.

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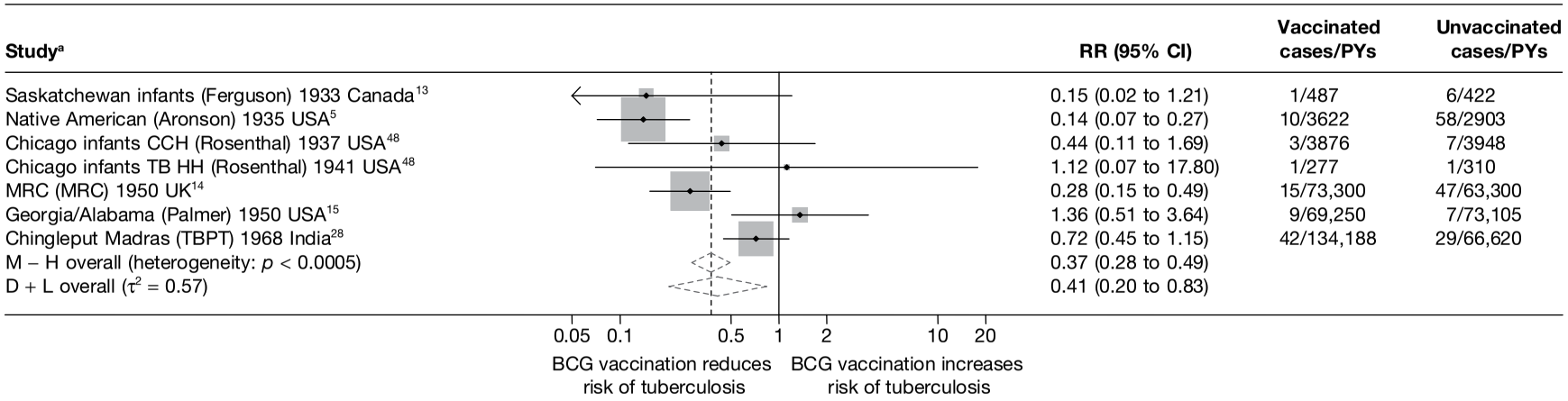

FIGURE 87 Rate ratios (with 95% CI) comparing incidence of pulmonary tuberculosis among BCG vaccinated individuals with that in unvaccinated individuals, in RCTs, from 5 to 10 years of follow-up. a, Date of study publication was used if study start date was not available. CCH, Cook County Hospital; D+L, DerSimonian and Laird method; M–H, Mantel–Haenszel method; TB HH, tuberculosis households; TBPT, Tuberculosis Prevention Trial.

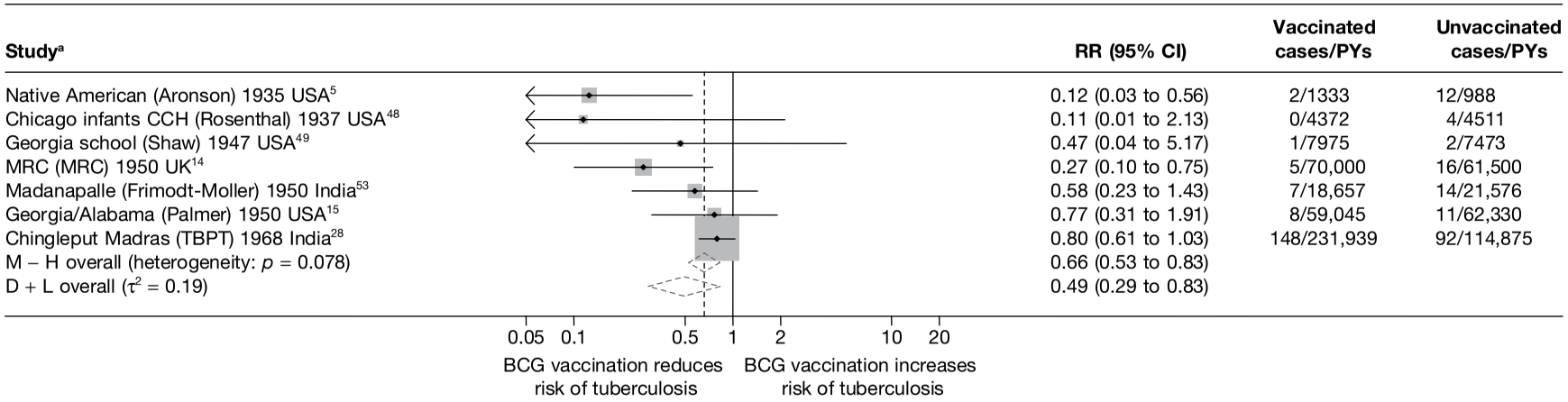

FIGURE 88 Rate ratios (with 95% CI) comparing incidence of pulmonary tuberculosis among BCG vaccinated individuals with that in unvaccinated individuals, in RCTs, from 10 to 15 years of follow-up. a, Date of study publication was used if study start date was not available. CCH, Cook County Hospital; D+L, DerSimonian and Laird method; M–H, Mantel–Haenszel method; TBPT, Tuberculosis Prevention Trial.

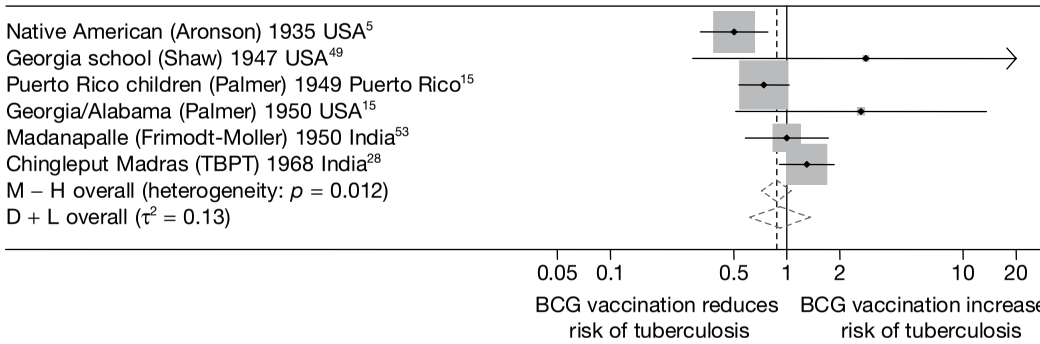

FIGURE 89 Rate ratios (with 95% CI) comparing incidence of pulmonary tuberculosis among BCG vaccinated individuals with that in unvaccinated individuals, in RCTs, beyond 15 years of follow-up. a, Date of study publication was used if study start date was not available. This graph contains two additional studies (Puerto Rico Children[15] and Chingleput study[28]) compared with the graphs in *Figure 81* with data beyond 15 years. This is because the effects in *Figure 81* were averaged over some years. D+L, DerSimonian and Laird method; M–H, Mantel–Haenszel method; TBPT, Tuberculosis Prevention Trial.

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TABLE 26 Rate ratios (with 95% CI) comparing incidence of pulmonary tuberculosis among vaccinated individuals with that in unvaccinated individuals and vaccine efficacy (with 95% CI) in the first 10 years of, and after 10 years of, follow-up; and ratio of rate ratios (with 95% CI) after 10 years compared with first 10 years of study

	Protection in first 10 years of follow-up		Protection post 10 years of follow-up		Waning efficacy measure
Trial	Rate ratio (95% CI) for effect of BCG vaccination in the first 10 years	VE (95% CI) for effect of BCG vaccination in the first 10 years	Rate ratio (95% CI) for effect of BCG vaccination after 10 years	VE (95% CI) for the effect of BCG vaccination after 10 years	Effect of BCG vaccination after the first 10 years compared with the first 10 years ratios of the rate (95% CI)
Native American[5]	0.19 (0.14 to 0.26)	81 (74 to 86)	0.50 (0.32 to 0.78)	50 (22 to 68)	2.62 (1.52 to 4.50)
Chicago Infants CCH[48]	0.33 (0.18 to 0.59)	67 (41 to 82)	0.51 (0.05 to 5.62)	49 (–462 to 95)	1.54 (0.13 to 18.27)
Georgia (School)[49]	0.47 (0.04 to 5.17)	53 (–417 to 96)	2.81 (0.29 to 27.06)	–181 (–2606 to 71)	6.01 (0.22 to 162.7)
Puerto Rico Children[15]	0.69 (0.50 to 0.95)	31 (5 to 50)	0.74 (0.53 to 1.03)	26 (–3 to 47)	1.08 (0.68 to 1.71)
Georgia/Alabama[15]	0.83 (0.42 to 1.64)	17 (–64 to 58)	1.06 (0.49 to 2.28)	–6 (–128 to 51)	1.27 (0.45 to 3.53)
Madanapalle[53]	0.17 (0.04 to 0.77)	83 (23 to 96)	1.07 (0.66 to 1.73)	–7 (–73 to 34)	6.13 (1.28 to 29.34)
Chingleput[28]	1.03 (0.8 to 1.32)	–3 (–32 to 20)	1.06 (0.82 to 1.37)	–6 (–37 to 18)	1.03 (0.72 to 1.47)

CCH, Cook County Hospital.
The waning efficacy measure is the comparison of the effect estimates (rate ratios) after 10 years of follow-up compared with the first 10 years of study follow-up.

Based on an assumption of a linear trend in log of rate ratio over time, we investigated the change in efficacy over time, by estimating the ratio of rate ratios per 5 years for the whole of the study periods in *Figure 91* and excluding the first 5 years of study in *Figure 92*. Apart from the Chingleput[28] and Puerto Rico[15] studies, all studies showed an increasing rate ratio (declining protection) for each 5 years of follow-up, with a summary ratio of rate ratios per 5 years of follow-up of 1.16 (95% CI 1.01 to 1.33) and little between-study heterogeneity ($\tau^2 = 0.013$) (see *Figure 91*). *Figure 92* shows that if data from the first 5 years of follow-up were excluded, the decline in protective effect was more pronounced [summary ratio of rate ratio 1.32 (95% CI 1.10 to 1.59)]. There was again little between-study heterogeneity ($\tau^2 = 0.02$).

Temporal changes in efficacy

The scatter plots displayed in *Figures 93* and *94* show the change in rate ratio per 5 years' follow-up compared with the overall rate ratio for each study, including and excluding the first 5 years of follow-up. There is little evidence of an association between change in efficacy over time and overall efficacy across studies, similarly to *Figures 84* and *85*.

Temporal changes in efficacy in relation to overall efficacy

Study efficacy by follow-up period

The forest plots in *Figures 95–98* show the effectiveness of BCG vaccination against all forms of tuberculosis, within the successive follow-up periods 0 to 5 years, 5 to 10 years, 10 to 15 years and > 15 years following vaccination. During the first 5 years, there was substantial heterogeneity in the effect of BCG vaccination ($\tau^2 = 0.56$). While there was evidence of a protective effect, ranging from low protection 31% in Puerto Rico children[15] to high protection 89% (95% CI 0.09% to 99%) in Haiti,[55] the Chingleput Study[28] showed a potentially negative effect of BCG vaccination in first 5 years of study [rate ratio 2.26 (95% CI 1.36 to 3.76)] (see *Chapter 5* , *Discussion*, for an explanation).

Among the eight trials[5,13–15,28,48] with data on protection between 5 and 10 years after vaccination, there was substantial between-study heterogeneity ($\tau^2 = 0.54$) (see *Figure 96*). Although there was little evidence of protection in the Chicago infants (TB HH),[48] Puerto Rico,[15] Georgia/Alabama[15]

TABLE 27 Ratios of rate ratios (with 95% CI) comparing the incidence of pulmonary tuberculosis among vaccinated individuals compared with unvaccinated individuals for the longest duration of follow-up (see *Table 3*) in RCTs, according to univariate meta-regression analysis

			Univariable model		
Variable	Number of trials	Univariable waning efficacy measure (95% CI)	Ratio of waning efficacy measures (95% CI)	*p*-value	τ^2
Null model	7				0.182
Latitude					
>40°	2	2.55 (0.92 to 7.12)	1.00 (ref.)		
20–40°	2	1.45 (0.22 to 9.66)	0.57 (0.09 to 3.72)		
0–20°	3	1.11 (0.65 to 1.89)	0.43 (0.16 to 1.19)	0.184	0.000
Age at vaccination/tuberculin testing combined					
Neonatal	1	1.54 (0.00 to 1.39×10^7)	1.00 (ref.)		
School age/stringent	2	2.67 (0.08 to 85.45)	1.73 (0.01 to 444.78)		
School age/non-stringent	1	1.07 (0.05 to 21.36)	0.70 (0.01 to 173.17)		
Other age/stringent	1	6.13 (0.01 to 16×10^5)	3.97 (0.01 to 2436.92)		
Other age/non-stringent	2	1.06 (0.12 to 9.28)	0.68 (0.01 to 162.76)	0.251	0.000
Diagnostic quality					
Lower risk of bias	4	1.89 (0.74 to 4.86)	1.00 (ref.)		
Higher risk of bias	3	1.25 (0.40 to 3.98)	0.66 (0.17 to 2.63)	0.477	0.233
Was the allocation sequence adequately generated?					
Lower risk of bias	1	1.03 (0.27 to 4.03)	1.00 (ref.)		
Higher risk of bias	6	1.86 (0.82 to 4.22)	1.80 (0.41 to 7.83)	0.350	0.207
Was treatment allocation adequately concealed?					
Lower risk of bias	1	1.03 (0.27 to 4.03)	1.00 (ref.)		
Higher risk of bias	6	1.86 (0.82 to 4.22)	1.80 (0.41 to 7.83)	0.350	0.207
Was knowledge of the allocated intervention prevented during the study?					
Lower risk of bias	2	1.60 (0.50 to 5.11)	1.00 (ref.)		
Higher risk of bias	5	1.67 (0.56 to 4.97)	1.05 (0.24 to 4.58)	0.937	0.297
Were incomplete outcome data adequately addressed?					
Lower risk of bias	3	1.13 (0.40 to 3.23)	1.00 (ref.)		
Higher risk of bias	4	2.05 (0.82 to 5.13)	1.81 (0.50 to 6.54)	0.290	0.196
Are reports of the study free from the suggestion of selective outcome reporting?					
Lower risk of bias	6	1.40 (0.75 to 2.63)	1.00 (ref.)		
Higher risk of bias	1	6.13 (0.54 to 70.08)	4.36 (0.42 to 44.83)	0.165	0.131
Was ascertainment of cases complete?					
Lower risk of bias	6	1.40 (0.75 to 2.63)	1.00 (ref.)		
Higher risk of bias	1	6.13 (0.54 to 70.08)	4.36 (0.42 to 44.83)	0.165	0.131

ref., reference category; τ^2, estimated between-study variance.
The univariable waning efficacy measures are the comparison of rate ratios after 10 years of study against the rate ratios in the initial 10 years of study, stratified by different variables. The ratio of waning efficacy measures compares the measures of waning of protection in each strata with the reference category.

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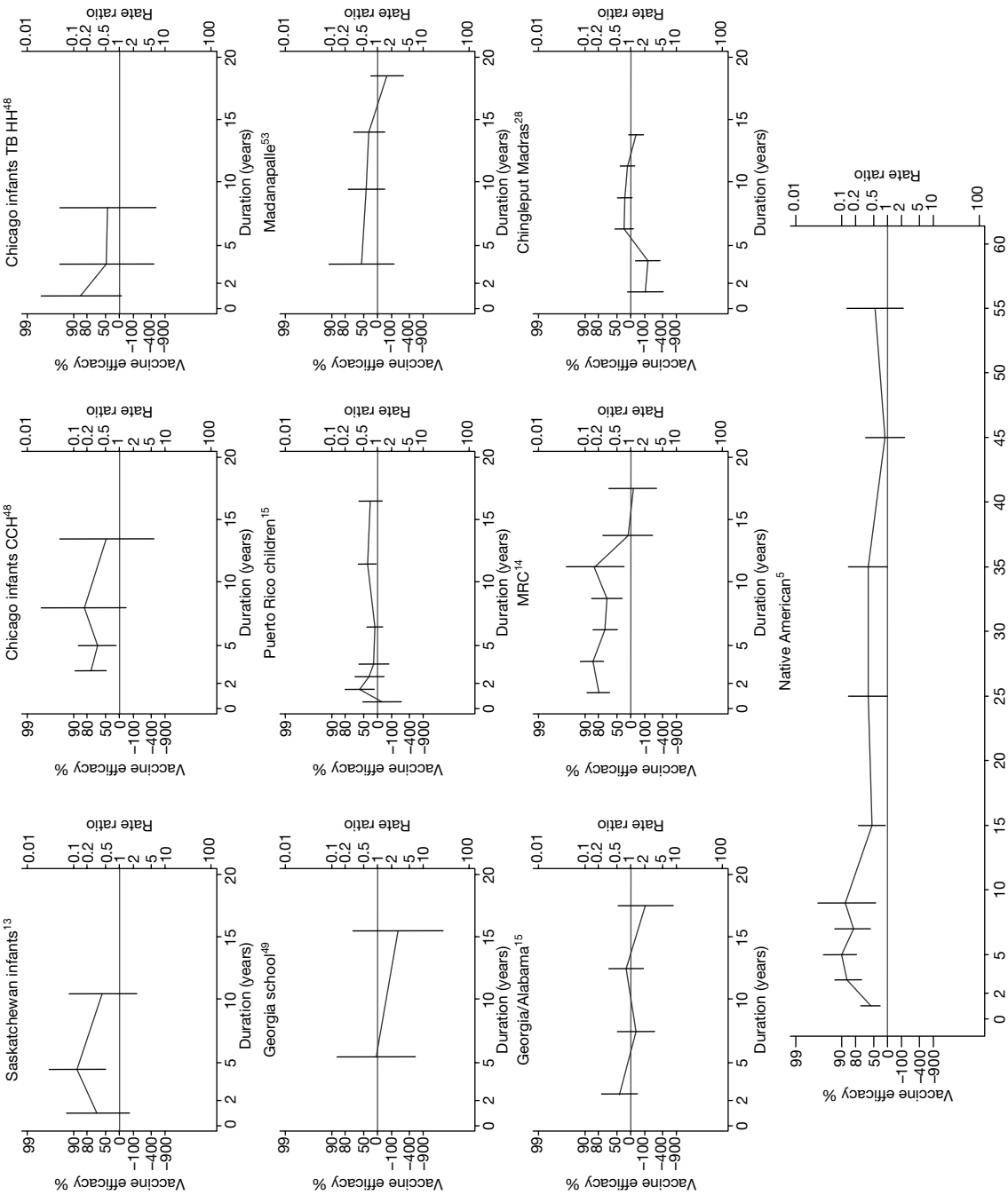

FIGURE 90 Vaccine efficacy and rate ratios (with 95% CI) comparing the incidence of all tuberculosis morbidity outcomes among BCG vaccinated individuals with that in unvaccinated individuals, in RCTs, over time. CCH, Cook County Hospital; TB HH, tuberculosis households.

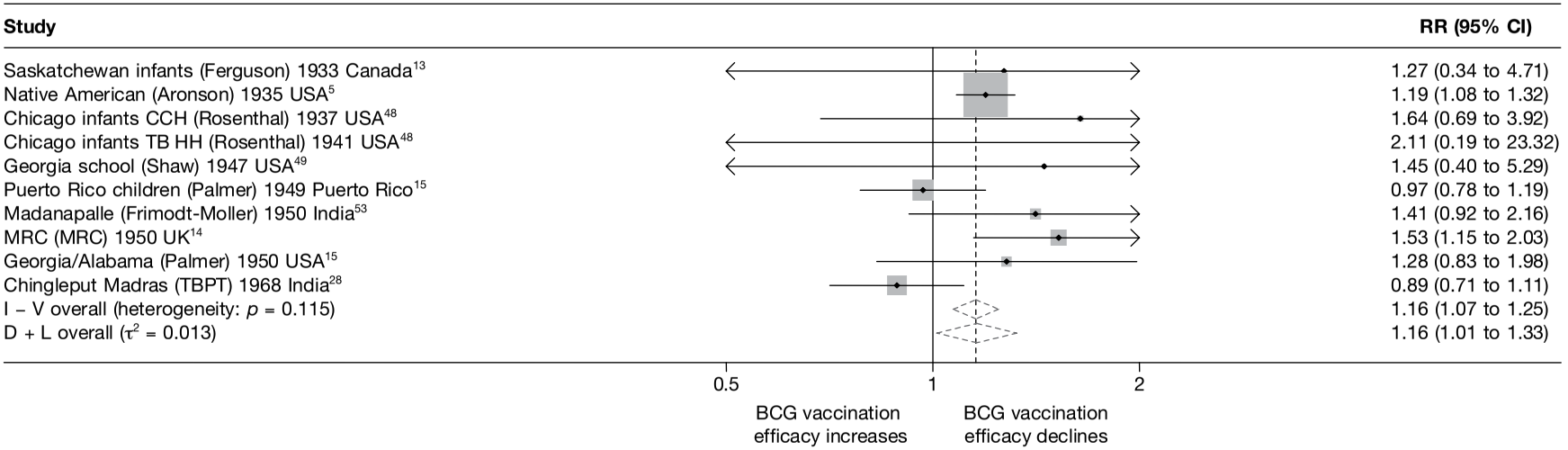

FIGURE 91 Change per 5 years (with 95% CI) in the rate ratio comparing the incidence of all tuberculosis morbidity outcomes among BCG vaccinated individuals with that in unvaccinated individuals in RCTs for the longest follow-up period (see *Table 3*), including the first 5 years of data for each study. CCH, Cook County Hospital; D + L, DerSimonian and Laird method; I–V, inverse variance method; TB HH, tuberculosis households; TBPT, Tuberculosis Prevention Trial.

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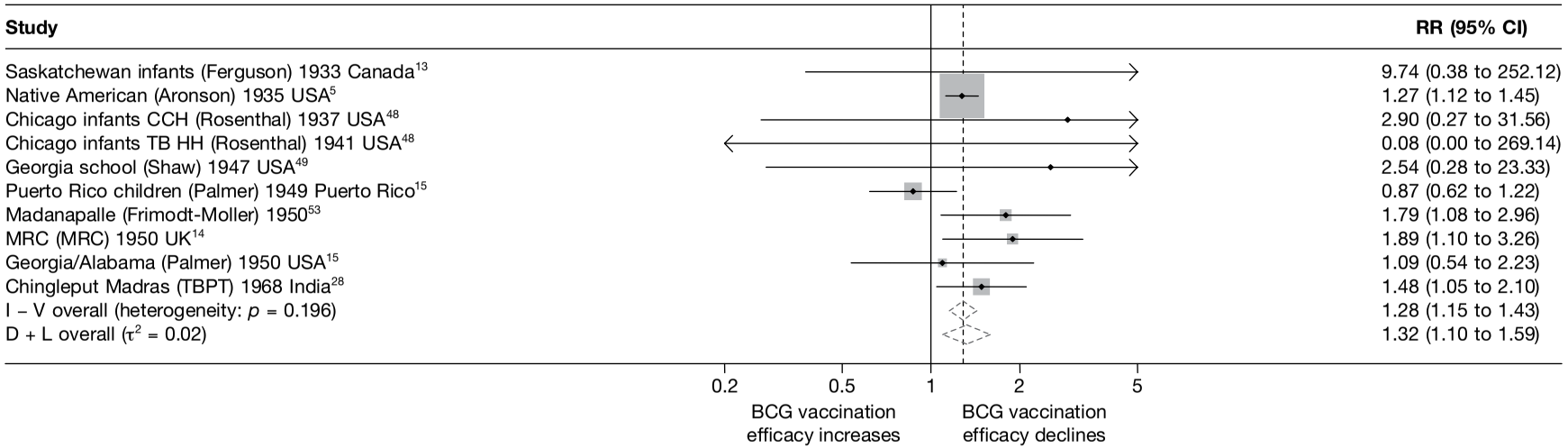

FIGURE 92 Change per 5 years (with 95% CI) in the rate ratio comparing the incidence of all tuberculosis morbidity outcomes among BCG vaccinated individuals with that in unvaccinated individuals in RCTs for the longest follow-up period (see *Table 3*), excluding the first 5 years of data for each study. CCH, Cook County Hospital; D+L, DerSimonian and Laird method; I–V, inverse variance method; TB HH, tuberculosis households; TBPT, Tuberculosis Prevention Trial.

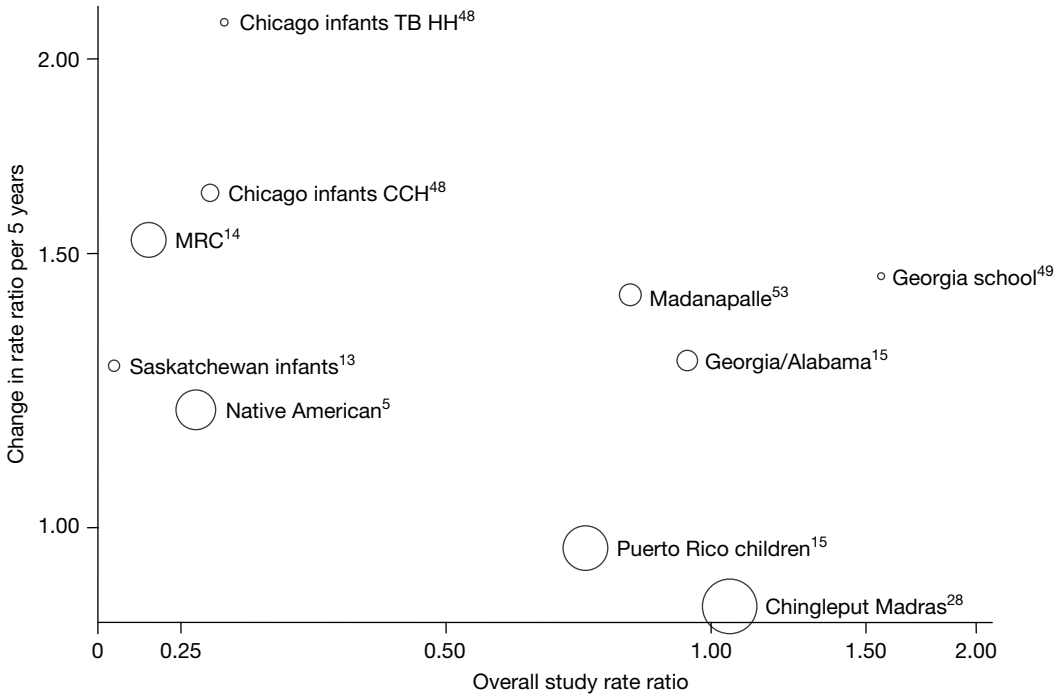

FIGURE 93 Scatterplot of change per 5 years in rate ratio compared with overall rate ratio, comparing incidence of all tuberculosis morbidity outcomes among BCG vaccinated individuals with that in unvaccinated individuals, in RCTs, including the first 5 years of data for each study. The area of the circles is proportional to the inverse of the variance of the log-rate ratio comparing vaccinated with unvaccinated individuals. CCH, Cook County Hospital; TB HH, tuberculosis households.

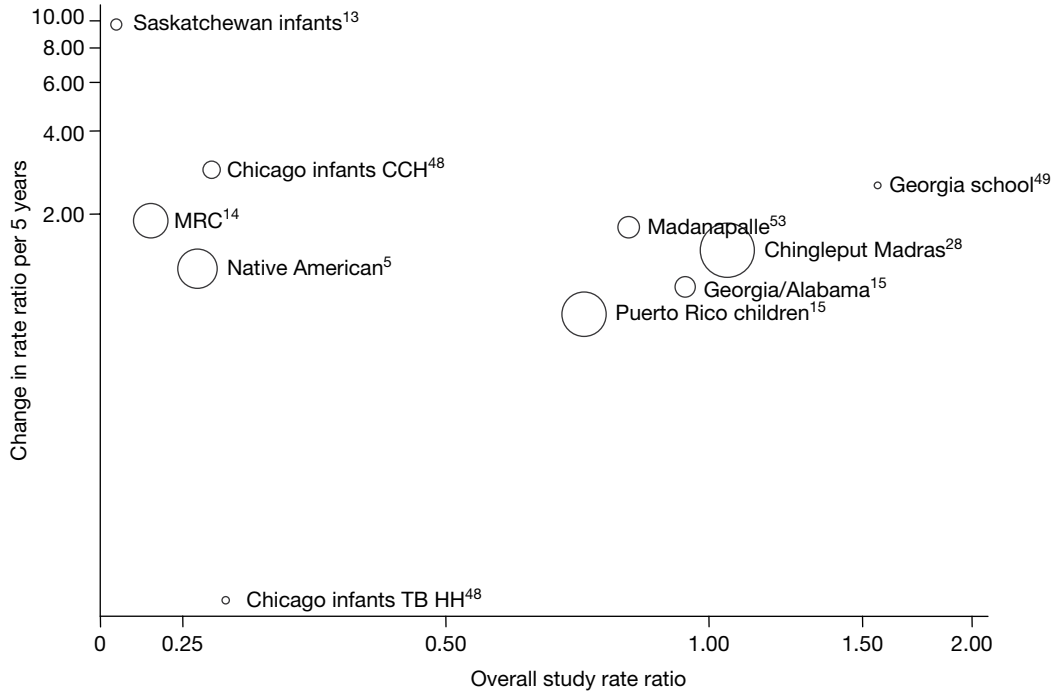

FIGURE 94 Scatterplot of change per 5 years in rate ratio compared with overall rate ratio, comparing incidence of all tuberculosis outcomes among BCG vaccinated individuals with that in unvaccinated individuals, in RCTs, excluding the first 5 years of data for each study. The area of the circles is proportional to the inverse of the variance of the log-rate ratio comparing vaccinated with unvaccinated individuals. CCH, Cook County Hospital; TB HH, tuberculosis households.

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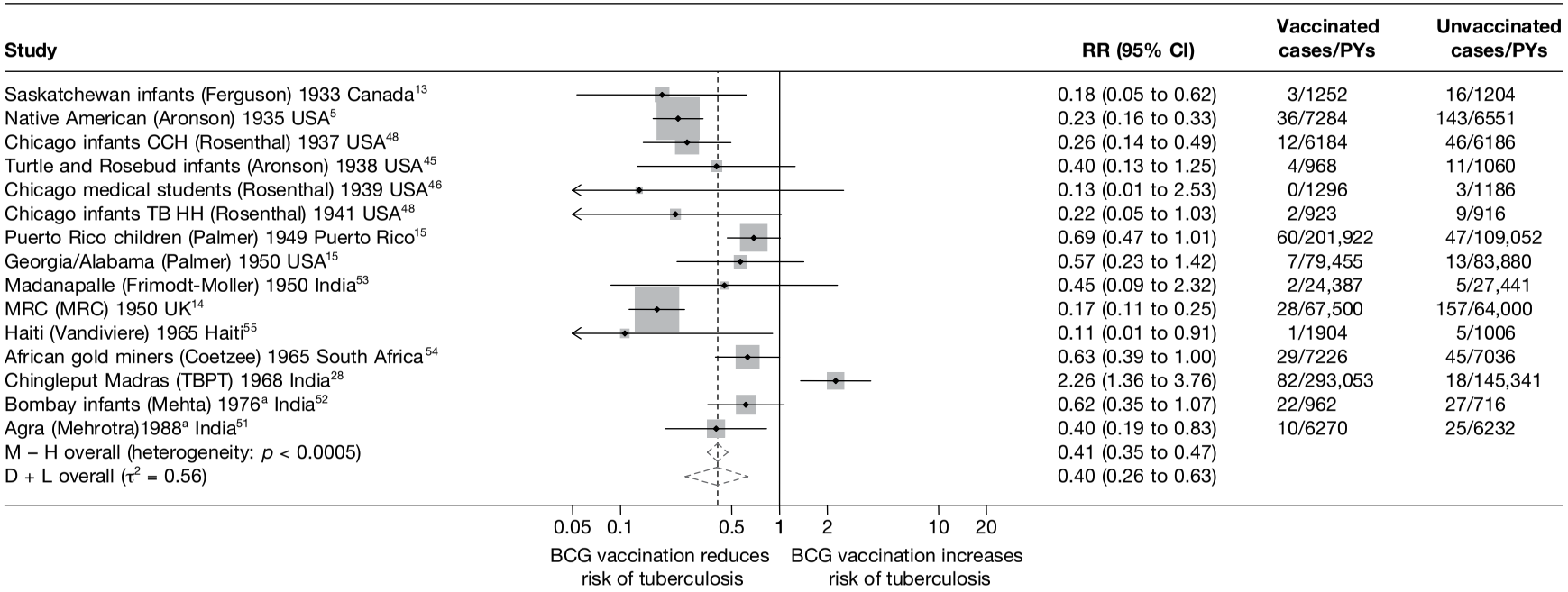

FIGURE 95 Rate ratios (with 95% CI) comparing incidence of all tuberculosis morbidity outcomes among BCG vaccinated individuals with that in unvaccinated individuals, in RCTs in the first 5 years of follow-up. a, Date of study publication was used if study start date was not available. CCH, Cook County Hospital; D+L, DerSimonian and Laird method; M–H, Mantel–Haenszel method; TB HH, tuberculosis households; TBPT, Tuberculosis Prevention Trial.

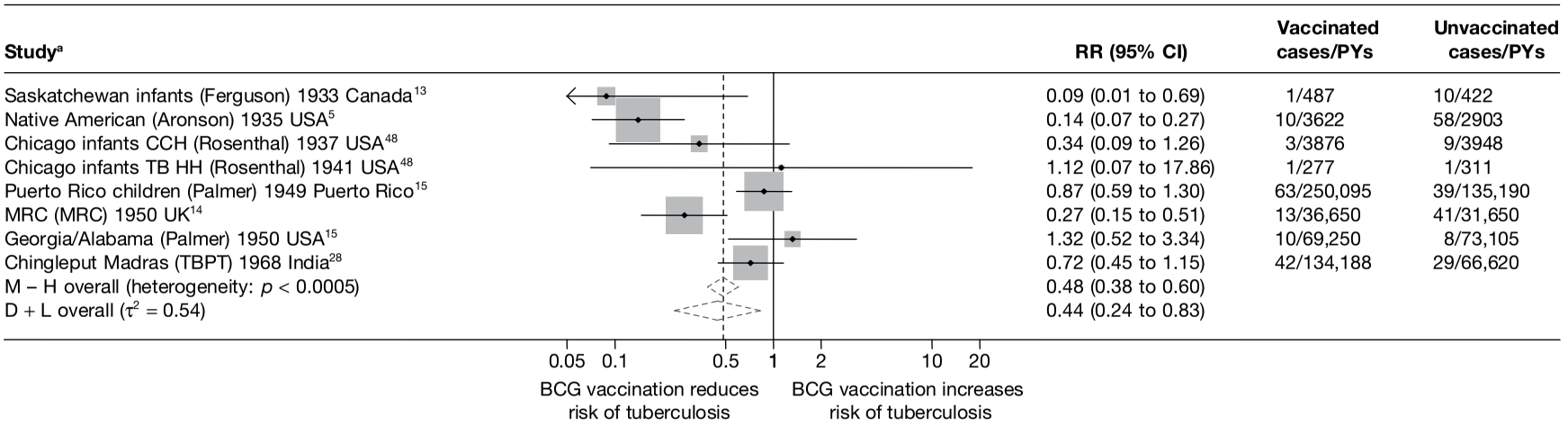

FIGURE 96 Rate ratios (with 95% CI) comparing incidence of all tuberculosis morbidity outcomes among BCG vaccinated individuals with that in unvaccinated individuals, in RCTs, from 5 to 10 years of follow-up. a, Date of study publication was used if study start date was not available. CCH, Cook County Hospital; D+L, DerSimonian and Laird method; M–H, Mantel–Haenszel method; TB HH, tuberculosis households; TBPT, Tuberculosis Prevention Trial.

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and Chingleput trials,[28] estimated vaccine efficacy was good, at 73% (95% CI 49% to 85%) in the MRC study[14] and high [91% (95% CI 31% to 99%)] in the Saskatchewan trial.[13]

Figure 97 shows results from nine trials,[5,13–15,28,48,49,53] with relevant data on the protective effect of BCG vaccination between 10 and 15 years after vaccination. The number of events in the vaccinated and unvaccinated arms was small, for most studies; however, data from the MRC[14] and Native American trials[5] show evidence of substantial protection, with VEs ranging from good [VE 74% (95% CI 49% to 87%)] to high [VE 88% (95% CI 44% to 97%)], respectively. There was evidence of between-study heterogeneity but this was lower than for earlier time periods of follow-up ($\tau^2 = 0.16$).

Seven studies[5,14,15,28,49,53] provided estimates of BCG vaccination efficacy beyond 15 years after vaccination (see *Figure 98*). There was evidence of between-study heterogeneity ($\tau^2 = 0.16$), although this was less than for periods before 10 years' follow-up. Only the Native American study[5] showed evidence of a protective effect beyond 15 years [rate ratio 0.48 (95% CI 0.32 to 0.72)], equivalent to a moderate VE of 52% (95% CI 28% to 68%), whereas the remaining studies showed very little evidence of protection by BCG vaccination beyond 15 years after vaccination.

Measure of waning efficacy

Table 28 shows the rate ratio for the effect of BCG vaccination in the first 10 years and 10 years after vaccination, together with the ratio of these rate ratios (i.e. the change in effect of BCG vaccination before compared with after 10 years) for the eight trials with relevant data. In general, most cases occurred in the first 10 years' follow-up and so the estimated rate ratios are similar to the overall rate ratios displayed in *Figure 7*. For seven of the eight trials, the effect of BCG vaccination was smaller after 10 years than before 10 years (ratio of rate ratio > 1).

Meta-regression analysis

Univariable analysis of the waning efficacy measure (which compares the rate ratio after 10 years of follow-up with the rate ratio in the first 10 years) of trials for all tuberculosis morbidity outcomes provided some evidence that latitude was associated with the waning efficacy measure ($p = 0.058$). The between-study variation (null $\tau^2 = 0.249$) was accounted for both by stratification on latitude and by stratification on age at vaccination/tuberculin testing stringency (both $\tau^2 = 0.000$) (*Table 29*).

Combined meningeal/miliary tuberculosis

Only the MRC trial[14] had data on combined meningeal/miliary tuberculosis divided by duration, but there were no cases in the BCG vaccination group over the follow-up period so no summary measures could be calculated for changes in the rate ratio over time.

Extrapulmonary tuberculosis

Three studies[5,14,15] provided sufficient data to assess the duration of protection of BCG vaccination against extrapulmonary forms of tuberculosis (excluding meningeal or miliary tuberculosis) (*Figure 99*). Both the Native American[5] and MRC trials[14] showed consistently high levels of protection, for the whole duration of the trial. The study conducted in Georgia/Alabama[15] showed no evidence of protection in the first 10 years following vaccination, with a final estimate of lower protection after 15 years.

Temporal changes in efficacy

Figures 100 and *101* show the change in rate ratio per 5 years for the three studies with data on extrapulmonary tuberculosis outcomes. These studies demonstrate a decrease in BCG vaccination efficacy over time, with a slightly greater decrease if the first 5 years of data are excluded.

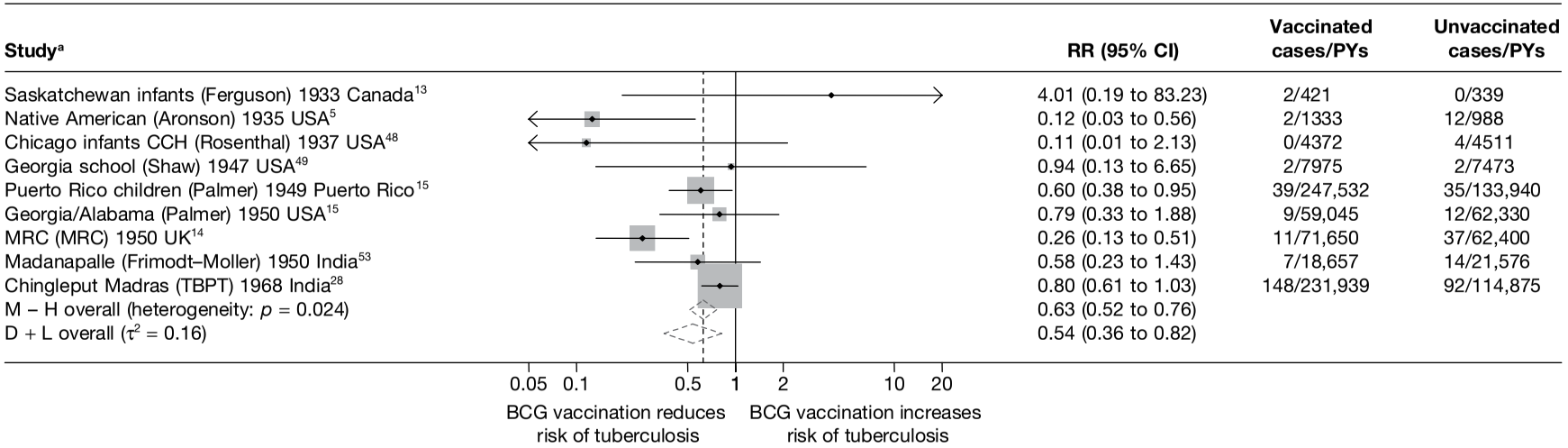

FIGURE 97 Rate ratios (with 95% CI) comparing incidence of all tuberculosis morbidity outcomes among BCG vaccinated individuals with that in unvaccinated individuals, in RCTs, from 10 to 15 years of follow-up. a, Date of study publication was used if study start date was not available. CCH, Cook County Hospital; D+L, DerSimonian and Laird method; M–H, Mantel–Haenszel method; TBPT, Tuberculosis Prevention Trial.

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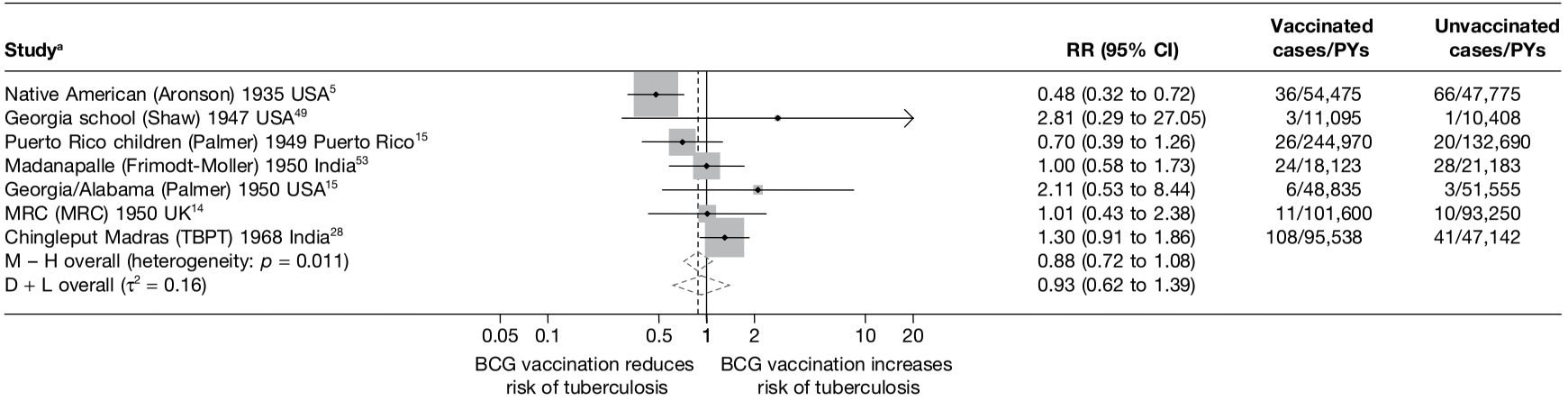

FIGURE 98 Rate ratios (with 95% CI) comparing incidence of all tuberculosis morbidity outcomes among BCG vaccinated individuals with that in unvaccinated individuals, in RCTs, beyond 15 years of follow-up. a, Date of study publication was used if study start date was not available. This graph contains one additional study (Chingleput study[28]) compared with the graphs in *Figure 90* with data beyond 15 years. This is because the effects in *Figure 81* were averaged over some years. D+L, DerSimonian and Laird method; M−H, Mantel–Haenszel method; TBPT, Tuberculosis Prevention Trial.

TABLE 28 Rate ratios (with 95% CI) comparing incidence of all tuberculosis morbidity outcomes among vaccinated individuals with that in unvaccinated individuals and VE (with 95% CI) in the first 10 years of and after 10 years of follow-up, and ratio of rate ratios (with 95% CI) after 10 years compared with first 10 years of study

	Protection in first 10 years of follow-up		Protection post 10 years of follow-up		Waning efficacy measure
Trial	Rate ratio (95% CI) for effect of BCG vaccination in the first 10 years	VE (95% CI) for effect of BCG vaccination in the first 10 years	Rate ratio (95% CI) for effect of BCG vaccination after 10 years	VE (95% CI) for the effect of BCG vaccination after 10 years	Effect of BCG vaccination after the first 10 years compared with the first 10 years of ratio of the rate (95% CI)
Native American[5]	0.19 (0.14 to 0.26)	81 (74 to 86)	0.48 (0.32 to 0.72)	52 (28 to 68)	2.49 (1.49 to 4.16)
Chicago Infants CCH[48]	0.27 (0.15 to 0.47)	73 (53 to 85)	0.51 (0.05 to 5.62)	49 (–462 to 95)	1.91 (0.16 to 22.56)
Georgia (School)[49]	0.94 (0.13 to 6.65)	6 (–565 to 87)	2.81 (0.29 to 27.06)	–181 (–2606 to 71)	3.00 (0.15 to 59.95)
Puerto Rico Children[15]	0.77 (0.59 to 1.02)	23 (–2 to 41)	0.64 (0.45 to 0.92)	36 (8 to 55)	0.83 (0.53 to 1.30)
Georgia/Alabama[15]	0.85 (0.45 to 1.62)	15 (–62 to 55)	1.06 (0.52 to 2.16)	–6 (–116 to 48)	1.24 (0.47 to 3.23)
Madanapalle[53]	0.17 (0.04 to 0.77)	83 (23 to 96)	1.07 (0.66 to 1.73)	–7 (–73 to 34)	6.13 (1.28 to 29.34)
MRC[14]	0.20 (0.15 to 0.27)	80 (73 to 85)	0.56 (0.28 to 1.12)	44 (–12 to 72)	2.78 (1.31 to 5.93)
Chingleput[28]	1.03 (0.80 to 1.32)	–3 (–32 to 20)	1.06 (0.82 to 1.37)	–6 (–37 to 18)	1.03 (0.72 to 1.47)

CCH: Cook County Hospital.
The waning efficacy measure is the comparison of the effect estimates (rate ratios) after 10 years of follow-up compared with the first 10 years of study follow-up.

Study efficacy by follow-up period

The forest plots in *Figure 102–105* show the effectiveness of BCG vaccination against extrapulmonary tuberculosis, within the successive follow-up periods 0–5 years, 5–10 years, 10–15 years and > 15 years following vaccination. During the first 5 years, there was substantial heterogeneity in the effect of BCG vaccination ($\tau^2 = 1.1$). Two trials showed evidence of a strong protective effect, ranging from good protection 78% (95% CI –2% to 95%) in the Native American[5] study to high protection [VE 87% (95% CI 72% to 94%)] in the MRC trial,[14] whereas the Georgia/Alabama study[15] showed no evidence of clinical benefit (note: very small number of events).

Among the three trials[13,14,49] with data on protection between 5 and 10 years after vaccination, there was no heterogeneity ($\tau^2 = 0$) (see *Figure 103*), with the protective effect ranging from a rate ratio of 0.14 (95% CI 0.03 to 0.63) to 0.62 (95% CI 0.10 to 3.74), equivalent to a range of vaccine efficacy from 38% (95% CI –274% to 90%) to a high 86% (95% CI 37% to 97%).

Figure 104 shows results from four trials[5,14,15] with relevant data on the protective effect of BCG vaccination between 10 and 15 years after vaccination. The number of events in the vaccinated and unvaccinated arms was small for most studies; however, data from the Native American[5] and MRC trials[14] show evidence of substantial protection beyond 10 years (VE ranging from good protection at 76% to a high protective effect at 87%). There was some evidence of between-study heterogeneity ($\tau^2 = 0.29$).

Two studies[5,15] provided details on BCG vaccination efficacy beyond 15 years after vaccination (see *Figure 105*). There was no evidence of between-study heterogeneity ($\tau^2 = 0$). Only the Native American[5] study showed a protective effect beyond 15 years [rate ratio 0.31 (95% CI 0.11 to 0.88)], equivalent to a good VE of 69% (95% CI 12% to 89%), whereas the Georgia/Alabama trial[15] showed only little evidence of protection by BCG vaccination beyond 15 years after vaccination.

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TABLE 29 Ratios of rate ratios (with 95% CI) comparing the incidence of all tuberculosis morbidity outcomes among vaccinated individuals compared with unvaccinated individuals for the longest duration of follow-up (see *Table 3*) in RCTs, according to univariable meta-regression analysis

			Univariable model		
Variable	Number of trials	Univariable waning efficacy measure (95% CI)	Ratio of waning efficacy measures (95% CI)	*p*-value	τ^2
Null model	8				0.249
Latitude					
>40°	3	2.56 (1.32 to 4.96)	1.00 (ref.)		
20–40°	2	1.34 (0.32 to 5.71)	0.53 (0.12 to 2.30)		
0–20°	3	1.01 (0.65 to 1.56)	0.39 (0.19 to 0.82)	0.058	0.000
Age at vaccination/tuberculin testing combined					
Neonatal	1	1.91 (0.01 to 430.48)	1.00 (ref.)		
School age/stringent	3	2.59 (1.03 to 6.50)	1.35 (0.02 to 78.56)		
School age/non-stringent	1	0.83 (0.30 to 2.24)	0.43 (0.01 to 25.39)		
Other age/stringent	1	6.13 (0.20 to 190.73)	3.20 (0.03 to 367.95)		
Other age/non-stringent	2	1.06 (0.51 to 2.19)	0.55 (0.01 to 31.40)	0.113	0.000
Diagnostic quality					
Lower risk of bias	5	2.03 (0.99 to 4.19)	1.00 (ref.)		
Higher risk of bias	3	1.03 (0.38 to 2.78)	0.50 (0.16 to 1.62)	0.202	0.198
Was the allocation sequence adequately generated?					
Lower risk of bias	1	1.03 (0.24 to 4.36)	1.00 (ref.)		
Higher risk of bias	7	1.87 (0.89 to 3.91)	1.80 (0.39 to 8.43)	0.383	0.281
Was treatment allocation adequately concealed?					
Lower risk of bias	1	1.03 (0.24 to 4.36)	1.00 (ref.)		
Higher risk of bias	7	1.87 (0.89 to 3.91)	1.80 (0.39 to 8.43)	0.383	0.281
Was knowledge of the allocated intervention prevented during the study?					
Lower risk of bias	2	1.57 (0.50 to 4.93)	1.00 (ref.)		
Higher risk of bias	6	1.75 (0.71 to 4.30)	1.11 (0.28 to 4.44)	0.858	0.346
Were incomplete outcome data adequately addressed?					
Lower risk of bias	3	1.16 (0.40 to 3.34)	1.00 (ref.)		
Higher risk of bias	5	2.01 (0.90 to 4.52)	1.73 (0.49 to 6.14)	0.328	0.262
Are reports of the study free from the suggestion of selective outcome reporting?					
Lower risk of bias	7	1.48 (0.80 to 2.71)	1.00 (ref.)		
Higher risk of bias	1	6.13 (0.58 to 64.89)	4.15 (0.41 to 42.27)	0.184	0.204
Was ascertainment of cases complete?					
Lower risk of bias	7	1.48 (0.80 to 2.71)	1.00 (ref.)		
Higher risk of bias	1	6.13 (0.58 to 64.89)	4.15 (0.41 to 42.27)	0.184	0.204

ref., reference category; τ^2, estimated between-study variance.
The univariable waning efficacy measures are the comparison of rate ratios after 10 years of study against the rate ratios in the initial 10 years of study, stratified by different variables. The ratio of waning efficacy measures compares the measures of waning of protection in each strata with the reference category.

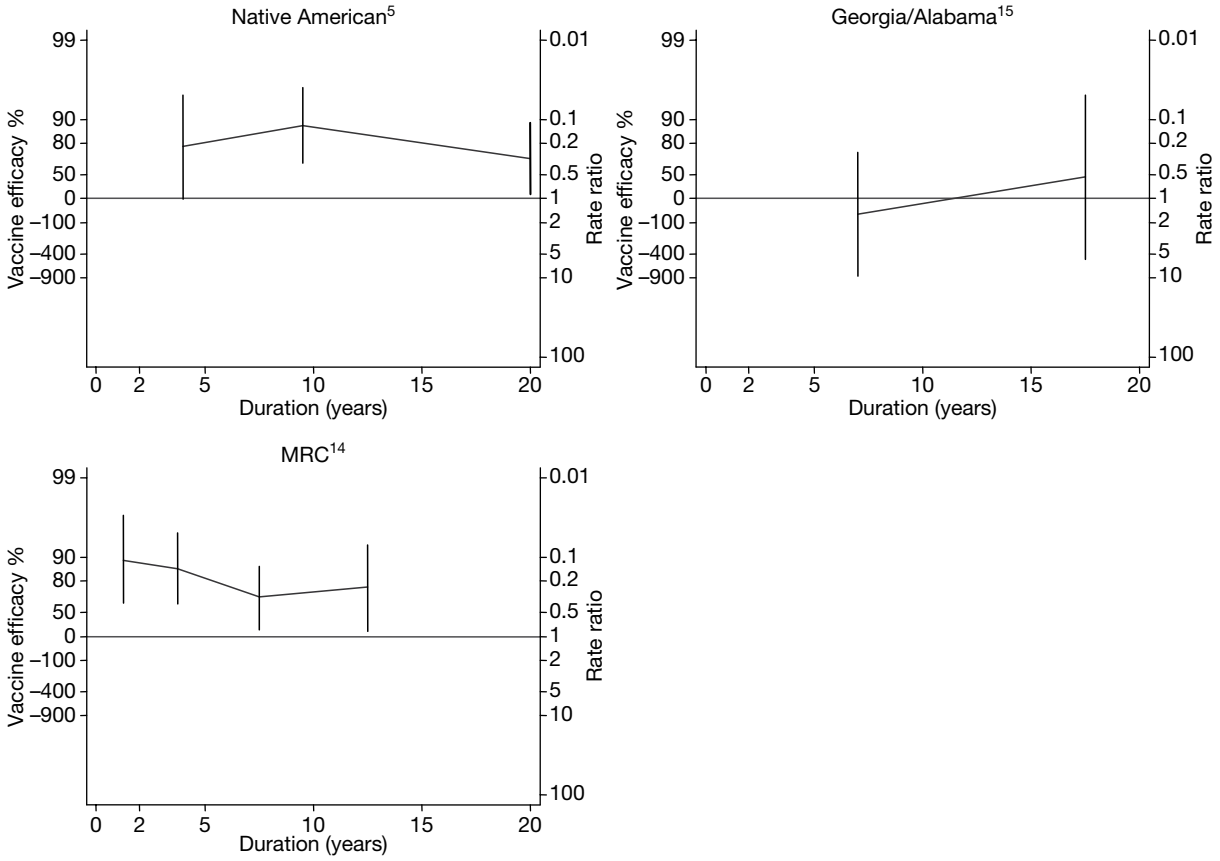

FIGURE 99 Vaccine efficacy and rate ratios (with 95% CI) comparing the incidence of extrapulmonary tuberculosis (non-tuberculosis meningitis or miliary tuberculosis) among BCG vaccinated individuals to that in unvaccinated individuals, in RCTs, over time.

Measure of waning efficacy

The rate ratios for the effect of BCG vaccination in the first 10 years after vaccination, and after the first 10 years, along with associated VE and the ratio of these rate ratios (waning efficacy measure) are shown in *Table 30*. Both the Native American[5] and MRC trials[14] showed evidence of high protection before 10 years and good protection 10 years after vaccination. The Georgia/Alabama trial[15] showed an increase in protection after 10 years to a moderate protective effect, compared with the first 10 years after vaccination.

Tuberculosis mortality

Only the Native American trial[5] provided data on mortality showing strong evidence that BCG vaccination affords protection against death associated with tuberculosis, for up to 25 years after vaccination (*Figure 106*). The annual change in rate ratio per 5 years for the Native American[5] study was 1.06 (95% CI 1.01 to 1.11). If the first 5 years of data are excluded, the decrease in the rate ratio of effect of BCG vaccination on tuberculosis mortality per 5 years was more pronounced [annual change in rate ratio 1.54 (95% CI 1.10 to 2.14)] (*Table 31*).

Measure of waning efficacy

Vaccine efficacy against tuberculosis mortality in the Native American trial[5] was high for the first 10 years after vaccination, estimated at 89%. This protective effect was found to be almost four times lower after 10 years since vaccination.

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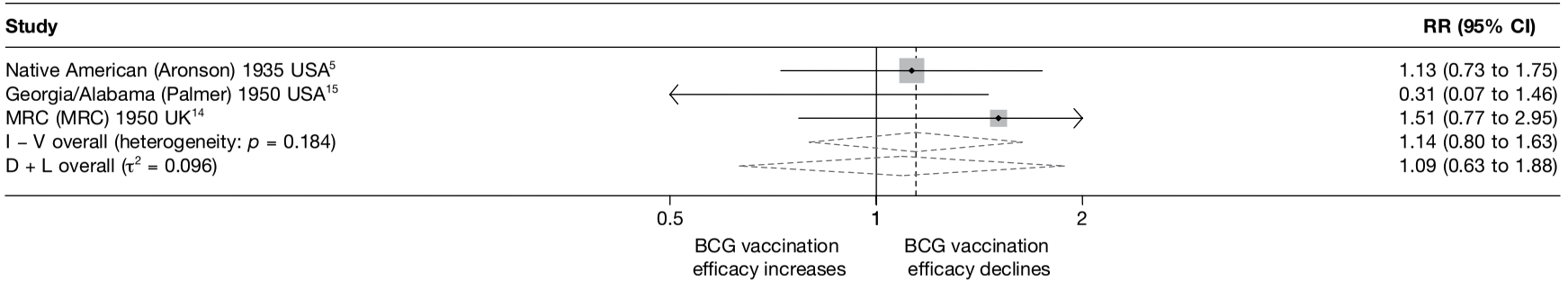

FIGURE 100 Change per 5 years (with 95% CI) in the rate ratio comparing the incidence of extrapulmonary tuberculosis (excluding meningeal or miliary tuberculosis) among BCG vaccinated individuals with that in unvaccinated individuals in RCTs for the longest follow-up period (see *Table 3*), including the first 5 years of data for each study. D+L, DerSimonian and Laird method; I–V, inverse variance method.

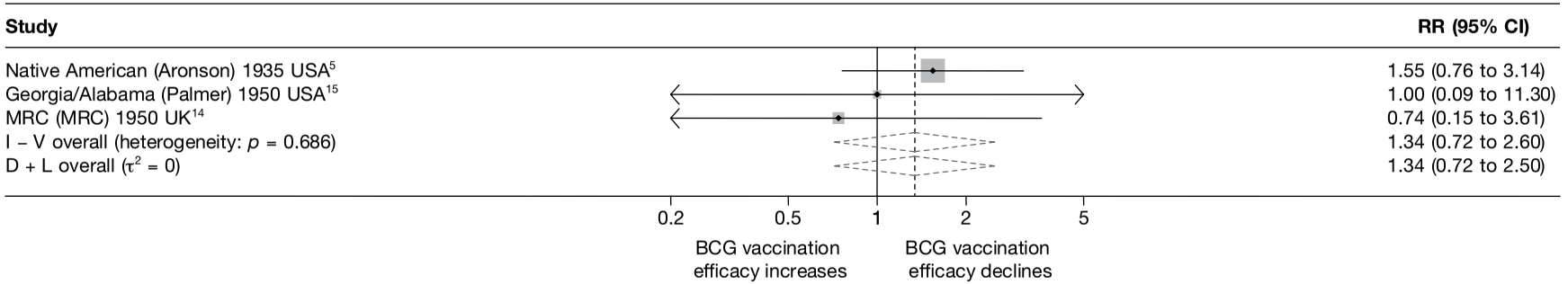

FIGURE 101 Change per 5 years (with 95% CI) in the rate ratio comparing the incidence of extrapulmonary tuberculosis (excluding meningeal or miliary tuberculosis) among BCG vaccinated individuals with that in unvaccinated individuals in RCTs for the longest follow-up period (see *Table 3*), excluding the first 5 years of data for each study. D+L, DerSimonian and Laird method; I–V, inverse variance method.

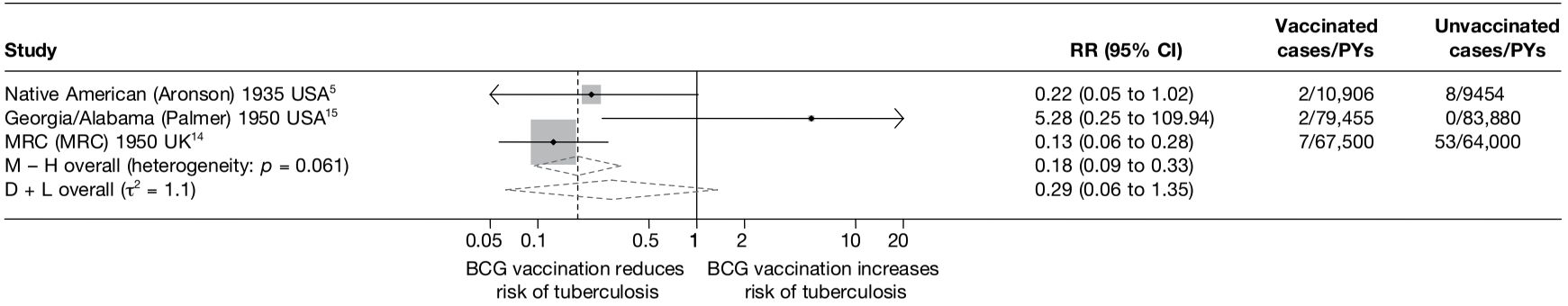

FIGURE 102 Rate ratios (with 95% CI) comparing incidence of extrapulmonary tuberculosis (excluding meningeal or miliary tuberculosis) among BCG vaccinated individuals with that in unvaccinated individuals, in RCTs, in the first 5 years of follow-up. D+L, DerSimonian and Laird method; M–H, Mantel–Haenszel method.

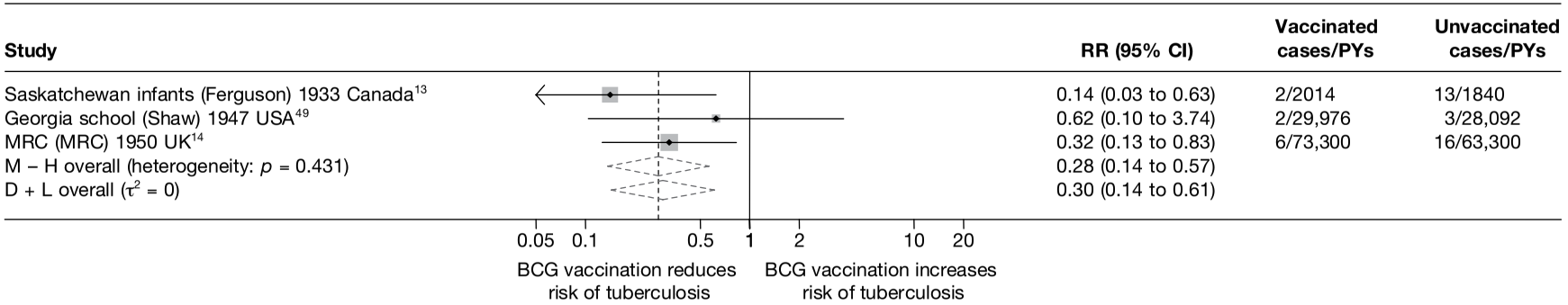

FIGURE 103 Rate ratios (with 95% CI) comparing incidence of extrapulmonary tuberculosis (excluding meningeal or miliary tuberculosis) among BCG vaccinated individuals to that in unvaccinated individuals, in RCTs, from 5 to 10 years of follow-up. D+L, DerSimonian and Laird method; M–H, Mantel–Haenszel method.

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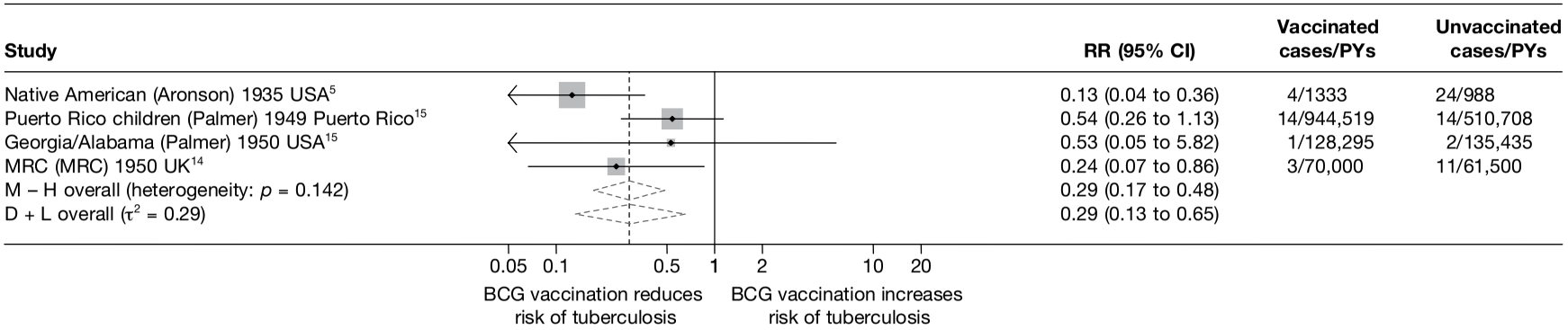

FIGURE 104 Rate ratios (with 95% CI) comparing incidence of extrapulmonary tuberculosis (excluding meningeal or miliary tuberculosis) among BCG vaccinated individuals with that in unvaccinated individuals, in RCTs, from 10 to 15 years of follow-up. D+L, DerSimonian and Laird method; M–H, Mantel–Haenszel method.

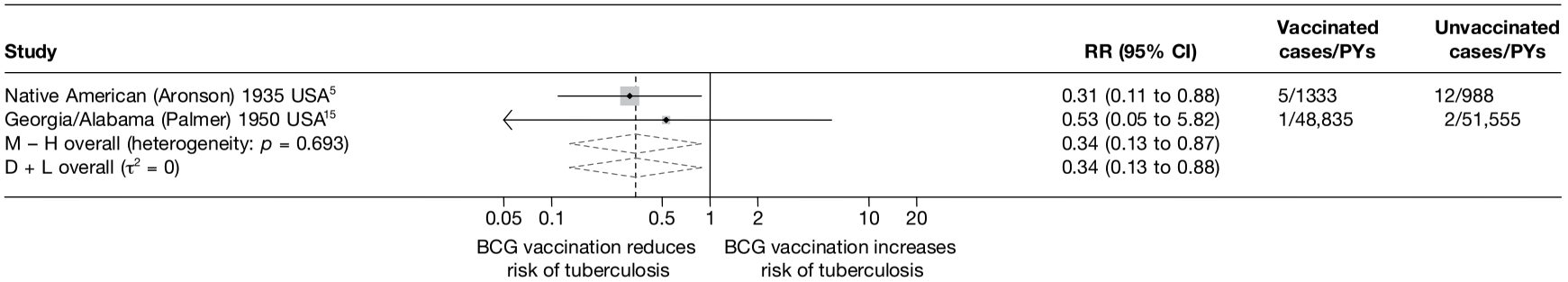

FIGURE 105 Rate ratios (with 95% CI) comparing incidence of extrapulmonary tuberculosis (excluding meningeal or miliary tuberculosis) among BCG vaccinated individuals with that in unvaccinated individuals, in RCTs, beyond 15 years of follow-up. D+L, DerSimonian and Laird method; M–H, Mantel–Haenszel method.

TABLE 30 Rate ratios (with 95% CI) comparing incidence of extrapulmonary tuberculosis (excluding meningeal or miliary tuberculosis) among vaccinated individuals with that in unvaccinated individuals and VE (with 95% CI) in the first 10 years of, and after 10 years of, follow-up, and ratio of rate ratios (with 95% CI) after 10 years compared with first 10 years of study

	Protection in first 10 years of follow-up		Protection post 10 years of follow-up		Waning efficacy measure
Trial	Rate ratio (95% CI) for effect of BCG vaccination in the first 10 years	VE (95% CI) for effect of BCG vaccination in the first 10 years	Rate ratio (95% CI) for effect of BCG vaccination after 10 years	VE (95% CI) for the effect of BCG vaccination after 10 years	Effect of BCG vaccination after the first 10 years compared with the first 10 years of ratio of the rate ratios (95% CI)
Native American[5]	0.16 (0.07 to 0.38)	84 (62 to 93)	0.31 (0.11 to 0.88)	69 (12 to 89)	1.93 (0.5 to 7.52)
Georgia/Alabama[15]	1.58 (0.26 to 9.48)	–58 (–848 to 74)	0.53 (0.05 to 5.82)	47 (–482 to 95)	0.33 (0.02 to 6.65)
MRC[14]	0.17 (0.09 to 0.31)	83 (69 to 91)	0.24 (0.07 to 0.86)	76 (14 to 93)	1.41 (0.34 to 5.75)

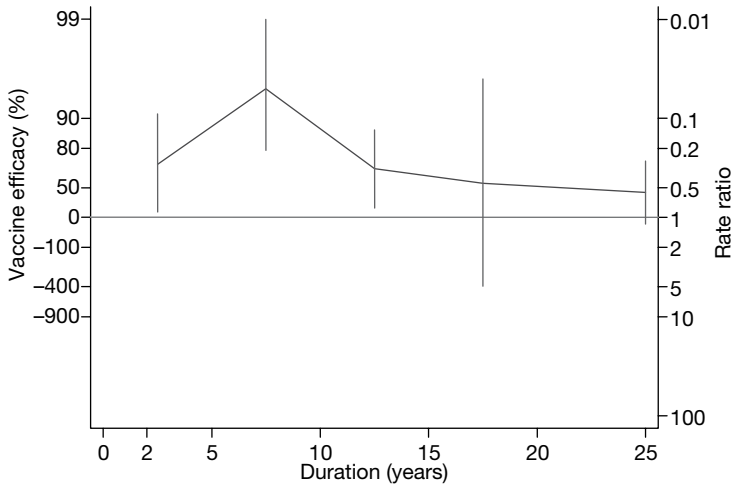

FIGURE 106 Vaccine efficacy and rate ratios (with 95% CI) comparing the incidence of tuberculosis mortality among vaccinated individuals with that in unvaccinated individuals, in RCTs, over time.[5]

TABLE 31 Rate ratios (with 95% CI) comparing the tuberculosis mortality among vaccinated individuals with that in unvaccinated individuals for the longest duration of follow-up (see *Table 3*) and VE (with 95% CI) in first 10 years of study and after 10 years of study, and ratio of rate ratios (with 95% CI) after 10 years compared with first 10 years of study

	Protection in first 10 years of follow-up		Protection post 10 years of follow-up		Waning efficacy measure
Trial	Rate ratio (95% CI) for effect of BCG vaccination in the first 10 years	VE (95% CI) for effect of BCG vaccination in the first 10 years	Rate ratio (95% CI) for effect of BCG vaccination after 10 years	VE (95% CI) for the effect of BCG vaccination after 10 years	Effect of BCG vaccination after the first 10 years compared with the first 10 years of ratio of the rate ratios (95% CI)
Native American[5]	0.11 (0.05 to 0.27)	89 (73 to 95)	0.45 (0.26 to 0.77)	55 (23 to 74)	3.93 (1.43 to 10.80)

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Observational studies

Pulmonary tuberculosis

One case–control[62] and one cross-sectional study[178] provided sufficient data to estimate the duration of protection by BCG vaccination against pulmonary tuberculosis (*Figures 107* and *108*). No cohort or case population study provided temporal data for this outcome. Both studies showed evidence of protection against pulmonary tuberculosis during the study follow-up periods. The Nagpur hospital case–control study[62] showed a consistent level of protection beyond 20 years, whereas the Togo children study[177] showed a level of protection varying from high to moderate from 2 to 7 years following vaccination (see *Figure 108*).

Temporal changes in efficacy

We examined the changes in effectiveness over time by estimating the ratio of ORs and RRs per 5 years of follow-up. The annual change in ORs per 5 years for Nagpur Hospital[62] [OR 1.07 (95% CI 0.94 to 1.21)] and in RRs for the Togo children cross-sectional study[177] [RR 1.32 (95% CI 0.76 to 2.32)] both suggested a modest evidence of a decline in protection per 5 years.

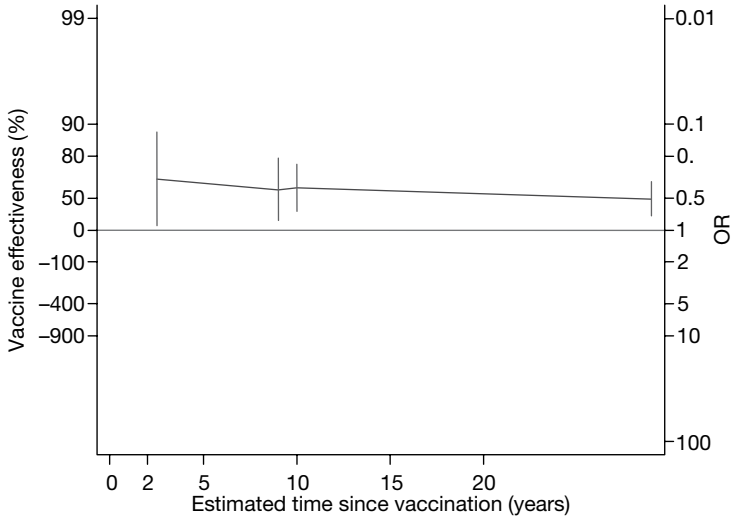

FIGURE 107 Vaccine effectiveness and ORs (with 95% CI) comparing the BCG vaccination status of pulmonary tuberculosis cases and control subjects over time in a case–control study.[62]

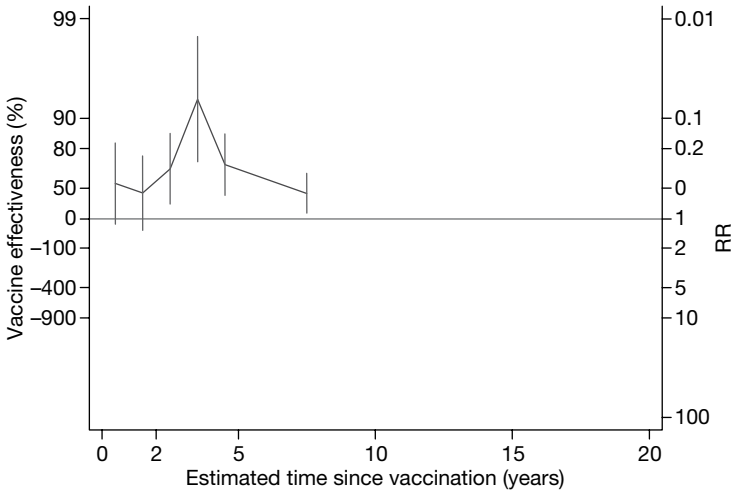

FIGURE 108 Vaccine effectiveness and RRs (with 95% CI) comparing the prevalence of pulmonary tuberculosis among BCG vaccinated individuals with that in unvaccinated individuals over time in a cross-sectional study.[178]

All tuberculosis disease outcomes

Nine case–control studies,[32,33,56,64,65,73,74,76,77] five cohort studies,[6,109,120,121,123] five case population studies[152,153,163,165,167] and three cross-sectional studies[175,186,188] provided sufficient data to investigate the duration of protection afforded by BCG vaccination against all forms of tuberculosis disease (*Figures 109–112*). In the majority of studies, there was evidence of protection during the first 5 years of follow-up, whereas the Bangalore children[56] and Indonesia case–control[73] studies showed no evidence of protection at baseline. In most studies, the protection afforded by BCG vaccination appeared to decline after the first 5 years.

Case–control studies

See *Figure 109*.

Cohort studies

See *Figure 110*.

Case population studies

See *Figure 111*.

Cross-sectional studies

See *Figure 112*.

Temporal changes in efficacy

Data on the change in effectiveness against all tuberculosis morbidity over time were consistent for all observational study types. *Figures 113–116* display these estimated RRRs per 5 years' follow-up (and ORs for case–control studies), showing that on average, the protective effect of BCG vaccination declined over time [summary ratio of ORs for case–control studies 1.59 (95% CI 1.21 to 2.10)], the summary ratio of rate ratios for cohort studies was 1.47 (95% CI 1.10 to 1.98), RRs for case population was 1.59 (95% CI 1.27 to 1.98) and summary RRs for cross-sectional studies [RR 1.29 (95% CI 0.78 to 2.12)].

Case–control studies

See *Figure 113*.

Cohort studies

See *Figure 114*.

Case population studies

See *Figure 115*.

Cross-sectional studies

See *Figure 116*.

Combined meningeal and/or miliary tuberculosis

Figures 117 and *118* show a summary of the ORs, and rate ratios over time for three case–control studies and one case population study which provided data on the duration of protection by BCG vaccination against tuberculosis meningitis. No case–control or case population study provided data for duration for miliary tuberculosis and no cohort or cross-sectional study provided data for duration for meningeal and/or miliary tuberculosis.

None of the case–control studies provided data to assess duration of protection beyond 10 years. Although all three studies[61,62,74] showed evidence of protection against these severe forms of disease at 2 years, only the Nagpur study[62] showed a protective effect at 10 years.

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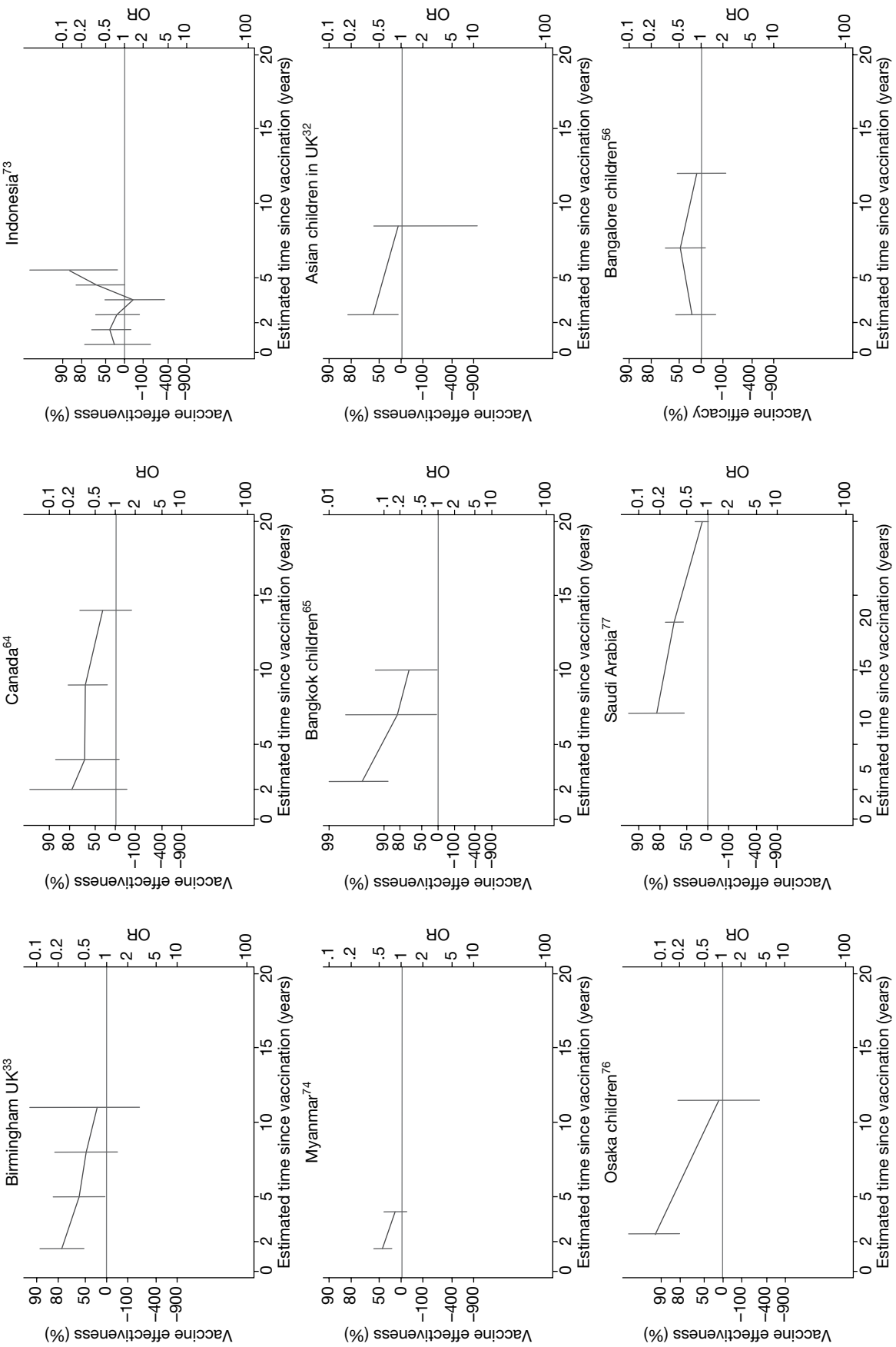

FIGURE 109 Vaccine effectiveness and ORs (with 95% CI) comparing the BCG vaccination status of all tuberculosis morbidity outcomes cases and control subjects over time in case–control studies.

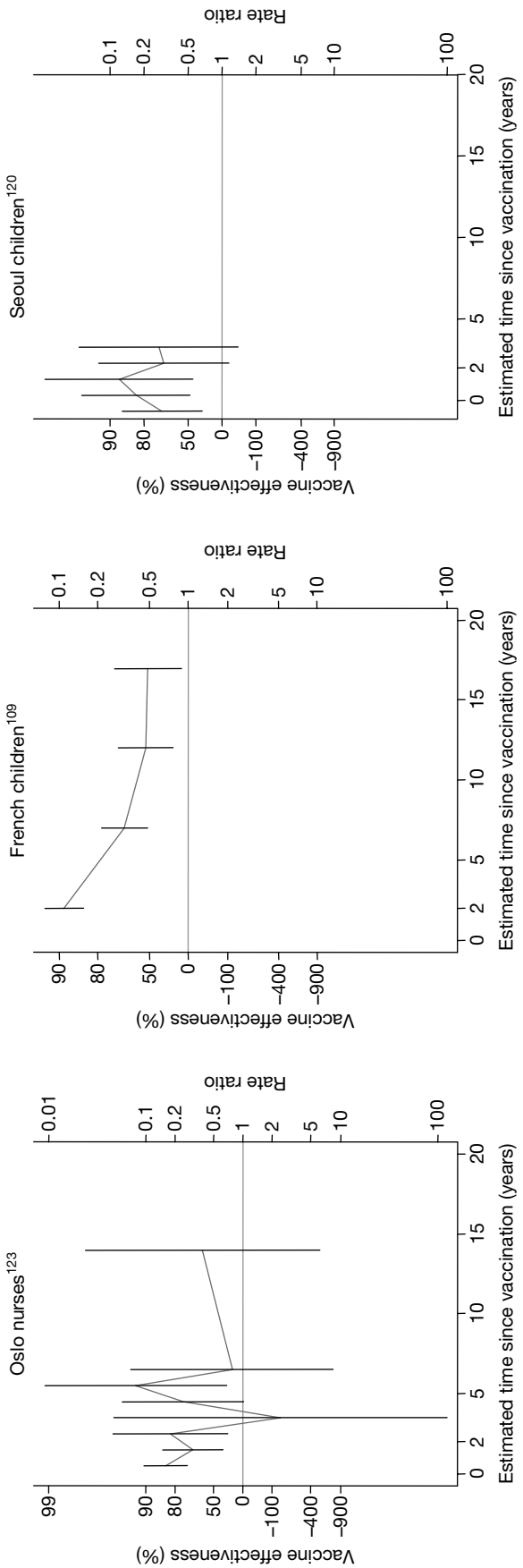

FIGURE 110 Vaccine effectiveness and rate ratios (with 95% CI) comparing the incidence of all tuberculosis morbidity outcomes among BCG vaccinated individuals with that in unvaccinated individuals over time, in cohort studies.

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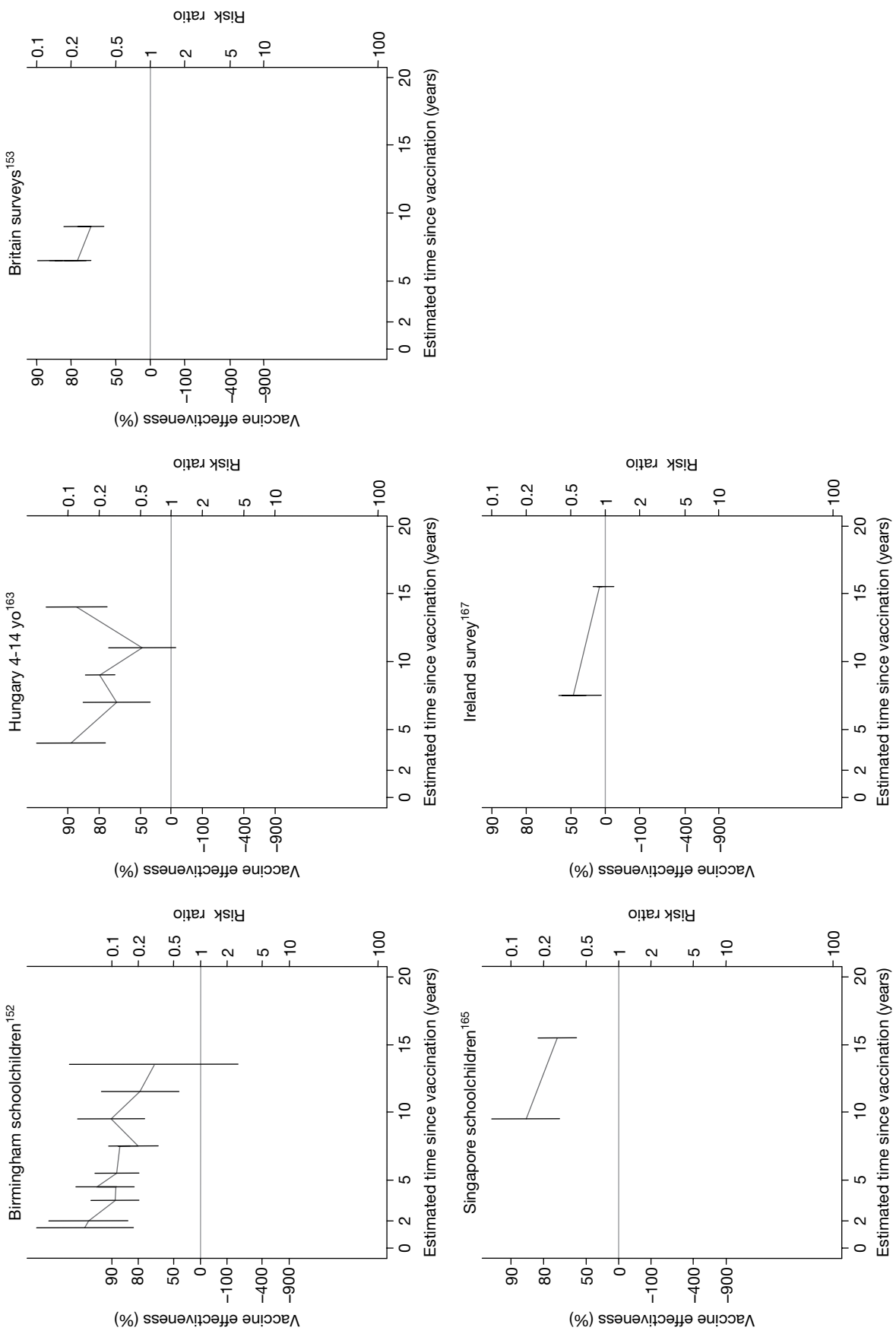

FIGURE 111 Vaccine effectiveness and rate ratios (with 95% CI) comparing the incidence of all tuberculosis morbidity outcomes among BCG vaccinated individuals with that in unvaccinated individuals over time, in case population studies.

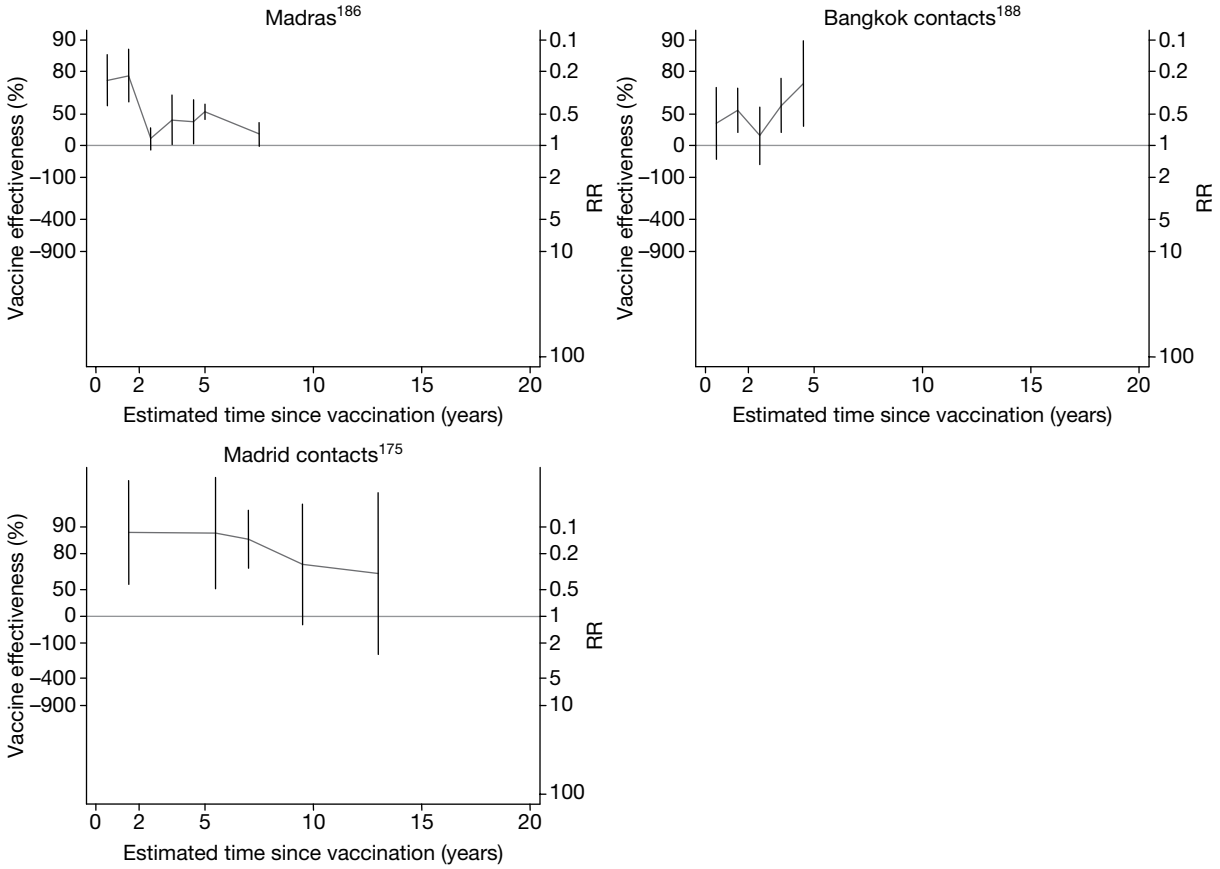

FIGURE 112 Vaccine effectiveness and RRs (with 95% CI) comparing the prevalence of all tuberculosis morbidity outcomes among BCG vaccinated individuals with that in unvaccinated individuals for over time in cross-sectional studies.

Case–control studies

See *Figure 117*.

Case population studies

See *Figure 118*.

Figure 119 shows that on average, the protective effect of BCG vaccination against tuberculosis meningitis declines over time, with a summary ratio of ORs per 5 years' follow-up 1.23 (95% CI 0.68 to 2.23) for case–control studies, whereas the annual change in RR in the Czechoslovakia Meningitis case population[161] study was found to be 0.78 (95% CI 0.03 to 21.09) per 5 years' follow-up.

Extrapulmonary tuberculosis

Only one case–control study[62] provided sufficient data to estimate the duration of protection by BCG vaccination against extrapulmonary tuberculosis (*Figure 120*). This study showed evidence of protection beyond 20 years after vaccination. The study showed modest evidence of a decline in protection with an annual change in the OR of 1.07 (95% CI 0.83 to 1.37) per 5-year follow-up. No cohort, case population or cross-sectional study provided data for duration for extrapulmonary tuberculosis.

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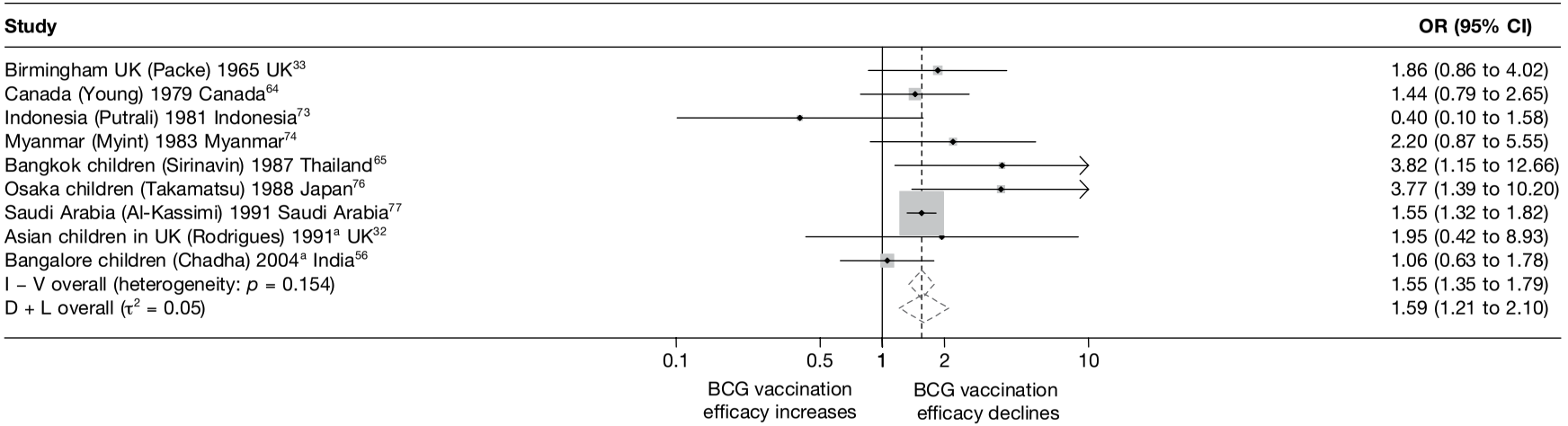

FIGURE 113 Change per 5 years (with 95% CI) in the OR comparing the BCG vaccination status of all tuberculosis outcome cases and control subjects in case–control studies. a, Date of study publication was used if study start date was not available. D+L, DerSimonian and Laird method; I–V, inverse variance method.

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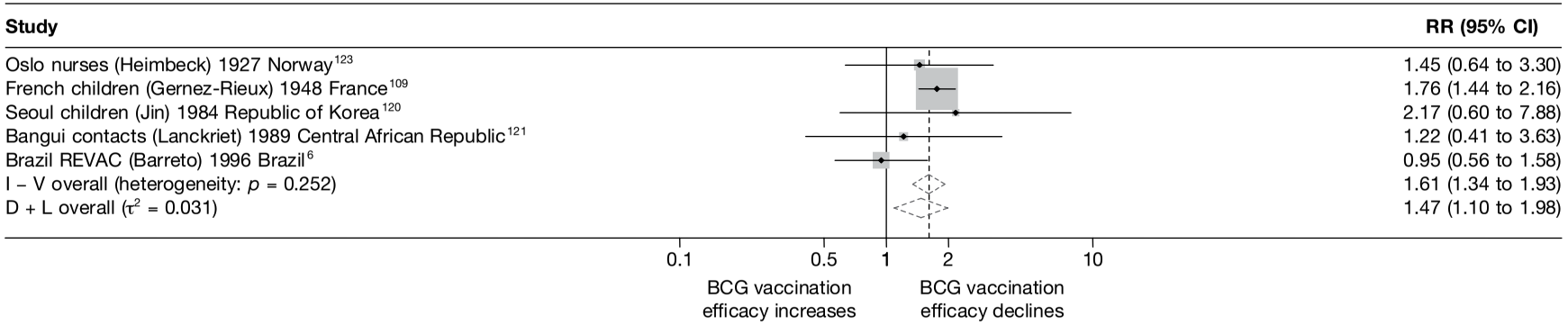

FIGURE 114 Change per 5 years (with 95% CI) in the rate ratio comparing the incidence of all tuberculosis morbidity outcomes among BCG vaccinated individuals with that in unvaccinated individuals in cohort studies. D+L, DerSimonian and Laird method; I–V, inverse variance method.

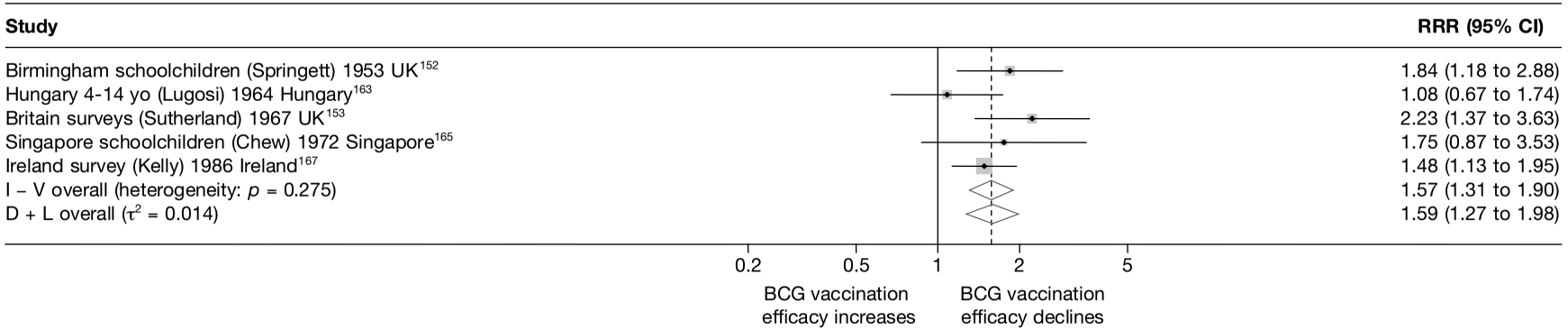

FIGURE 115 Change per 5 years (with 95% CI) in the rate ratio comparing the incidence of all tuberculosis outcomes among BCG vaccinated individuals with that in unvaccinated individuals in case population studies. D+L, DerSimonian and Laird method; I–V, inverse variance method.

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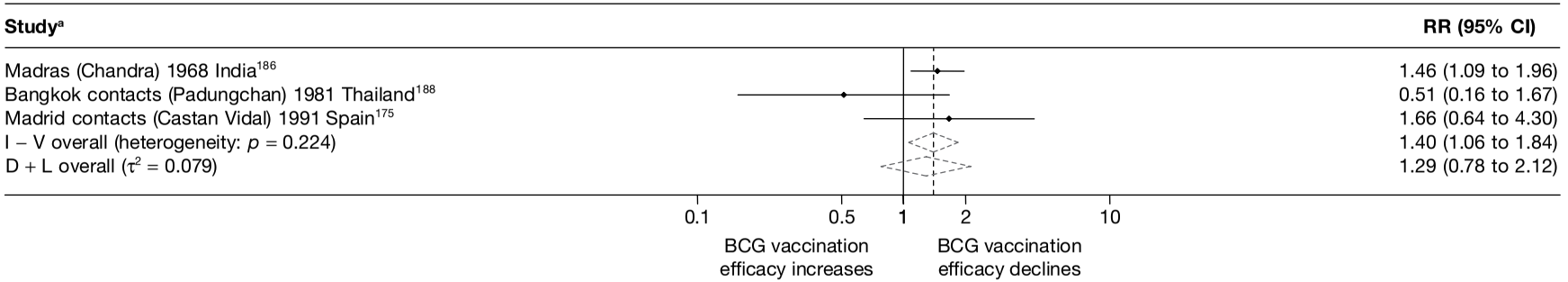

FIGURE 116 Change per 5 years (with 95% CI) in the RR comparing prevalence of all tuberculosis morbidity outcomes among BCG vaccinated individuals with that in unvaccinated individuals over time in cross-sectional studies. a, Date of study publication was used if study start date was not available. D + L, DerSimonian and Laird method; I – V, inverse variance method.

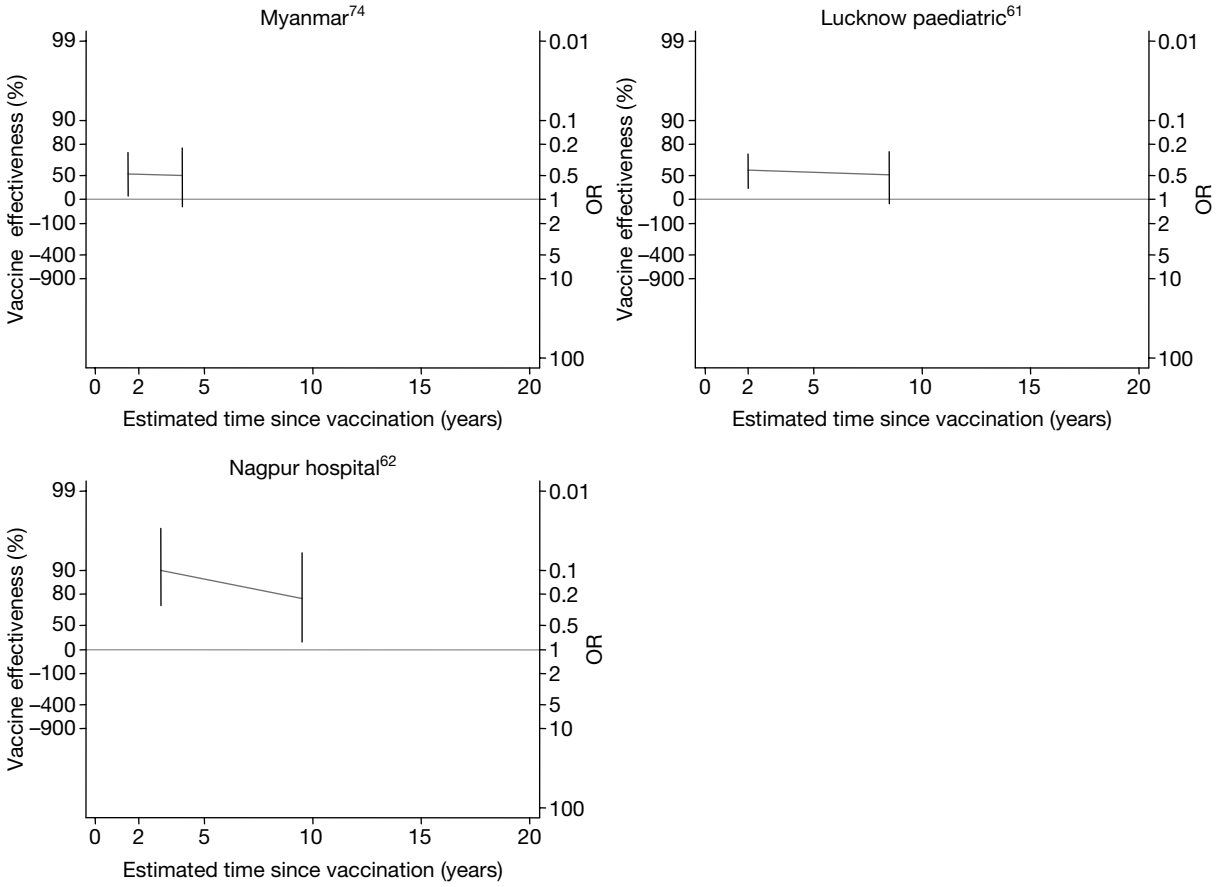

FIGURE 117 Vaccine effectiveness and ORs (with 95% CI) comparing the BCG vaccination status of tuberculosis meningitis cases and control subjects over time, in case–control studies.

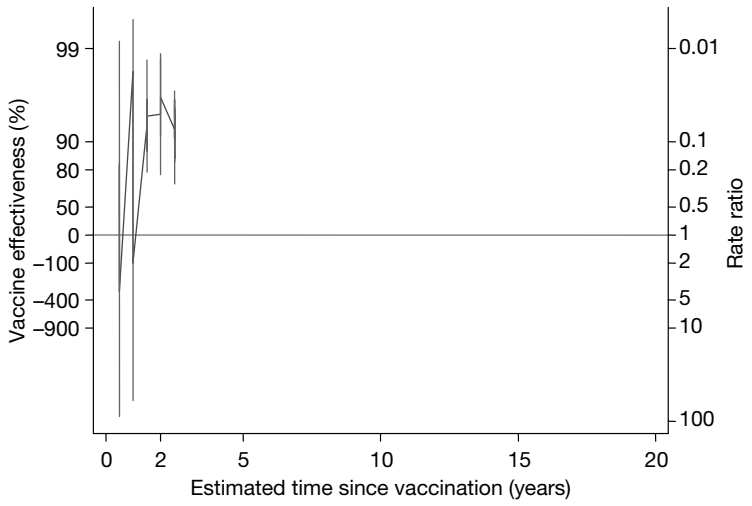

FIGURE 118 Vaccine effectiveness and rate ratios (with 95% CI) comparing the prevalence of tuberculosis meningitis among BCG vaccinated individuals with that in unvaccinated individuals over time, in a case population study.[170]

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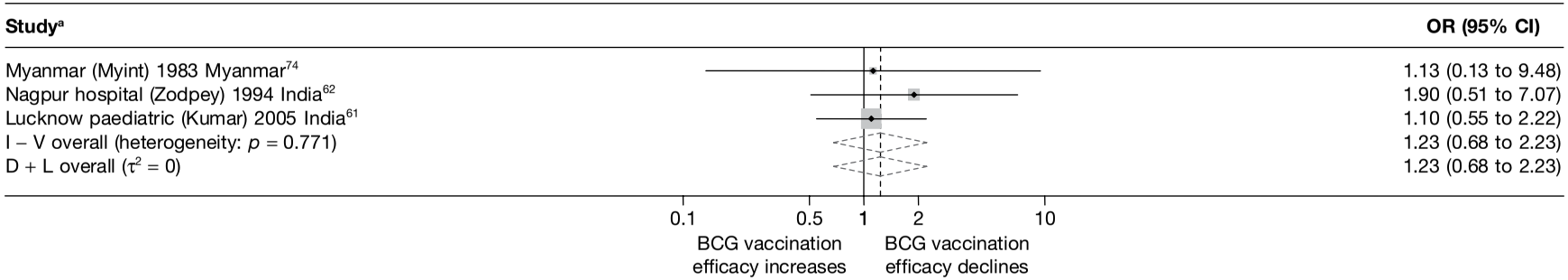

FIGURE 119 Change per 5 years (with 95% CI) in the OR comparing the BCG vaccination status of tuberculosis meningitis cases and control subjects in case–control studies. a, Date of study publication was used if study start date was not available. D+L, DerSimonian and Laird method; I–V, inverse variance method.

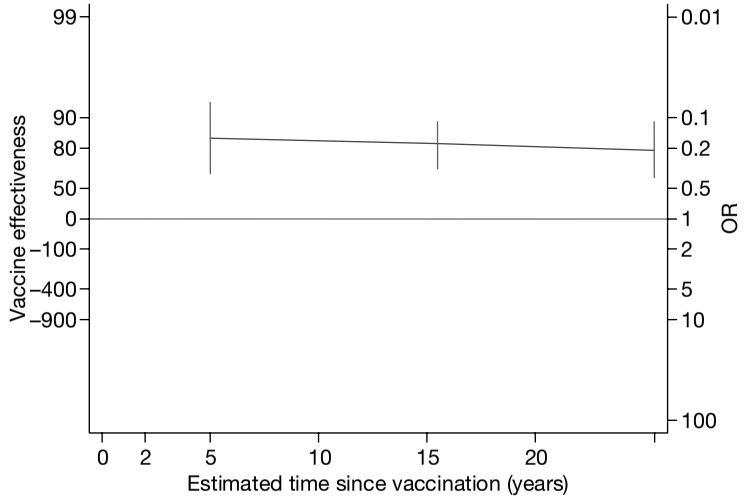

FIGURE 120 Vaccine effectiveness and ORs (with 95% CI) comparing the BCG vaccination status of extrapulmonary tuberculosis cases and control subjects over time in a case–control study.[62]

Case–control studies

Tuberculosis mortality

No observational studies provided data on tuberculosis mortality.

Duration of efficacy after 15 years

Randomised controlled trials

Pulmonary tuberculosis

Six studies[5,15,28,49,53] (see *Figure 89*) provide data on the efficacy of BCG vaccination at and beyond 15 years after vaccination. The Native American study,[5] with the longest follow-up, showed evidence consistent with a strong protective effect against pulmonary tuberculosis up to 20 years after vaccination. None of the other studies showed evidence of a protective effect beyond 15 years.

All tuberculosis disease outcomes

Seven[5,14,15,28,49,53] of the 10 trials[5,13–15,28,48,49,53] providing duration data investigated protection beyond 15 years (see *Figure 98*). The Native American trial,[5] which provided data on 60 years of follow-up after vaccination against any tuberculosis morbidity outcome, showed some evidence of protection beyond 15 years, although this declined to low efficacy levels in later years. The Puerto Rico Children[15] trial also provided evidence of some low levels of efficacy remaining beyond 15 years post vaccination, whereas the other trials did not show evidence of a protective effect beyond 15 years.

Extrapulmonary tuberculosis

Both the Native American[5] and Georgia/Alabama[15] trials investigated the protection afforded by BCG vaccination against non-meningeal and/or miliary forms of extrapulmonary tuberculosis, and both indicated that some efficacy remained beyond 15 years of vaccination.

Tuberculosis mortality

Only the Native American study[5] showed some evidence of BCG vaccination protective effect against tuberculosis mortality 15 years after vaccination; this protection remained constant up to 25 years of follow-up.

Observational studies

Pulmonary tuberculosis

Only one study, the Nagpur case–control[62] study, provided evidence of some protection of BCG vaccination against pulmonary tuberculosis up to and beyond 20 years after vaccination.

All tuberculosis disease outcomes

Of nine case–control studies,[32,33,56,64,65,73,74,76,77] only the Saudi Arabian study[77] investigated evidence for protection beyond 15 years, indicating some protection which declines beyond 20 years after vaccination. Among five cohort studies, the Brazil REVAC[6] and the French children studies[109] were the only studies that investigated protection against all tuberculosis disease outcomes, with both studies showing evidence of protection beyond 15 years. The only case population study (Ireland Survey[167]) investigating the effect of BCG vaccination beyond 15 years did not show a long-term protective effect. No cross-sectional study provided information on duration of BCG vaccination protection beyond 15 years.

None of the observation studies provided data on the duration of protection against meningeal and/or miliary tuberculosis beyond 15 years.

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Extrapulmonary tuberculosis

The Nagpur hospital case–control study[62] showed some evidence of BCG vaccination protection against non-meningeal and/or miliary forms of extrapulmonary tuberculosis beyond 15 years after vaccination.

Chapter 5

Discussion

Bacillus Calmette–Guérin vaccination is recommended by the WHO for infants at risk of tuberculosis and is one of the more widely used vaccines globally. The rationale for this recommendation is based on systematic reviews showing consistent evidence of protection against primary progressive forms of tuberculosis, such as miliary tuberculosis and tuberculosis meningitis.[3,18] Furthermore, economic analyses suggest that this is a cost-effective intervention, especially in high tuberculosis burden countries.[4]

It has long been recognised that the apparent effectiveness of BCG vaccines in protecting against tuberculosis (particularly pulmonary disease) varies considerably between populations, to an extent which cannot be attributed to chance alone. Because of this heterogeneity, single pooled estimates of effect (e.g. Colditz *et al.*[16]) are inappropriate. Several factors have been suggested as contributors to the observed variation in effectiveness. These include causal determinants such as BCG strain,[42] genetic differences in immune response, infecting strain of *M. tuberculosis*, force of infection, sunlight, nutrition, helminths, non-tuberculous mycobacteria[23,206] and indicators that have been explored in order to make inferences as to the causal determinants (e.g. age at vaccination or exposure to mycobacteria, latitude,[23] tuberculin screening, socioeconomic factors or year of study). The extent to which each of these factors might explain variability in the observed effect of BCG vaccination against tuberculosis has been explored in previous reviews, but questions still remain over the relative contribution of these several factors and how they relate to each other.

As the majority of trials and observational studies assessed in this systematic review do not measure potential causal factors such as human genetics, force of infection, infecting strain of mycobacteria or non-tuberculous mycobacteria exposure, this discussion is focused on indicators. The complex relationship between particular indicators (latitude, age at vaccination) and a potential underlying causative factor (exposure to non-tuberculous mycobacteria) is explored in detail. The potential role of strains of BCG vaccine is also discussed. Further analysis of the potential role of other causative factors have been explored in detail in other reviews[207] with the majority of opinion concluding that these factors are not likely explanations for the observed variation in effect.

It is widely assumed that the BCG vaccination does not protect those already infected with *M. tuberculosis*. Several lines of evidence support this view: (1) if antigens of *M. tuberculosis* itself are insufficient to induce a protective response in an infected individual, it is unlikely that related antigens (e.g. of BCG) could induce such a response; (2) there is evidence of increased tuberculosis incidence over a short period after vaccination in some studies, in particular the Chingleput trial,[28] which has been interpreted as the result of BCG vaccination having been given to individuals already infected with *M. tuberculosis*; and (3) animal studies found that prior exposure to *M. tuberculosis* induced an effective resistance against a subsequent challenge with *M. tuberculosis*.[208]

In addition to summarising overall estimates of efficacy/effectiveness and the duration of protection from all published studies, as a function of age, latitude, mycobacterial exposure and BCG strain, this review investigates levels of protection against different clinical forms of tuberculosis (pulmonary, all sites, extrapulmonary, meningeal and miliary tuberculosis).

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In discussing efficacy (in trials) and effectiveness (in observational studies) we use the following arbitrary criteria for describing the magnitude of protection: 'high' ≥ 80%, 'good' 60 to 80%, 'moderate' 40 to 60%, 'low' ≤ 40% (but significantly > 0).

Summary of evidence on efficacy of bacillus Calmette–Guérin vaccination

Pulmonary tuberculosis

The results of all trials taken together show that protection against pulmonary tuberculosis is variable and is, in general, correlated with latitude (higher away from the equator). Protection is also higher when the vaccine is given to infants or to school-age children, with stringent exclusion of those with previous sensitisation to PPD (normally assumed to reflect previous tuberculosis infection) but lower when administered at older ages.

Observational studies also contribute evidence on the effect of BCG vaccination against pulmonary tuberculosis. However, owing to poor reporting of site of disease and study limitations, the best evidence is provided by trials. Although few case–control studies were considered suitable for inclusion in this review, their results were consistent with the observation of the effect of latitude and age at vaccination on the protective effect of BCG vaccination as seen in trials. We included only cohort studies that had stringent exclusion of those sensitised to tuberculin. Among all included cohort studies, there was evidence of good protection by BCG vaccination against pulmonary tuberculosis. Greater protection was found at higher latitude, where BCG vaccination was given to infants and in studies that used a retrospective design.

Extrapulmonary (excluding meningeal and miliary tuberculosis)

Although numbers of cases are in general too small to provide strong evidence, the results of trials suggest that BCG vaccination protection against extrapulmonary tuberculosis (excluding meningeal and miliary tuberculosis) was similar to that against pulmonary disease. It also varied by latitude, age at vaccination and stringency of exclusion on the basis of prior tuberculin sensitivity. The results of individual trials suggest that protection has been high when BCG vaccination was given in infancy or to school-age children following stringent exclusion for prior tuberculosis infection.

Meningeal and miliary tuberculosis

Although there were small numbers of cases of meningeal and miliary tuberculosis in trials, all but one trial indicated a protective effect of BCG vaccination against meningeal and miliary tuberculosis. Among case–control studies, good protection was observed against meningeal and miliary tuberculosis with no statistical evidence of variation by latitude or by age at vaccination. Similarly, cohort studies showed evidence of good to high protection, which did not vary by latitude or age at vaccination. Although the level of protection was uniformly high for cohort studies, retrospective studies found a slightly lower, but still good, protective effect.

All tuberculosis morbidity outcomes

Many of the trials and cohort studies reported only overall tuberculosis outcomes and not results for specific sites of disease. As expected, the observed effect of BCG vaccination on all tuberculosis outcomes was consistent with those on pulmonary and extrapulmonary disease.

Mortality

Very few studies assessing the effect of BCG vaccination met our inclusion criteria. Of included studies, moderate-to-good levels of protection against mortality were observed from both trials and observational studies.

Bacillus Calmette–Guérin strain

Our analysis found that the protective effect of BCG vaccination did not differ by the strain of BCG vaccine used in trials. Further details are provided in the section '*Strain of* Mycobacterium bovis *bacillus Calmette-Guérin in vaccines*', below.

Summary of evidence on duration of protection

We found good evidence from trials and observational studies that BCG vaccination protects against pulmonary and extrapulmonary tuberculosis for up to 10 years, and in two trials (Puerto Rico[15] and Native American trials[5]) beyond 10 years, with one trial (Native American[5]) providing evidence for protective efficacy of up to 52% for all tuberculosis outcomes beyond 15 years. The strength of protection appears to decline with time. Most studies either did not follow up participants for long enough to detect change over time or else have very few cases after 15 years. The absence of evidence from the majority of trials can therefore not be taken as an absence of effect. Similarly, just a few observational studies provide evidence of long protection: two case–control studies (Saudi Arabia[62] and Nagpur in India[77]) and two cohort studies (French Children[6] and Brazil Revaccination[109]) found evidence of protection against all tuberculosis disease after 15 years of 20%, 50% and 50%, 40%, respectively. The protective effect found in the observational studies and the North American Indian trial[5] requires further confirmation.

There is some variation in the rate of decline with time in trials and observational studies. The number of trials with information to enable investigation of the reason behind the decline was small, but the pattern was similar. The rate of decline was greater in studies further away from the equator, in trials conducted among infants, and with the highest level of stringency in exclusion of tuberculin positives. Too few observational studies reported on duration of protection to contribute to the explanation for the variation in the rate of decline.

Efficacy and duration of protection

In summary, this review found that in situations in which BCG vaccination was given only to either infants or to children after stringent exclusion of tuberculin positives, there was evidence of a good protective effect with limited variation by form of disease (although magnitude of protection appeared to be consistently higher for meningeal and miliary tuberculosis than other forms of disease) or study design. Efficacy also seems to vary by latitude, but there were not enough studies to disentangle the effects of prior tuberculin sensitivity, age at vaccination and latitude. Efficacy declined with time, but in five studies there was measurable protection at beyond 15 years after vaccination. The rate of decline varied between populations and studies, and although these trends failed to reach statistical significance, the pattern of decline was consistent with faster decline in latitudes further from the equator and in situations where BCG vaccination was given only to either infants or to children after strict screening for tuberculin sensitivity.

Interpreting the heterogeneity in protection offered by bacillus Calmette–Guérin vaccination

The heterogeneity in protection by BCG vaccination is too large to be explained by chance, as assessed by the tau-squared statistical measure used in this report. Our review of the global literature shows that three factors were particularly associated with the differences in magnitude of protection: age (higher protection when BCG vaccination given in infancy rather than at older ages); stringency of exclusion criteria based on tuberculin testing (higher protection when the

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exclusion was stringent); and latitude (higher protection at higher latitudes, i.e. further from the equator). As has been pointed out in the past, each of these observations is consistent with a hypothesis that BCG vaccination is more effective in an immunologically naive individual or population than in individuals or populations sensitised to mycobacterial antigens. Infants are less likely than older individuals to have been exposed to mycobacteria, stringent exclusion of tuberculin-sensitive individuals ensures that participants are immunologically naive, and there is evidence that environmental mycobacteria are less prevalent further away from the equator.

The hypothesis that exposure to non-tuberculous mycobacterial antigens could influence the observed effectiveness of BCG vaccination was first articulated during the 1960s, by Palmer *et al.*,[209] to explain the striking difference between the low protection observed in trials carried out in southern USA compared with the high protection observed in trials carried out in the UK (it was found that populations in southern USA, where the trials were carried out, have a high prevalence of sensitivity to *M. intracellulare* and other environmental mycobacteria). The hypothesis has been supported by extensive animal and human population studies over the past 50 years.[23,206,210]

We point out below how the observations in this global review are consistent with this hypothesis, and use these data to explore subsidiary mechanistic hypothesis: whether the influence of environmental mycobacteria is mediated through 'blocking' the effect of BCG vaccination (i.e. prior sensitivity somehow prevents BCG vaccination from inducing an appropriate immune response) or 'masking' the effect of BCG vaccination (i.e. exposure to environmental mycobacteria before or after BCG vaccination induces an immune response similar to that induced by BCG vaccination, and against which BCG vaccination can add little).[211]

Why higher protection when bacillus Calmette–Guérin vaccination is given at birth or at school age with stringent sensitivity testing?

Stringent tuberculin sensitivity testing permits the identification of children sensitised by mycobacteria (either tuberculous or non-tuberculous). Children vaccinated in the first year of life are unlikely to have been infected by mycobacteria (either tuberculous or non-tuberculous). Our results appear to suggest that the BCG vaccination will be protective to any child or young adult who is not sensitised (i.e. as long as there is exclusion of tuberculin-sensitive children). Although many trials and cohort studies did undertake tuberculin skin testing, there was considerable variation in the concentration of PPD used and of the cut-off point considered for exclusion. Our criterion of 'stringent' testing, which is based on two-stage testing with retesting of initial non-reactors with a stronger dose of tuberculin, should exclude children previously sensitised with *M. tuberculosis*. It is, nevertheless, possible that the criteria to declare a person previously infected have not always been sensitive enough.

Our stringent criteria should also exclude children previously sensitised with most species of non-tuberculous (sometimes called 'environmental' or 'atypical') mycobacteria. Evidence from a variety of approaches supports the role of exposure to non-tuberculous mycobacteria in explaining the observed variation in protection. First, animal studies show less protection by BCG vaccination in guinea pigs previously exposed to non-tuberculous mycobacteria.[209] Second, there is likely to be differential exposure to non-tuberculous mycobacteria in different settings, and this would explain the latitude gradient in protection.[23,211,212] Third, follow-up of more than 1 million US naval personnel showed that tuberculosis incidence was lowest in the group who were sensitive to *M. intracellulare* or *M. gaussi* antigens, but not to *M. tuberculosis* antigens.[210] Fourth, several studies have shown a J-shaped relationship between tuberculin reactivity and subsequent risk of tuberculosis, with lowest risk among individuals with low (around 5 mm) levels of tuberculin reactivity, an observation which has been interpreted as evidence that individuals with some non-specific mycobacterial sensitivity are at lowest risk of tuberculosis. Finally, data

from randomised controlled studies in the UK and Malawi, comparing the whole-blood PPD and delayed-type hypersensitivity response to PPD before and after BCG vaccination in infants, suggest that differential sensitisation due to exposure to environmental mycobacteria is the most important determinant of the observed differences in immunogenicity[213] (although the study did not explore differences on actual protection). It is important to note that the immunological response induced by different mycobacteria is likely to differ.[208]

Prior sensitisation to mycobacteria and non-tuberculous mycobacteria provides an explanation for the lack of protective effect observed in the Chingleput study,[28] where the majority of cases of active tuberculosis arose among tuberculin-sensitive adults.

This review has found consistent evidence of protection when BCG vaccination is given to infants and to school-age children with stringent sensitivity testing. The issue of infant vaccination overlaps with previous tuberculin sensitivity as, by definition, most infants would not be tuberculin skin test positive. The data were less consistent for the effect of BCG vaccination given at other ages and/or all age groups. Nevertheless, the observation that BCG vaccination, when given in infancy and school age, was protective against pulmonary tuberculosis calls for further research into what is the optimum stringency of tuberculin skin testing to identify adults who will be protected by BCG vaccination in these other age groups.

Taken together, these observations suggest that BCG vaccination works well, even against pulmonary disease, as well as in adolescents, as long as they are not sensitised to mycobacteria (tuberculous or non-tuberculous mycobacteria) prior to BCG vaccination. Prior sensitisation, at least in part, explains the variable reduction in protective efficacy against pulmonary tuberculosis.

Latitude: is this the same effect as that of age and stringency?

The findings of this review confirm that the latitude of the study explains a substantial element of the observed heterogeneity in protection against pulmonary disease irrespective of study type. The observation in this review that studies conducted at latitudes closer to the equator show lower levels of protection than studies conducted at more distant latitudes (mainly northern locations presumably with lower exposure to non-tuberculous mycobacteria) is also consistent with the explanation that exposure to non-tuberculous mycobacteria may explain at least a part of the differences between studies. We did not have a sufficient number of studies to separate the effect of age at vaccination/prior sensitisation from that of study latitude.

Blocking compared with masking

Two non-mutually exclusive hypotheses potentially explain the effect of exposure to tuberculous and non-tuberculous mycobacteria on the observed effect of BCG vaccination. First, previous exposure to mycobacteria might lead to lower efficacy (blocking) because the study population is already sensitised to mycobacteria, and this somehow hampers BCG vaccination from causing immunity. In a sense, this is an extension of the assumption that BCG vaccination does not protect those already infected with *M. tuberculosis*, but extends it to those already sensitised with either *M. tuberculosis* or various species of non-tuberculous mycobacteria, and thus there is a need for stringent criteria to define sensitisation. For blocking, exposure to mycobacteria after vaccination is irrelevant. Our data suggest that blocking may be an important determinant behind the variation in protection against pulmonary disease.

The second proposed mechanism, masking, proposes that exposure to mycobacteria provides protection, and continuing exposure following vaccination leads to a gradual reduction in the observed effect of BCG vaccination through increased protection caused by exposure to mycobacteria of unvaccinated participants (masking). The exact mechanism is likely to vary depending on the kind of mycobacteria (and other microbes that share antigens with them) and

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exposure levels (doses, routes) that all differ greatly between populations. Heterologous exposure/sensitisation is unlikely to be a simple all-or-none affair. An important consideration is whether or not the protection imparted by such heterologous exposure works by similar mechanisms/pathways as BCG vaccination does.[214] We will return to masking when discussing reduction in efficacy with time.

Strain of *Mycobacterium bovis bacillus Calmette–Guérin* in vaccines

Several previous reports have attributed variation in the results of trials to genetic differences in BCG vaccines. Two studies[215,216] reported differences in the effect of two different strains of BCG (Paris and Glaxo vaccines), albeit in different directions. Others have argued that manufacturers may have selected strains over time to lower adverse effects, thereby inadvertently selecting less effective strains, although the latitude of the location of the evaluation studies largely explains the observed differences.

It has long been known that the there are genetic differences between BCG vaccines.[217] Behr and Small[43] showed, using restriction fragment length polymorphism typing, that BCG strains have undergone evolution since 1921. For example, the region of difference 2 (RD2) marker is absent in strains derived after 1925 (i.e. in Pasteur-1173 P2, Copenhagen-1331 and Glaxo-1077) and present in derivatives of the earlier Pasteur BCG strains (i.e. Brazilian/Moreau strain, Tokyo-172 and Russian substrains), and all strains of BCG lack region of difference 1 (RD1) genes. However, Kozak and Behr[218] have shown, using animal models, that the loss of RD2 in vaccine strains lowered immunogenicity but not protection against pulmonary tuberculosis. Another study compared the whole genomes of 13 BCG strains and found six large sequence polymorphisms affecting genes that encode known virulence factors.[219] More recently, Brosch *et al.*[41] used genome sequencing to postulate that 'early' BCG vaccines (those derived before 1930 or 1940) may be superior to more recent and widely used variants.[41] They identified tandem duplications, known as DU1 and DU2, which differ between BCG strains. Only BCG Pasteur contains a copy of DU1, whereas other strains include variants of DU1, with older strains (e.g. BCG Russia, Moreau and Japan) having DU2-I. Newer strains, such as BCG Danish/Prague and BCG Tice/Phipps, include DU2-III and DU2-IV variants, respectively. The hypothesis proposed is that repeated passage has led to the loss of immunogenicity in the newer strains of BCG. The analysis presented by Brosch *et al.*[41] supports the view that genetic differences may explain the observed variation in protection, although data were presented only to support differences in gene expression levels and immunogenicity. Furthermore, Brosch *et al.*[41] postulate that, after 1925, the strain initially distributed (such as BCG Japan) was replaced by another derivative that is possibly less virulent or reactogenic. As none of the trials was conducted with this earlier strain, the variation in protection observed is not related to the original replacement. Indeed, another study, which used a guinea pig model to compare early strain BCG Japanese and evolutionarily late strains, such as those in DU2 group III (BCG Danish and Glaxo) and group IV (BCG Connaught, Pasteur, and Tice), found no significant difference in protection against *M. tuberculosis* challenge.[220]

Our review fails to find evidence that BCG strain is a significant contributor to variation. Furthermore, the distribution of efficacy estimates from trials was not correlated with specific types/groups of vaccines determined using the evolutionary tree postulated by Brosch *et al.*[41] Our result supports a previous systematic review, which reached the view that strain variation is not behind the variation in protection against pulmonary disease.[17] Further support for our conclusion can be found in the UK MRC trial,[14] which found equivalent protection from the Copenhagen strain of BCG and an *Mycobacterium microti*-derived vaccine (vole bacillus).[21]

The Chingleput study

Throughout this report, the results of the Chingleput study[28] have stood out in comparison with the other trials. The reasons for the observed increase in tuberculosis among vaccinated

compared with unvaccinated individuals during the first few years after vaccination have been explored in detail in previous reports.[22] In brief, the majority of cases during this period occurred in tuberculin-sensitive adults suggesting an abnormal reaction to BCG vaccination. The data from this study suggest a complex interaction of age and time effects. Further analysis of data from the Chingleput study[28], restricted to those with a tuberculin skin reaction of < 8 mm, suggested that BCG vaccination did provide protection to children of < 15 years of age, but no protection for subjects ≥ 15 years old, and may even have imparted negative protection among these older individuals.[22,221]

Summing up the evidence for variation

It is likely that more than one factor plays a role in explaining the observed differences. Meta-regression analysis indicates that latitude and age at vaccination are the key factors that explain the observed variation in effect between studies. Studies conducted in latitudes further away from the equator and/or where the vaccine was given to naive individuals (either infants or children who had stringent tuberculin sensitivity testing prior to enrolment) were therefore most likely to detect an appreciable protective effect.

Duration

Why lower (or even negative) protection in the first 5 years after bacillus Calmette–Guérin vaccination in some trials?

There is evidence that BCG vaccination is not protective when given to children already infected with *M. tuberculosis*. Our results suggest that in trials of subjects of all ages, without stringent sensitivity testing, there is an increase in rates of active tuberculosis in the first 5 years, and excluding the first years of each study leads to a greater protective efficacy, which supports this hypothesis.[22] In particular, a review by Fine[23] explores the reasons for the harm observed in the first 5 years of the Chingleput study.[28] The majority of cases of active tuberculosis arose among tuberculin-sensitive adults. Indeed, further analysis suggests that BCG vaccination might have been protective in tuberculin skin test-negative children.[22,221]

How long can bacillus Calmette–Guérin vaccination protect?

This review provides the most comprehensive analysis to date of studies on the duration of protection by BCG vaccination. This, in part, has informed cost-effectiveness analysis underlying vaccination policy [National Institute for Health and Care Excellence (NICE)].

Previous systematic reviews[7,23] have noted the absence of evidence of any protection by BCG vaccination beyond 15 years after vaccination, based on a limited number of studies. The failure to observe longer-term protection in trials may be related to small numbers as the study population ages, including overall small numbers in the intervention and control groups as well as declining number of individuals who might be exposed to tuberculosis; coincidental fall in tuberculosis incidence in many countries, leading to a lower probability of subsequent exposure; or perhaps because protection is mainly against primary progressive disease and not against reactivation at a later age.

As further data accumulate, mainly from observational studies but also from trials, evidence is emerging showing that BCG vaccination protection can last for much longer periods. A question therefore exists about what might be behind the loss of protection with time.

Reasons behind the loss of protection with time

There is consistent evidence of a decline in protection from all study designs examined and across disease outcome types. Decreasing protection with time may reflect true deterioration due to

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a waning immune memory or it may arise from exposure to mycobacteria giving protection to the unvaccinated subjects such that, with time, the 'apparent' protection measured by comparing vaccinated and unvaccinated subjects decreases ('masking').

There were too few studies examining duration of protection for the majority of tuberculosis outcomes reviewed here to investigate the factors associated with the apparent variation in effect. Trials examining all tuberculosis outcomes provided the largest group of studies. Meta-regression analysis of the characteristics of these trials suggests that latitude and the composite variable 'age at vaccination and/or prior tuberculin skin testing' explained the majority of the observed variation.

The waning in protective effect against pulmonary disease was more marked when BCG vaccination was given to individuals not previously sensitised, which could reflect a progressive erosion of the naiveté of the vaccinated and unvaccinated populations over time due to exposure to mycobacteria. Although not explicitly proven with measurements of tuberculin sensitivity in the studies described in this report, the observed effects of latitude, tuberculin sensitivity screening and age at vaccination on the effectiveness of BCG vaccination leads us to this conclusion. This is consistent with the masking mechanism. The waning was more marked away from the equator, where the prevalence of non-tuberculous mycobacteria is presumed to be lower. However, this is at least in part explained by the lower initial efficacy observed in trials closer to the equator.

Strengths and limitations of the review

Limited number of trials and studies

Although we reviewed 132 studies, and we identified a clear pattern behind the variation in protection against pulmonary disease, we did not have enough studies with sufficient data to explore separately the effect of exclusion of sensitised subjects (by neonatal vaccination or stringent tuberculin sensitivity testing) and the effect of latitude. The small number of studies in each study design limited the usefulness of the evidence they provided.

Comprehensive search but many trials/studies had limited information about sensitivity testing, selection of control subjects and case definition

We undertook a comprehensive search of the literature and screened a large number of papers with no language restrictions, therefore reducing the probability of bias. Nevertheless, it is possible that we have missed some studies. In addition, due to views about the efficacy of BCG vaccination based on the results of trials in the UK, it is possible that studies with a negative effect have had a lower probability of being submitted or published in Europe. In the USA, where BCG vaccination has not been recommended owing to the negative results of trials, there might be a publication bias favouring negative studies. This is unlikely to be a major factor, but we have not formally tested for publication bias.

Although we reviewed a large number of studies, many were quite old and published before a clear understanding of comprehensive reporting or format of reporting were agreed. Many of the studies do not report information now recognised to be important (e.g. concentration of the PPD used, or cut-off point used to define a positive TST) and this limited the usefulness of the data they provided for analysis of the reasons behind variation of protection, or variation in the rate of decline of protection. This was regrettable, as analysis of the trials and observational studies that did provide that information suggests that this alone, or maybe in conjunction with latitude, may explain the majority of the variation of BCG vaccination protection.

For all objectives, insufficient data points limited our ability to undertake important subgroup analyses, for example on protection in HIV-infected populations, which are an increasingly important global concern.

Study design/quality

Owing to the limited number of trials available, we included evidence from observational studies in several areas. This was mainly important for meningeal and miliary tuberculosis, as these outcomes are relatively rare and thus uncommon in trials but were reported in case–control studies. Although we have used meta-regression analysis to attempt to explain the observed variation in the effect of BCG vaccination, it is important to acknowledge that meta-regression, especially of observational studies, is still subject to the underlying biases affecting each study design. Furthermore, meta-regression is akin to an ecological analysis treating each study as the unit of observation. Nevertheless, this approach has allowed us, for the first time, to explore the effects of numerous factors and adjust for the relative effect of other variables in the same model.

Randomised controlled trials provide the best evidence for the effectiveness of any intervention. Unfortunately, data from trials investigating BCG vaccination efficacy are limited largely by the fact that most were conducted decades prior to the development of robust standard methods for RCTs. Therefore, it is not surprising that they are subject to several potential biases, and some failed to report essential information, for example on the strength of PPD used for tuberculin sensitivity testing. Nevertheless, the data reviewed provide good trial-based evidence of efficacy against miliary tuberculosis, tuberculous meningitis, pulmonary tuberculosis and mortality. The data from observational studies are also consistent with a protection by BCG vaccination against forms of disease. Retrospective cohort studies appear to show a greater protective effect than prospective studies for some outcomes (e.g. pulmonary tuberculosis), although both types of studies were associated with a beneficial effect.

A previous appraisal by Clemens *et al.*[40] provided a framework for our assessment of trial quality. Following careful consideration, we abstracted the quality criteria outlined in this review but a priori selected one criterion – blinding of study staff who assessed outcome on BCG vaccination status or the use of active surveillance – to inform our judgement about quality in the statistical models. Based on these criteria, which we described as diagnostic detection bias, studies with a lower risk of bias had a more significant protective effect compared with those with a higher risk of bias. This is contrary to the usual pattern in which biased studies are generally associated with an exaggeration of effect size.

Although we provided the duration of each trial and how protection varied during the follow-up, in our analysis of the reasons for variation in protective efficacy between studies, we used the average protection over the duration of follow-up and did not include study duration as a covariate. This, inappropriately, averages the effect size over different durations, likely underestimating efficacy as protection declines with time. Nevertheless, the identification of the same covariates as the main drivers of variation in the analysis of protection duration suggests that the analysis of effectiveness is valid.

Our interpretation

From this meta-analysis, of the alternative explanations for variations in BCG vaccination protection, we have concluded that BCG strain is not relevant. We did not, however, explore human genetic differences, genotypic differences between infecting mycobacteria or a variety of other explanations proposed for the variation in protection by latitude, such as differences in exposure to UV light (owing to its mycobacterial killing effect), levels of vitamin D,

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helminthic infestation and the effect of poor nutrition on immune response. Previous reviews have concluded that these factors are less plausible explanations for the observed variation in protection.[207] Furthermore, although this review did not set out to confirm or refute these potential explanations, our comprehensive search of the literature found no evidence to support any of these, whereas the combination of age at vaccination, stringency of testing and latitude explained a large proportion of the variation. Previous reviews did not explore stringency of tuberculin skin testing in detail.

It is likely that more than one factor plays a role in explaining the observed differences. We carried out meta-regression analysis on the data available, which was limited, from many studies. With all its limitations, the analysis demonstrated that young age at BCG vaccination, with stringent testing and exclusion, provides consistently high protection even for pulmonary disease, and that variations in age at vaccination, stringency of tuberculin skin testing and latitude are the key factors explaining most of the variation in the observed effectiveness of BCG vaccination between studies.

Studies conducted at latitudes closer to the equator and/or those with less stringent tuberculin sensitivity testing prior to enrolment were therefore likely to have failed to detect a significant protective effect due to the effect of prior infection with *M. tuberculosis* or non-tuberculous mycobacteria. This failure to detect an effect is not necessarily a failure of the study design, as vaccines are known not to provide protection under certain circumstances. Prior infection may block BCG vaccination by the induction of an ineffective immune response that impairs induction of an adequate immune response after subsequent BCG vaccination.

When examining duration of protection we present additional evidence that BCG vaccination can provide longer duration than previously described. While there is clear evidence of variation in the waning in protection, factors that might explain the observed variation in the rate of decline are less clear (there are not enough studies to provide strong evidence but there is some suggestion that waning is faster in studies where initial protection was higher, and that the same factors associated with high protection are associated with fast waning). However, it is worth acknowledging that a decline is more likely where the initial level of protection is high because there is less room for a decline in settings where there is no protection in the first place. The number of studies with sufficient data both on efficacy at different time periods and stringency of testing, however, is limited; thus the evidence is only suggestive.

Chapter 6

Conclusions

Summary

This review extends the evidence from clinical trials and observational studies that BCG vaccines provide protection against tuberculosis. The apparent effectiveness of BCG vaccines in protecting against tuberculosis varies considerably between populations, to an extent that cannot be attributed to chance alone. Latitude, age at which the vaccine was given and pre-vaccination tuberculin sensitivity status were the factors that explained most of the observed variation. There was no evidence that other factors, such as BCG vaccine strain, explain the observed variation. BCG vaccination appears to work best when given to naive individuals, and these individuals are compared with naive unvaccinated individuals.

Our results suggest that there is good evidence that BCG vaccination protects against pulmonary and extrapulmonary tuberculosis for up to 10 years. The strength of protection appears to decline with time. Data on protection beyond 15 years are limited. Most studies either do not follow up participants for long enough, or have very few cases after 10 years. The only trial which has now followed up participants for several decades suggests that BCG vaccination may protect against tuberculosis beyond 15 years.[5] The absence of evidence from the majority of trials should therefore not be taken as an absence of effect.

Recommendations for research

This review provides a comprehensive and up-to-date summary of evidence on the duration of protection by BCG vaccination, and identifies the fundamental dependency of BCG vaccination efficacy on tuberculin sensitivity at vaccination. While this review does not address all pending issues about BCG vaccination, it does permit the rephrasing some of the old controversies regarding why protection from BCG vaccine varies in terms of tuberculin sensitivity status before BCG vaccination, using stringent criteria.

For bacillus Calmette–Guérin research

1. Further research into the duration of protection conferred by BCG vaccination would be useful to inform future vaccination policy. We would recommend a case–control study taking into account PPD status of participants at vaccination, as this approach is likely to be cheaper and provide results in the least amount of time.
2. Further research into the effectiveness of BCG vaccination in those > 35 years of age should be carried out.
3. Studies should investigate the role of stringent tuberculin skin testing in the protective effect of BCG vaccination.
4. The issues of whether BCG vaccination protects individuals from acquiring tuberculosis infection and its role in preventing tuberculosis arising from reactivation and re-infection are also areas where there is a need for further knowledge. Our understanding of BCG vaccines and the global effort to develop new vaccines will be enhanced by greater clarity on these aspects of tuberculosis pathogenesis.

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5. Although the effect of repeated BCG vaccination appears to be limited,[26,222] given the variation in the effect of the first dose of BCG vaccine, replication of these findings in other settings will be useful. This is supported by the variable results demonstrated in observational studies (albeit of poor quality) from Eastern Europe[112,223] and Venezuela,[224] as well as data from the effect of BCG revaccination on leprosy.[222] The fact that BCG revaccination did enhance protection against leprosy, although not against tuberculosis, in Malawi indicates that, under some circumstances, a second BCG vaccination can have a beneficial immunological effect, although it may not be sufficient to enhance observable protection against tuberculosis.[24] Ideally, replication of the Brazil REVAC[6] study in other settings to see whether similar or different results would be obtained in different environments may also be beneficial.
6. There is some recent evidence, based on a positive interferon-gamma release assay as a proxy for latent tuberculosis infection, that suggests that BCG vaccination may protect against tuberculosis infection.[225–227] One study,[228] however, found no protective effect of BCG vaccination against infection in a school outbreak. If further work confirms that BCG vaccination can protect against infection, at least under some circumstances, this may explain the observation in this review that BCG vaccination provides a beneficial effect against both pulmonary and extrapulmonary tuberculosis. This review did not specifically examine the evidence for protection against *M. tuberculosis* infection.
7. A recent study also suggested that previous BCG vaccination (as determined by a scar) may improve sputum conversion rates after 2 months of treatment.[229] If this is confirmed in subsequent studies, it may imply a form of protective immunity that potentially influences the clinical course, even in those who succumb to tuberculosis disease.
8. Our analysis shows that BCG vaccination given to adults may provide some protection which is important in the era of HIV infection and multidrug resistance; however, data are limited. Further research on this subject, perhaps using occupational health cohorts or a case–control study, may shed more light and inform future policy.

For new vaccines against tuberculosis

1. Given the limited protection conferred by BCG vaccination against post primary adult pulmonary disease, new tuberculosis vaccines against these forms of disease are of high priority.
2. BCG vaccination appears to offer little or no protection to those previously infected with *M. tuberculosis*. Vaccines that are effective in this group ('post-exposure vaccines') should be a priority for research. Among the problems is the appropriateness of animal models for the assessment of vaccine effects against reactivation disease.
3. Future studies need to take into account the observation from this review that prior tuberculin sensitivity is a key determinant of whether a trial shows significant evidence of protection by BCG vaccination. This is particularly pertinent as most trials of new vaccines will be undertaken in high tuberculosis incidence countries that also have a high burden of non-tuberculous mycobacterial infection.
4. Investigating the mechanism behind the failure of BCG vaccination to protect previous sensitised individuals will provide useful information for the development of new vaccines against tuberculosis. This should be assessed for different non-tuberculous mycobacteria, prior BCG vaccination and tuberculosis exposure.
5. Future research should also investigate whether the efficacy of new vaccines differ depending on the predominant strain of *M. tuberculosis* circulating in the population, as well as the interaction between the predominant circulating strains of *M. tuberculosis* and human genetic polymorphisms that affect susceptibility to tuberculosis. There is also a need for studies in HIV-infected individuals.

For further research to inform UK vaccination programme

With regard to duration of protection from BCG vaccination, this review confirmed previous observations that BCG vaccination protects against tuberculosis for at least 10 years. There is also some evidence that BCG vaccination might protect beyond 15 years after vaccination. Unfortunately, this was observed in a limited number of studies owing to the lack of long-term follow-up or dwindling of the number of participants, as well as secular downward trends in tuberculosis incidence in the populations where the studies were undertaken. In the UK, a substantial part of the programme is aimed at protecting children against severe (miliary and meningeal) tuberculosis and so infants in high-risk groups are vaccinated. However, most tuberculosis occurs in adults. Further research is therefore needed to update estimates of duration of protection and to inform sensitivity criteria in the cost-effectiveness analysis of BCG vaccination policy.

Questions remain about the effect of BCG vaccination among adults > 35 years of age. Only two trials provide data on the efficacy of BCG vaccination in adults > 35 years of age (Madanapalle[53] and Chingleput[28]), both showing no significant protective effect, in two populations very different from the UK population. This issue is important because national guidelines currently limit the use of BCG vaccination to < 35 years of age, except in certain occupational groups. The limited evidence from this review showing a protective effect against pulmonary tuberculosis, if given to immunologically naive individuals, has implications for the vaccination of older individuals.

The most important consideration internationally is whether BCG vaccination protects against adult pulmonary disease. This review shows evidence of protection against pulmonary tuberculosis under certain conditions, although with considerable variation between different studies and limited data on protection in adults.

Implications for UK vaccination programme and practice

In addition to the research recommendations outlined above, further work is required:

- The economic analysis to inform the tuberculosis incidence threshold at which universal BCG vaccination becomes cost-effective should be re-examined if further evidence emerges that BCG vaccination protects for longer than 15 years.
- Outline whether all individuals should be tested to identify those likely to benefit from BCG vaccination, especially with the increased use of interferon-gamma release assays for contact investigation. To date, the rationale for tuberculin sensitivity testing prior to giving BCG vaccinations in the UK has been phrased largely with reference to concerns about increased local reactions when giving BCG vaccinations to already sensitised individuals.

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Professor Ibrahim Abubakar (Consultant Epidemiologist and Head of Section) was the principal investigator of the project; he contributed to the design of the project, oversaw publication screening and data extraction, and undertook the write-up of the report.

Ms Laura Pimpin (Scientist, Epidemiology) conducted publication retrieval and screening, data extraction, overseeing of screening and data extraction of non-English publications by translators, write-up of the report and preparation of the report for publication.

Mr Cono Ariti (Lecturer in Medical Statistics) conducted the analysis of all data, and preparation of figures and tables for publication.

Ms Rebecca Beynon (Research Associate) conducted publication retrieval and screening, data extraction and participated in the write-up and review of the report.

Dr Punam Mangtani (Clinical Senior Lecturer in Epidemiology) contributed to the design of the project, oversaw publication screening and data extraction, and participated in the write-up and review of the report.

Professor Jonathan AC Sterne (Professor of Medical Statistics and Epidemiology) contributed to the design of the project, oversaw data analysis, and participated in the write-up and review of the report.

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Appendix 1

Search strategy

The search strategies for all databases and websites consulted are detailed below.

MEDLINE

Database: MEDLINE Ovid 1950 to present

1. exp Tuberculosis/ (131,795)
2. tb.tw. (14038)
3. tuberculous.tw. (20,272)
4. tuberculos$2.tw. (106,603)
5. tubercular.tw. (1989)
6. phthisis.tw. (552)
7. tuberculoma$1.tw. (1796)
8. pott$ disease.tw. (526)
9. tuberculid$1.tw. (230)
10. scrofuloderma$1.tw. (135)
11. scrofula$1.tw. (88)
12. Mycobacterium bovis/ (7156)
13. Mycobacterium tuberculosis/ (26,004)
14. tubercle bacill$.tw. (3059)
15. mycobacterium africanum.tw. (96)
16. mycobacterium microti.tw. (105)
17. mycobacterium canetti.tw. (3)
18. mycobacterium bovis.tw. (3937)
19. or/1-18 (169,014)
20. BCG Vaccine/ (14,856)
21. BCG.tw. (15,276)
22. (bacill$ adj3 Calmette$).tw. (4601)
23. tubercul$ vaccin$.tw. (448)
24. Calmette Vaccin$.tw. (14)
25. or/20-24 (21,429)
26. 19 and 25 (12,143)
27. exp animals/ not humans/ (3,377,110)
28. 26 not 27 (8768)
29. limit 25 to yr=‘1945 - 1965’ (2571)
30. 29 not 27 (2383)
31. 28 or 30 (10,087)

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Database: Old MEDLINE Ovid 1950–65

1. BCG Vaccine/ (277)
2. BCG.tw. (824)
3. (bacill$ adj3 Calmette$).tw. (10)
4. tubercul$ vaccin$.tw. (11)
5. Calmette Vaccin$.tw. (1)
6. or/1-5 (888)
7. exp animals/ not humans/ (11,811)
8. 6 not 7 (876)

Database: MEDLINE Ovid In-Process & Other Non-Indexed Citations – current week 15 May 2009

1. exp Tuberculosis/ (5)
2. tb.tw. (1123)
3. tuberculous.tw. (381)
4. tuberculos$2.tw. (2434)
5. tubercular.tw. (74)
6. phthisis.tw. (10)
7. tuberculoma$1.tw. (23)
8. pott$ disease.tw. (12)
9. tuberculid$1.tw. (6)
10. scrofuloderma$1.tw. (3)
11. scrofula$1.tw. (0)
12. Mycobacterium bovis/ (0)
13. Mycobacterium tuberculosis/ (0)
14. tubercle bacill$.tw. (84)
15. mycobacterium africanum.tw. (2)
16. mycobacterium microti.tw. (0)
17. mycobacterium canetti.tw. (0)
18. mycobacterium bovis.tw. (130)
19. or/1-18 (3485)
20. BCG Vaccine/ (0)
21. BCG.tw. (261)
22. (bacill$ adj3 Calmette$).tw. (120)
23. tubercul$ vaccin$.tw. (27)
24. Calmette Vaccin$.tw. (0)
25. or/20-24 (303)
26. 19 and 25 (174)
27. exp animals/ not humans/ (9)
28. 26 not 27 (174)
29. limit 25 to yr='1920 - 1965' (8)
30. 29 not 27 (8)
31. 28 or 30 (179)

Appendix 2

Data extraction and quality assessment forms

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BCG Data Extraction Form: Baseline Data

Study_ID: 250007

Date extracted:		Reviewer:	
Ref ID:		Study Name:	
Author:		Year:	
Study IDs for additional extracted papers:		Study IDs for duplicates not extracted:	
Why was this publication selected for extraction?:			
Study Design:		Other	
Number of trial arms:		Comparator intervention:	
Comparator Details:			
Country:		City/Region:	

Recruitment Details:

Year recruitment started:		Year recruitment ended:

	Source of population/Cases:	*Source of preferred controls:*	*Source of other controls:*
General Population	☐	☐	☐
Outbreak	☐	☐	☐
Single hospital	☐	☐	☐
Multiple hospital	☐	☐	☐
National Surveillance	☐	☐	☐
Local Survillance	☐	☐	☐
Population subgroup	☐		
Neighbourhood		☐	☐
Other	☐	☐	☐
Not specified	☐	☐	☐
Details of source pop (if not covered above):			
Were cases and control matched?:			
If yes, what factors were they matched on?			

Participant Details:

Were patients with existing TB infection excluded at study start?	
Were patients with existing TB infection excluded at time of vaccination?	
In which groups were those with TB infection excluded?	
Was a tuberculin test part of the diagnostic procedures for cases?:	
Please list other inclusion criteria:	

Age at vaccination

Mean:		Infant (<1 year)	☐
Median:		Young childhood (1-5 years)	☐
Range:		Older childhood (6-11 years)	☐
		Teen (12-18 years)	☐
		Adult (19+ years)	☐
		All ages	☐

Socioeconomic bacground:

Bacground risk of disease in source population			
Proportion Asian:	0	Proportion Native American:	0
Proportion Black:	0	Proportion White:	0
Proportion Hispanic:	0	No information on ethnicity provided	☐
Other details of ethicity:			
Were any participants HIV infected?		Proportion infected:	
Number in vaccinated group/cases at baseline:		Number in control group at baseline:	

Vaccination Details

Were regional vaccine policies for vaccination period described?	No
What were the vaccination policies?	

Reason for vaccination		*Vaccine strain*	
Neonatal/Childhood vaccination	☐	Connaught	☐
"Booster" vaccination	☐	Copenhagen	☐
Occupational related	☐	Danish (Statens)	☐
Research study related	☐	Glaxo	☐
Other	☐	Moreau (Brazillian)	☐
Not stated	☐	Pasteur	☐
Details, if other		Russian (Moscow)	☐
		Tice (BCG)	☐
How was vaccination status ascertained?		Tice (rBCG30)	☐
Medical Records	☐	Tckyo (Japanese)	☐
Vaccinatoin Card	☐	Volebaccilus	☐
Participant Recall	☐	Sophia (Bulgaria)	☐
Parent of Participant Recall	☐	Madras	☐
BCG Scar	☐	Coded by number only	☐
Other	☐	Other	☐
Not stated	☐	Not Stated	☐
Details, if other:		Vaccine strain number:	
		Details, if other	

Year vaccination started:		Year vaccination ended:	
Single or multi puncture?		Vaccine administration:	

Reviewer comments:

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BCG Data Extraction Form: Results

Result_ID: 250029
Study_ID: 250007

Date assessed:		Reviewer:	
Baseline Ref ID:		Study Name:	
Paper ref ID:			

What sample do these data relate to?:

Sample details

Details same as previous forms with exception of completed fields ☐

Age at vaccination:	
Age at outcome assessment:	
Years between vaccination and outcome:	
Gender:	
Duration of follow-up to determine outcome:	
Outcome:	Details, if other:

Was this outcome measured but results data were not available? ☐

How were cases identified at follow-up?

Names matched to surveillance data	☐
Names matched to mortality data	☐
All participants were contacted	☐
Medical Records	☐
Hospital data	☐
TB registries	☐
Not stated	☐
Queried at follow-up	☐
Symptomatic participants assessed at follow-up	☐
Morbidity reports	☐
Medical records of all parts reviewed at follow-up	☐
Other	☐

Details, if other:

Case definition (include % for each subdefinition):

Were efforts made to determine what happened to those not cases?	
VacUnvacc:	
Were there any originally unvaccinated who subsequently were vaccinated?:	
How was this handled in the study?	
Control/Comparator Group:	
Intervention arm:	

Result Number:

2 x 2 Results:

	TB	*No TB*	*Person years:*
BCG			
Not vaccinated			

Summary Results:	*Effect measure*	*Adjusting details*	*Result*	*95% CI*	
Crude:			0	0	0
Age and sex adjusted:			0	0	0
Fully adjusted:			0	0	0
Factors adjusted for in fully adjusted model:					
If the controls were matched to cases, were matched analyses conducted?:					
Response rate for cases (%):					
Response rate for controls (%):					
Reviewer comments:					

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BCG Quality Assessment Form : RCTs

Study_ID: 250008

Ref ID:	1	Study Name:	
Author:		Reviewer:	

1. Randomisation

Method for generating randomization sequence:	
Randomisation method	
Was the allocation sequence adequately generated?	

2. Concealment of treatment allocation

Method for concealing treatment allocation	
Was allocation adequately concealed?	

3. Withdrawals

% drop-outs in the BCG group:	
% drop-outs in the non-vaccinated group:	
Were reasons for withdrawals similar across groups?	
Were reasons for withdrawals related to the outcome?	
IF YES TO ABOVE, give details	
Were appropriate methods used to impute missing data?:	
Was an intention-to-treat analysis conducted?	
Were incomplete outcome data adequately addressed?	

4. Blinding

Were outcome assessors blinded?	
Were participants blinded?	
Were vaccine administrators blinded?	
Was knowledge of the allocated intervention prevented during the study	

5. Selective outcome reporting

Were data reported for all pre-specified outcomes?:	
Were data reported for all pre-specified sub-group analyses?	
Are reports of the study free of suggestion of selective outcome reporting?	

6. Case ascertainment

Were methods of ascertainment of cases identical for vaccinated and unvaccinated groups?	
Was ascertainment of cases complete?	

Notes:

BCG Quality Assessment Form : Other study designs

Study_ID: 250009

Ref ID: 1111 Study Name: 1

Author:

1. Cohort studies	Supporting data	Rating
Was follow-up independent of vacciation status?:		
Was case ascertainment blinded to vaccination status?		
Were methods of ascertainment of cases identifical for vaccinated and unvaccinated groups?		
Were data reported for all pre-specified sub-group analyses?		
Were incomplete outcome data adequately addressed?:		
% withdrawals in BCG group:		
% withdrawals in non-vaccinated group:		
Were reasons for withdrawals similar across groups?:		
Were reasons for withdrawals related to outcome		
Were missing data imputed using appropriate methods?:		
Was an intention to treat analysis conducted?:		
2. Cross-sectional and case-control studies		
Were vaccination definitions the same for everyone (cases and controls) in the study?:		
Was disease status blinded to BCG assessors?		
Were controls selected from the same population as the cases? (CC only)		
Were cases and controls ascertained independent of vaccine status?:		
3. Case population studies		
Were cases and population the same?		
In terms of geography?		
In terms of time?		
In terms of age?		

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Notes:

Appendix 3

Included study characteristics

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Randomised control trials

Study name	Author (year) Country/region	Additional/duplicate references	Recruitment period	Randomisation protocol	Number BCG vaccinated/number unvaccinated
Native American[5]	Aronson (2004) USA (South East AK, AZ, ND, SD and WY)	Additional: [45, 230–235] Duplicate: [236–238]	1935–8	Quasi-randomisation, two arms, comparator intervention: placebo	1551/1457
Turtle and Rosebud infants[45]	Aronson (1948) USA (ND and SD)	Additional: [235]	1938–40	Quasi-randomisation, two arms, no comparator intervention	123/139
Illinois mentally handicapped[50]	Bettag (1964) USA (IL)	None	1947	Randomisation unclear, two arms, no comparator intervention	531/494
African gold miners[54]	Coetzee (1968) South Africa	None	1965–8	Quasi-randomisation, two arms, no comparator intervention	8317/7997
Saskatchewan infants[13]	Ferguson (1949) Canada (SK)	None	1933–45	Randomisation unclear, two arms, no comparator intervention	306/303
Madanapalle[53]	Frimodt-Moller (1960) India (Madanapalle)	Additional: [239–241] Duplicate: [242]	1950–5	Individual randomisation, two arms, no comparator intervention	5069/5803
New York infants randomised[12]	Levine (1938) USA (NY)	Additional: [125, 243]	1933–9999	Quasi-randomisation, two arms, no comparator intervention	463/476
MRC[14]	MRC (1956) UK (London, Birmingham, Manchester)	Additional: [21,244–246] Duplicate: [247–249]	1950–2	Quasi-randomisation, three arms, no comparator intervention	20,800/13,300
Agra[51]	Mehrotra (1988) India (Agra)	None	9999–9999	Randomisation unclear, two arms, no comparator intervention	1259/1259
Bombay infants[52]	Mehta (1976) India (Mumbai)	None	9999–9999	Randomisation unclear, two arms, no comparator intervention	396/300
Georgia/ Alabama[15]	Palmer (1958) USA (Muscogee county, GA and Russell county, AL)	Additional: [31; 250 251] Duplicate: [252]	1950	Quasi-randomisation, two arms, no comparator intervention	16,913/17,854
Puerto Rico children[15]	Palmer (1958) USA Minor Outlying Islands (Puerto Rico)	Additional: [251]	1949–51	Quasi-randomisation, two arms, no comparator intervention	50,634/27,338
Chicago nurses[47]	Rosenthal (1963) USA (Chicago, IL)	Additional: [44,253,254]	1940–52	Quasi-randomisation, two arms, comparator intervention: placebo (saline)	231/263

Source of participants (gender)	Inclusion criteria/tuberculin testing	BCG vaccination administration type, strain and reason	Age at BCG vaccination	BCG vaccination ascertainment
Native American and Alaskan natives (both genders)	Normal chest radiographs; PPD negative at 0.00002 and 0.005 mg of PPD tuberculin; living on reservations; children attending Indian Service Schools and denominational boarding schools	Intradermal injection Strain: Pasteur 317 used at US sites; 575 used at Alaskan sites, for research	0–20 years, median: 7.6 years	Research study records
Native American Infants (both genders)	Born in hospitals in Turtle Mountain and Rosebud reservation agencies	Intradermal injection Strain: not specified, for research	Neonatal (< 1 year)	Research study records
Mentally handicapped institution (Lincoln State School) (both genders)	Resident of the Lincoln school in 1947, tuberculin negative and negative chest radiograph in 1947	Percutaneous injection Strain: not specified, for research	Older children (6–11 years), teen (12–18 years), adult (> 19 years)	Medical records
Miners in one South African mine. (males only)	New miners entering a single gold mine (all men) irrespective of tuberculin reactivity	Not specified Strain: Glaxo, for research	Adult (> 19 years), median: 30 years	Research study records
Canadian Natives (both genders)	Infants born in Qu'Appelle Indian Health area	Intradermal injection Strain: Pasteur 450-S1, 468-S1, for research	0–10 days	Medical records
General population (both genders)	An induration of ≤ 4 mm if tested with 5TU	Intradermal injection Strain: Madras, for research	All ages	Research study records
Infants from tuberculous families (both genders)	All children had to come from households with tuberculosis and have no indication to tuberculosis by PPD, chest radiograph, or physical examination if older than 1 month	Subcutaneous and intradermal injection Strain: not specified, for research	0–3 years	Research study records
Secondary schools. (both genders)	Children in their penultimate term with parental consent (60%), no history of recent tuberculosis in family, negative chest radiograph, two negative tuberculin skin tests, no previous BCG vaccine	Intradermal injection Strain: Copenhagen, for research	14–15.5 years	Research study records, medical records
Children in slum in Agra (both genders)	Tuberculin negative (for vaccinated group)	Not specified Strain: not specified, for research	0–5 years	Research study records
Single hospital: well baby clinic (both genders)	Newborns in Well Baby Clinic at Bai Jerbai Wadia Hospital for children in Bombay	Intradermal injection Strain: Madras, for research	Neonatal (< 1 year)	Research study records
General population (both genders)	≥ 5 years old, residing in Muscogee or Russell counties, 5 TU PPD negative, chest radiograph negative (two independent reviewers); no obvious medical contradictions to vaccination	Intradermal injection Strain: Tice (BCG), for research	Young children (1–5 years), older children (6–11 years), teen (12–18 years), Adult (> 19 years) Range: 5–85 years	Research study records
School-aged children (both genders)	negative to first 1TU (≥ 5 years old), then 10TU. (< 6 mm)	Intradermal injection Strain: Copenhagen, RT-19–20–21, for research	1–18 years	Research study records
Student nurses (female)	Students entering nursing school at Cook County Hospital, Chicago, who were PPD negative (did not react to 2 TU, then 100 TU) and chest radiograph negative	Intradermal injection Strain: not specified, for research	Adult (> 19 years)	Research study records

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Study name	Author (year) Country/region	Additional/duplicate references	Recruitment period	Randomisation protocol	Number BCG vaccinated/number unvaccinated
Chicago medical students[46]	Rosenthal (1965) USA (Chicago, IL)	None	1939–52	Randomisation unclear, two arms, comparator intervention: placebo (unspecified type)	324/298
Chicago infants TB HH (from tuberculosis households)[48]	Rosenthal (1945) USA (Chicago, IL)	Additional: [44,253–256]	1941–9999	Quasi-randomisation, two arms, no comparator intervention	311/250
Chicago Infants CCH (Cook County hospital)[48]	Rosenthal (1945) USA (Chicago, IL)	Additional: [44,253,254,257,258] Duplicate: [259]	1937–48	Quasi-randomisation, two arms, no comparator intervention	5426/4128
Ida B Wells housing project[44]	Rosenthal (1948) USA (IL)	Additional: [253, 254]	1942–9999	Quasi-randomisation, two arms, comparator intervention: placebo (saline)	699/625
US mental health patients[44]	Rosenthal (1948) USA (IL)	None	1944	Quasi-randomisation, two arms, no comparator intervention	20/15
Georgia (school)[49]	Shaw (1951) USA (Muscogee County, GA)	Additional: [260; 261] Duplicate: [252]	1947	Quasi-randomisation, two arms, no comparator intervention	2498/2341
Chingleput[28]	Tuberculosis Prevention Trial (TBPT) (1979) India (Chingleput)	Additional: [19, 221, 262; 263] Duplicate: [264]	1968–71	Individual randomisation, five arms, comparator intervention: placebo (dextran)	73,459/36,404
Haiti[55]	Vandivière (1973) Haiti (District of Jeremie, Governmental Sector VI)	None	1965–6	Randomisation unclear, six arms, comparator intervention: placebo (small pox vaccine alone of with Isoniazid)	641/340

9999, missing.

Source of participants (gender)	Inclusion criteria/tuberculin testing	BCG vaccination administration type, strain and reason	Age at BCG vaccination	BCG vaccination ascertainment
Medical students (both genders)	None provided	Intradermal injection Strain: not specified, for research	Adult (>19 years)	Research study records
Single hospital: Special tuberculosis obstetrics clinic. Clinic and recruited (both genders)	Newborns from tuberculosis positive mother or with tuberculosis in household, with agreement of mother to have them placed in a foster home for 6 weeks to 2 months	Intradermal injection Strain: Pasteur Tice (BCG), for research	7 days to 3 months	Research study records
Single hospital: Obstetrics ward (both genders)	Newborns to mothers delivering at Cook County Hospital (CCH) from non-tuberculosis households. Cleared tuberculosis within 3 months of the child's birth within a family allowed inclusion of the child. Normal birth weight and negative syphilis serology in the mother	Percutaneous injection Strain: Pasteur, Tice (BCG), for research	3–7 days	Research study records
Children in one community living in the Ida B Wells federal housing project (both genders)	Children 10–12 years or younger living in the housing project surveyed, tuberculin negative (for vaccinated group)	Intradermal injection Strain: Pasteur, for research	0–12 years	Research study records
Mental health patients at an unknown single institute (both genders)	Tuberculin negative	Intradermal injection Strain: Pasteur, for research	All ages	Research study records
Public and private elementary and high schools (both genders)	Schoolchildren living in Muscogee county who were negative to first 5 TU PPD and second 100 TU (negative = < 5 mm)	Intradermal injection Strain: Tice (BCG)811K, 811L, 812E, 812L, 813E, for research	Young children (1–5 years), older children (6–11 years), teen (12–18 years)	Research study records
General population: 209 villages and one town (both genders)	>1 month old and no indication of pulmonary tuberculosis	Intradermal injection Strain: Danish-1331, Pasteur-1173 P2, for research	All ages (≥1 month)	Research study records
General population (both genders)	TST non-reactive (<6 mm 5TU), living in a mapped household of District of Jeremie	Intradermal injection Strain: Montreal, 1202–5, for research	0–85 years	Research study records

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Case–control studies

Study name	Author (year Country/Region	Additional/ duplicate references	Recruitment period	Number vaccinated/ unvaccinated	Source of cases/control subjects
Indonesia[73]	Putrali (1983) Indonesia (Jakarta)	None	1981–2	103/412	*Cases:* Multiple hospitals *Control subjects:* Multiple hospitals
Saudi Arabia[77]	Al-Kassimi (1995) Saudi Arabia	None	1991–2	537/5756	*Cases*: Survey (1991–1992) of seven tuberculosis centres in Ministry of Health hospitals *Control subjects:* General population from nationwide community survey of TU sensitivity and BCG scar
Delhi[57]	Bhattacharjee (1993) India (Delhi)	None	1989–90	21/42	*Cases:* Single hospital *Control subjects*: Neighbourhood
Madagascar children[79]	Boileau (1995) Madagascar (Antananarivo)	None	1992–4	52/122	*Cases:* Single hospital *Control subjects:* Single hospital
Brazil[67]	Camargos (1988) Brazil (Belo Horizonte MG)	None	1975–81	45/90	*Cases*: Single hospital *Control subjects*: Single hospital, *Other control subjects:* Single hospital
Bangalore children[56]	Chadha (2004) India (Bangalore City)	None	9999–9999	137/176	*Cases:* Multiple hospitals *Control subjects:* Neighbourhood (four houses either side of the suspected case's house)
Thailand[66]	Chavalittamrong (1986) Thailand (Bangkok)	None	1980–4	330/1106	*Cases*: Single hospital *Control subjects*: Single hospital

Inclusion criteria	Matching factors	BCG vaccination administration and type	Vaccination dates	BCG vaccination ascertainment	Reason for BCG vaccination	Age at BCG vaccination	Gender
Cases: ≥ 5 years old; BCG vaccinated in first year of life; tuberculosis diagnosed patient from eight hospitals *Control subjects:* Non-tuberculosis patients in the same eight hospitals; ≥ 5 years old	Age and sex	Assumed intradermal (BCG vaccination status assessed through scar) Strain: Pasteur, Tokyo	Not specified	Scar	Neonatal/ childhood	Infant (< 1 year)	Both
Cases and control subjects: ≤ 34 years old	Unmatched	Not specified Strain: not specified	Not specified	Scar	Neonatal/ childhood	Infant (< 1 year)	Both
Cases: 0–5 year old residents of Delhi with documented tuberculosis meningitis cases *Control subjects*: Never hospitalised or treated except for injuries and minor ailments	Age and sex	Assumed intradermal (BCG vaccination status assessed through scar) Strain: not specified	Not specified	Vaccination card, scar	Neonatal/ childhood	Infant (< 1 year)	Both
Cases: Children with diagnostic proof of tuberculosis admitted to paediatric centre *Control subjects*: Children hospitalised for pathology different to tuberculosis in same hospital from December 1994 to January 1995	Age	Assumed intradermal (BCG vaccination status assessed through scar) Strain: not specified	Not specified	Parent of participant recall, scar	Neonatal/ childhood	Infant (< 1 year)	Both
Cases: Admitted to hospital *Control subjects*: Admitted for acute diarrhoea (AD) *Other control subjects:* Admitted for acute non-tuberculosis bacterial pneumonias (BP)	Age at hospitalisation, date of hospitalisation and nutritional status	Intradermal injection Strain: Moreau	Not specified	Medical records	Neonatal/ childhood	Infant (< 1 year)	Both
Cases: All children 1–14 years suspected of tuberculosis and meeting the tuberculosis case definition and living within 30 km of the city centre (Stegen and Jones (SJ) score 7 or more to qualify as a case) *Control subjects*: SJ had to be < 4 to qualify as a control	Age, sex, residence	Assumed intradermal (BCG vaccination status assessed through scar) Strain: Danish 1331	Not specified	Scar	Neonatal/ childhood	1–14 years	Both
Control subjects: Tuberculin negative	Unmatched	Intradermal injection Strain: Pasteur (Mérieux)	Not specified	Parent of participant recall, scar	Neonatal/ childhood	Infant (< 1 year)	Both

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Study name	Author (year Country/Region	Additional/ duplicate references	Recruitment period	Number vaccinated/ unvaccinated	Source of cases/control subjects
Canada 1975[63]	Houston (1990) Canada (AB)	None	1975–9	132/232	*Cases*: Aboriginal Canadians surveillance *Control subjects*: Aboriginal Canadians listed on the Treaty Indian Register in the Medical Services of Alberta Province
Lucknow paediatric[61]	Kumar (2005) India (Lucknow)	None	Not specified	91/182	*Cases*: Single hospital (King George Children's Hospital) *Control subjects*: Single hospital (King George Children's Hospital)
Korea[71]	Kwong (1980) Republic of Korea	None	1979	76/62	*Cases*: Multiple hospitals *Control subjects and other control subjects*: Multiple hospitals *All*: paediatric departments of 25 hospitals)
Mexico[78]	Martinez-Gonzalez (2002) Mexico (Jalisco)	None	1991–5	42/84	*Cases*: Single hospital *Control subjects*: Single hospital
Argentina[72]	Miceli (1986) Argentina (Greater Buenos Aires area)	None	1981–2	51/256	*Cases*: Single hospital *Control subjects*: Single hospital
Dehli paediatric[58]	Mittal (1996) India (Delhi)	None	1993–5	128/182	*Cases*: Single hospital *Control subjects*: Single hospital

Inclusion criteria	Matching factors	BCG vaccination administration and type	Vaccination dates	BCG vaccination ascertainment	Reason for BCG vaccination	Age at BCG vaccination	Gender
Control subjects: Could not have a history of tuberculosis	Age ± 2 years, sex and treaty band (proxy for SES)	Assumed intradermal (BCG vaccination status assessed through scar) Strain: not specified	Not specified	Medical records	Neonatal/ childhood	4.4 years	Both
Cases: Consecutive admission of tuberculosis meningitis over a 1 year period *Control subjects*: Two children admitted on the same day as the case who did not have any neurological symptoms	Unmatched	Not specified Strain: not specified	Not specified	Scar, participant recall	Neonatal/ childhood	0–12 years	Both
Cases: Neonates with tuberculosis meningitis *Control subjects*: Pulmonary tuberculosis *Other control subjects*: Diseases other than tuberculosis and its related conditions (including leukaemia and acute cancer)	Age (+ or - 3 months)	Not specified Strain: not specified	Not specified	Not specified	Not specified	Infant (< 1 year)	Both
Cases: Extrapulmonary tuberculosis, complete medical files *Control subjects*: Appendicitis patients from the same hospital	Age, nutritional status and SES of hospital	Intradermal injection Strain: not specified	Not specified	Medical records, vaccination card, scar	Neonatal/ childhood	Infant (< 1 year)	Both
Control subjects: Inpatients with diseases unrelated to BCG vaccination or tuberculosis	Unmatched	Assumed intradermal (BCG vaccination status assessed through scar) Strain: not specified	Not specified	Scar	Neonatal/ childhood	Infant (< 1 year)	Both
Cases: All cases 12 years or younger admitted for the first time for paediatric tuberculosis meningitis for one consecutive calendar year (1993) *Control subjects*: All children paediatric ward without tuberculosis meningitis on 1 day in 1995 *Other control subjects:* All children on paediatric ward without tuberculosis meningitis on another day in 1995 3 weeks after the first vaccination	Unmatched	Not specified Strain: not specified	Not specified	Scar	Neonatal/ childhood	0–12 years	Both

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Study name	Author (year Country/Region	Additional/ duplicate references	Recruitment period	Number vaccinated/ unvaccinated	Source of cases/control subjects
Myanmar[74]	Myint (1987) Myanmar (Rangoon)	None	1983–5	311/1536	*Cases*: Single hospital *Control subjects*: Single hospital
Birmingham UK[33]	Packe (1988) UK (Birmingham)	[80]	1965–85	108/432	*Cases*: Local Surveillance *Control subjects*: Vaccination records
Asian children in UK[32]	Rodrigues (1991) UK (Bolton, Bradford, Brent, Dudley, Leicester, Manchester, Newham, Redbridge, Rochdale, Sandwell, Tameside, Walsall, Waltham Forest and Wolverhampton)	None	9999–9999	111/555	*Cases*: Local Surveillance *Control subjects*: Other district child health registry and school health records
Cali children[70]	Shapiro (1985) Colombia (Cali)	None	1977–1982	178/320	*Cases*: Multiple hospitals (12 municipal respiratory clinics) *Control subjects*: Household members

Inclusion criteria	Matching factors	BCG vaccination administration and type	Vaccination dates	BCG vaccination ascertainment	Reason for BCG vaccination	Age at BCG vaccination	Gender
Cases: Children < 5 years of age, residing in Rangoon, admitted to the children's hospital with the diagnosis of one of the various forms of tuberculosis *Control subjects*: Non-tuberculosis and non vaccine-preventable disease cases selected from both the inpatients and outpatients of the same hospital as tuberculosis cases during the 3 months in which the cases were registered	Age, sex and sector of residence	Intradermal injection Strain: Tokyo	Not specified	Vaccination card, parent of participant recall, scar	Neonatal/ childhood	Infant (< 1 year)	Both
Asian ethnic origin; born between 1965 and 1979. *Cases*: Registered between 1965 and 1985 notified subjects given anti-tuberculosis treatment, whether tuberculin positive or negative, who had no clinical, radiological or bacteriological evidence of tuberculous disease were considered to have received chemoprophylaxis were excluded	Month and year of birth, sex	Intradermal injection Strain: Glaxo	Not specified	Vaccination records	Neonatal/ childhood	0–3 months	Both
Children of Asian ethnic origin born in the UK *Cases*: Could not have had their diagnosis changed from tuberculosis or been given chemoprophylaxis only	Sex, age, place of residence	Not specified Strain: not specified	Not specified	Child health registry and school health records	Neonatal/ childhood	Infant (< 1 year)	Both
Cases: Diagnosis receiving tuberculosis treatment after 1977 through to current treatment in 1982; for those not on treatment in 1982 a positive source history of tuberculosis required *Control subjects*: < 15 years with no previous tuberculosis diagnosis, no tuberculosis symptoms, and negative chest radiograph. Only one case included per household (first diagnosis)	Household	Not specified Strain: Glaxo, Tokyo. Danish post 1978	Not specified	Vaccination card, parent of participant recall, scar	Neonatal/ childhood	0–15 years	Both

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Study name	Author (year Country/Region	Additional/ duplicate references	Recruitment period	Number vaccinated/ unvaccinated	Source of cases/control subjects
Bangkok children[65]	Sirinavin (1991) Thailand (Bangkok)	None	1987–8	75/207	*Cases*: Single hospital (Ramathibodi or Children's Hospital) *Control subjects*: Single hospital
Osaka Children[76]	Takamatsu (1995) Japan (Osaka)	None	1988–94	59/114	*Cases*: Single hospital (Osaka Prefectural Habikino Hospital) *Control subjects*: Single hospital
India[59]	Thilothammal (1996) India (Madras)	None	1990–2	107/321	*Cases*: Single hospital *Control subjects*: Single hospital
São Paulo[68]	Wunsch-Filho (1990) Brazil (São Paulo)	None	1981–3	72/586	*Cases*: Multiple hospitals *Control subjects*: Neighbourhood *Other control subjects*: Single hospital
Nagpur hospital[62]	Zodpey (1996) India (Nagpur)	Additional: [81–86] Duplicate: [87; 88]	1994	877/877	*Cases and control subjects*: Single hospital (Government Medical College Hospital)

Inclusion criteria	Matching factors	BCG vaccination administration and type	Vaccination dates	BCG vaccination ascertainment	Reason for BCG vaccination	Age at BCG vaccination	Gender
Cases: Children < 15 years old diagnosed between 1987–8 with tuberculosis *Control subjects*: The first 1–4 children identified from the same hospital as the case that could be matched to the case who were considered free from tuberculosis using the same diagnostic procedures as cases and who never received tuberculosis chemoprophylaxis	Age and district of birth	Intradermal injection Strain: Glaxo, Pasteur and Tokyo	Not specified	Participant recall	Neonatal/ childhood	Infant (< 1 year)	Both
Cases: All consecutive tuberculosis cases among children with known BCG vaccination status *Control subjects*: Two for each case; non-tuberculosis cases from the same paediatric department	Age, sex, year of admission, place of residence	Intradermal injection Strain: not specified	Not specified	Vaccination card, parent of participant recall	Neonatal/ childhood	Not specified	Both
Cases: Incident tuberculous meningitis cases treated before referral, with no chronic medical illness or malignancy and current immunosuppressive treatment *Control subjects*: children Attending the same hospital who had febrile convulsions without other neurological abnormality	Age and sex	Assumed intradermal (BCG vaccination status assessed through scar) Strain: not specified	Not specified	Medical records, parent of participant recall, scar	Neonatal/ childhood	6 months to 12 years	Both
Residents of the Metropolitan Region of São Paulo *Cases*: Notified cases of tuberculous meningitis born after 1978 with information on vaccination status *Control subjects*: Born after 1978 *Other control subjects*: Not suspected to have had tuberculosis or other vaccine-preventable diseases	Residence and SES. Sex and age	Assumed intradermal (BCG vaccination status assessed through scar) Strain: Moreau		Not stated, vaccination card, parent of participant recall, scar, health centre archives	Neonatal/ childhood	Infant (< 1 year), young childhood (1–5 years)	Both
Born 1962 or later *Cases*: Incident cases of tuberculosis presenting at hospital *Control subjects*: Patients admitted for conditions other than leprosy or tuberculosis who did not have a history of tuberculosis, family history of tuberculosis or history of isoniazid use	Age, sex, SES	Assumed intradermal (BCG vaccination status assessed through scar) Strain: not specified	1962 to 'not specified'	Vaccination card, parent of participant recall, scar	Neonatal/ childhood	Infant (< 1 year), 0 years	Both

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Study name	Author (year Country/Region	Additional/ duplicate references	Recruitment period	Number vaccinated/ unvaccinated	Source of cases/control subjects
Canada[64]	Young (1986) Canada (MB)	None	1979–83	71/213	*Cases*: Local Surveillance *Control subjects*: Neighbourhood
Lucknow children[60]	Awasthi (1999) India (Lucknow)	None	1995–7	192/70	*Cases and control subjects*: Single hospital (Paediatrics department at King George Medical College)
Nepal[75]	Pust (1984) Nepal (Gorkha District)	None	1983–4	100/100	*Cases*: Single hospital *Control subjects*: Single hospital
Papua New Guinea children[69]	Murtagh (1980) Papua New Guinea (Port Moresby)	None	1975–8	114/121	*Cases*: Single hospital *Control subjects*: Single hospital

9999, missing.

Inclusion criteria	Matching factors	BCG vaccination administration and type	Vaccination dates	BCG vaccination ascertainment	Reason for BCG vaccination	Age at BCG vaccination	Gender
Cases: new active cases of tuberculosis, born on or after 1 January 1965, < 15 years at diagnosis *Control subjects*: alive and born on or after 1 January 1965 from same communities as cases, never had active tuberculosis up to the time of the investigator's site visit	Unmatched	Intradermal injection Strain: not specified	Not specified	Medical records, vaccination card	Neonatal/ childhood	Infant (< 1 year)	Both
Children 1 month to 12 years old *Cases*: Admitted to with a diagnosis of tuberculosis meningitis *Control subjects*: Every paediatric patient admitted after the third consecutive case without CNS disorder	Unmatched	Not specified Strain: not specified	Not specified	Scar	Neonatal/ childhood	Infant (< 1 year)	Both
< 5 years old *Cases*: tuberculosis cases under treatment or beginning treatment in the last 3 years *Control subjects*: children with presentation that could not be attributed to tuberculosis, complaint did not include any cough of any duration, fever for > 2 days, neck adenopathy, spinal deformity, signs or symptoms or meningitis, psoas abscess or skin tuberculosis. Could not have a past history of cough or fever for > 3 days or any of the signs and symptoms that were used as inclusion for the cases	Age and sex	Intradermal injection Strain: not specified	Not specified	Scar, medical records	Neonatal/ childhood	Infant (< 1 year)	Both
Cases: Laboratory confirmed cases of tuberculosis with information on BCG vaccination status among children given anti-tuberculosis therapy *Control subjects*: Children admitted to the surgical ward of the children's section of an unnamed hospital	Unmatched	Not specified Strain: not specified		Vaccination card, scar	Neonatal/ childhood	9999	Both

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Cohort studies

Study name	Author (year) Country/ region	Additional/ duplicate references	Years of recruitment	*n* cohort (*n* BCG vaccinated/*n* unvaccinated)	Source of population
Contact studies					
Edinburgh 1977 contacts[97]	Capewell (1984) UK (Edinburgh area)	None	1977–81	5416 (1821/3595)	Local surveillance: index cases were notifications in the Edinburgh area
Seoul contacts[120]	Jin (1989) Republic of Korea (Western Seoul)	None	1984–6	1223 (806/417)	Multiple hospitals: index cases from seven health centres
Bangui contacts[121]	Lanckriet (1995) Central African Republic (Bangui)	None	1989–91	1000 (896/104)	Single hospital
Edinburgh contacts[98]	Rubilar (1995) UK (Edinburgh area including East Lothian, Midlothian and the City of Edinburgh)	None	1982–91	3366 (1605/1761)	National surveillance: tuberculosis notifications in the Edinburgh area
UK contacts[99]	Horne (1978) UK	None	1973–4	4668 (1081/3587)	Multiple hospitals: index cases from 37 clinics

Population inclusion criteria	Follow-up method	BCG vaccination administration and type	Vaccination period	BCG vaccination ascertainment	Reason for BCG vaccination	Age at BCG vaccination	Gender
Index cases: Notifications of tuberculosis during the period 1977–1981 *Contacts:* Both 'close' and 'casual' contacts were included according to the British Thoracic Association study criteria	Chest radiograph and tuberculin test at 3 and 6 months' follow-up	Not specified Strain: not specified		Not specified	Not specified	Not specified	Both
Index cases: smear positive pulmonary tuberculosis case *Contacts:* Children < 5 years of age living in the same home as the index case; contacts could also be children who had died in the 6 months preceding the detection of the index case	Chest radiograph at 3 months follow-up	Intradermal injection Strain: Pasteur, 1173P2		Vaccination card, parents of participant recall, scar	Neonatal	Neonatal (< 1 year)	Both
Index cases: Contagious tuberculosis cases with sputum smear positive for Koch's bacillus detected in the hospital's tuberculosis ward and living in Bangui *Contacts:* Children < 7 years old, living in the same concession as the index case	Chest radiograph at 3 and 6 months' follow-up	Intradermal injection Strain: Pasteur, Mérieux		Vaccination card, parents of participant recall, scar	Neonatal	Neonatal (< 1 year)	Both
Index cases: Tuberculosis cases *Contacts:* Close and casual contacts as defined by the British Thoracic Association study	Chest radiograph at 3 and 6 months and 1–2 years' follow-up	Not specified Strain: Not specified		Not specified	Not specified	Not specified	Both
Index cases: All newly notified cases of tuberculosis, whether respiratory or non-respiratory, culture positive or negative, were included in the study *Contacts:* Members of the same household as the index case who share kitchen and/or bathroom facilities, or who are very close associates	Chest radiograph every year for 2 years	Not specified Strain: not specified		Not specified	Not specified	Not specified	Both

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Study name	Author (year) Country/ region	Additional/ duplicate references	Years of recruitment	*n* cohort (*n* BCG vaccinated/*n* unvaccinated)	Source of population
Prospective cohorts					
Oslo nurses[123]	Heimbeck (1938) Norway (Oslo)	Duplicate: [88,126–131]	1927–36	785 (501/284)	Student nurses at Ulleval Hospital
Richmond infants[93]	Kendig (1957) USA (Richmond, VA)	None	1949–56	1533 (738/795)	Single hospital: Well Baby Clinic
Trysil Norway[104]	No author (1930) Norway (Trysil)	None	1927–9	1250 (1079/171)	Country district surveillance
Rzeszow children[118]	Kubit (1983) Poland (Rzeszow)	None	1965	4614 (2531/2083)	Rzeszow
New York infants[91]	Kereszturi (1929) USA (NY)	Additional: [12,125, 132–135]	1927–32	579 (157/422)	Infants from tuberculous families
Bougie schoolchildren[117]	Sarrouy (1957) Algeria (Bougie)	None	1950	4465 (1428/3037)	Schoolchildren (one school)
Northern France schoolchildren[109]	Gernez-Rieux (1973) France (Northern France)	Additional : [136–138]	1948–51	18,787 (15,618/3169)	Schoolchildren 6–14 years
Karonga[24]	Ponnighaus (1992) Malawi (Karonga district)	Duplicate: [124]	1979–89	83,455 (–/–)	Local surveillance: Karonga district
Norway 1947[101]	Borgen (1951) Norway (Aker/ Oslo)	None	1947–9	1696 (1102/594)	General population
Virginia infants[94]	Kendig (1969) USA (VA)	None	1948–68	105 (30/75)	Not specified
Boston nurses[89]	DeFriez (1957) USA (Boston, MA)	None	1947–51	149 (141/8)	Student nurses

Population inclusion criteria	Follow-up method	BCG vaccination administration and type	Vaccination period	BCG vaccination ascertainment	Reason for BCG vaccination	Age at BCG vaccination	Gender
Tuberculin negative	Medical records	Subcutaneous injection Strain: not specified		Research study records	Research	Adult (> 19 years)	Female
< 6 months old, TST of 0.1 mg and chest radiograph negative	Screening (chest radiograph and TST) every 6 months	Intradermal injection Strain: not specified		Research study records	Research	Neonatal (< 1 year)	Both
Tuberculin negative for vaccinated group	Not specified	Intradermal injection Strain: not specified		Not specified	Not specified	Not specified	Both
Children 1–14 years	Not specified	Intradermal injection Strain: not specified		Scar	Not specified	Young children (1–5 years)	Both
No indication to tuberculosis by PPD, chest radiograph, or physical examination if > 1 month old	Not specified	Subcutaneous and intradermal injection Strain: not specified		Research study records	Research	Neonatal (< 1 year), young children (1–5 years) Range: 0–6 years	Both
All children	Yearly screening (chest radiograph)	Intradermal injection Strain: not specified		Scar	School vaccination	Young children (1–5 years), older children (6–11 years), teen (12–18 years)	Both
Vaccinated: Negative IDR to 10 UI tuberculin *Control subjects:* Non -vaccinated if negative IDR to 10 UI tuberculin and not vaccinated through parental refusal or other circumstances	School records, yearly examinations (chest radiograph and tuberculin test). Questionnaire and house-visits participants lost to follow-up	Intradermal injection Strain: Pasteur		Medical records	Research	Older children (6–11 years), teen (12–18 years)	Both
No doubtful scar at examination and conflicting records or HIV positive (however, not all participants were HIV tested)	Participant recall from household survey and matching to hospital data	Intradermal injection Strain: Glaxo		Scar	Neonatal	Young children (1–5 years), older children (6–11 years), teen (12–18 years)	Both
Mass chest health survey *Vaccinated*: Tuberculin negative	Mass screening (chest radiograph)	Not specified Strain: not specified		Not specified	Not specified	Teen (12–18 years), adult (> 19 years)	Both
Children born to tuberculous mothers	Tuberculosis registry data	Intradermal injection Strain: not specified		Not specified	Neonatal	Neonatal (< 1 year)	Both
Vaccinated: Tuberculin negative	Medical records	Intradermal injection Strain: not specified		Not specified	Occupational	Adult (> 19 years)	Female

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Study name	Author (year) Country/ region	Additional/ duplicate references	Years of recruitment	*n* cohort (*n* BCG vaccinated/*n* unvaccinated)	Source of population
Bornholm[122]	Olsen (1953) Denmark (Bornholm)	Duplicate: [139]	1936–45	11,585 (4413/7172)	Local surveillance
Brazil REVAC[6]	Barreto (2005) Brazil (Salvador and Manaus)	Additional: [140]	1996–8	239,936 (124,342/115,594)	Local schools
Retrospective cohorts					
Lyon students[108]	Despierres (1966) France (Lyon)	None	1956–63	34,886 (7875/27,011)	University students
Norway[102]	Tverdal (1988) Norway	None	1956–73	1,047,550 (961,239/86,311)	General population
Dublin nurses[115]	Counihan (1956) Ireland (Dublin)	None	1949–54	80 (78/2)	Student nurses
Dutch nurses[112]	Bergsma (1950) Netherlands (Harderwijk)	Duplicate: [141]	1939–50	137 (60/77)	Single hospital: student nurses
Hesse 23 districts[106]	Daelen (1953) Germany (Hesse region)	None	1947–9	162,569 (70,424/92,145)	23 districts of Hesse
Hamburg children[105]	Ehrengut (1977) Germany (Hamburg)	None	9999–9999	46,258 (33,735/12,523)	Local surveillance: Hamburg
Strasbourg students[110]	Vaucher (1951) France (Strasbourg)	None	1947–9	2526 (1953/573)	Strasbourg university students
Philadelphia nurses[92]	Chakravarty (1958) USA (Philadelphia, PA)	None	1950–5	536 (513/23)	Student nurses from Philadelphia general hospital

Population inclusion criteria	Follow-up method	BCG vaccination administration and type	Vaccination period	BCG vaccination ascertainment	Reason for BCG vaccination	Age at BCG vaccination	Gender
Vaccinated: Tuberculin negative	Two mass screening (chest radiograph)	Intradermal injection Strain: Danish		Not specified	Adult and late childhood mass vaccination	Older children (6–11 years), teen (12–18 years), adult (>19 years)	Both
Children in state schools, in urban areas of cities, not for disabled children, were not closed for renovation during the study implementation and did not have <50 students	Matching to surveillance data	Intradermal injection Strain: Moreau		Scar	Research	Neonatal (<1 year)	Both
18- to 25-year-olds, proper BCG vaccination by official body or private GP who provided complete certificate of vaccination and controlled for post-vaccination allergy controlled 3–6 months after BCG vaccination and regular yearly control of allergy after this and a maximum of one year since the last allergy control and tuberculosis disease screen	Matching to surveillance data and medical records	Not specified Strain: not specified		Vaccination card	Not specified	Neonatal (<1 year), young children (1–5 years), older children (6–11 years), Teen (12–18 years)	Both
Tuberculin negative Norwegian children age 13 years between 1956 and 1972 with no prior tuberculosis before 13 years	Matching to surveillance data	Intradermal injection Strain: not specified		Mandatory school records	School vaccination	Teen (12–18 years)	Both
Normal chest radiographs on entry. Tuberculin negative for vaccinated group	Matching to hospital data	Not specified Strain: not specified		Not specified	Occupational	Adult (>19 years)	Female
Working at sanatorium for >6 months during study period	Occupational screening	Intradermal injection Strain: Danish		Occupational records	Occupational	Adult (>19 years)	Female
3- to 18-year-olds tested tuberculin negative in one or two tests (Moro and Mantoux)	Matching to surveillance data	Not specified Strain: Danish		Medical records	Neonatal	Young children (1–5 years), older children, (6–11 years), teen (12–18 years)	Both
Children born in 1954 and 1963 in Hamburg	Matching to surveillance data and medical records	Not specified Strain: not specified		Medical records	Neonatal	Neonatal (<1 year)	Both
Tuberculin negative	Screening	Intradermal injection Strain: not specified		University medical records	Vaccination upon entry to university	Adult (>19 years)	Both
Tuberculin negative	Biannual screen (chest radiography and clinical examination)	Percutaneous injection Strain: not specified		Research study records	Research	18–20 years	Female

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Study name	Author (year) Country/ region	Additional/ duplicate references	Years of recruitment	*n* cohort (*n* BCG vaccinated/*n* unvaccinated)	Source of population
US physicians[95]	Barrett-Connor (1979) USA	None	1974–5	3439 (509/2930)	US physicians who attended US medical schools
Jordan[119]	Batieha (1998) Jordan	None	1980–6	705,037 (492,776/212,261)	National surveillance
Chicago medical students[90]	Geiseler (1986) USA (Chicago, IL)	Duplicate: [142]	1938–81	2242 (1145/1097)	Medical school graduates from one institution
Uruguay infants[114]	Gomez (1994) Uruguay (Montevideo)	Duplicate: [143–145]	1943–52	5632 (3183/2449)	Single hospital: Pedro Visca Hospital
Medical students UK[100]	Verney (1955) UK (Aberdeen, Belfast, Birmingham, Cambridge, Dublin, Edinburgh, Glasgow, Leeds, Oxford and Sheffield)	None	1949–54	3022 (2630/392)	Medical students and student nurses
Siblings cohort[107]	Liebknecht (1957) Germany	None	1949–54	272 (264/8)	Children in health authority locally that authors belong to (no information on where that is)
Edinburgh[96]	Capewell (1997) UK (Edinburgh and Midlothian)	None	1985–93	48,706 (48,094/612)	Local surveillance
Dusseldorf children[7]	Trub (1970) Germany (Dusseldorf county)	None	1954–67	453,297 (187,607/265,690)	General population
Ancona children[111]	Mariotti (1956) Italy (Ancona)	None	1938–40	4933 (2467/2466)	General population

Population inclusion criteria	Follow-up method	BCG vaccination administration and type	Vaccination period	BCG vaccination ascertainment	Reason for BCG vaccination	Age at BCG vaccination	Gender
Tuberculin-negative physicians working in a state that has a legal although not necessarily enforced requirement for annual tuberculin testing or chest radiographs of all hospital employees	Participant recall/self-assessment from questionnaire	Not specified Strain: not specified		Participant recall	Occupational	Adult (> 19 years)	Both
From the 1980–6 birth cohort	Medical records/ hospital data	Intradermal injection Strain: Copenhagen		Records derived from surveys conducted by the Directorate of Chest Diseases	Neonatal	Neonatal (< 1 year), young children (1–5 years), older children (6–11 years)	Both
Graduates from 1938–81 who responded to a questionnaire *Vaccinated*: Tuberculin negative	Participant recall/self-assessment from questionnaire	Intradermal injection Strain: Pasteur		Participant recall	Occupational	Adult (> 19 years)	Both
Children 0–3 years admitted to paediatric service of hospital	Hospital data	Percutaneous injection Strain: not specified		Scar, ink tattoo of scar	Neonatal	Neonatal (< 1 year)	Both
Tuberculin negative	Screening (chest radiography compulsory for matriculation)	Intradermal injection Strain: Danish, Pasteur		Not specified	Occupational	Adult (> 19 years)	Both
Vaccinated: Children at risk of tuberculosis infection due to exposure to active tuberculosis source who were vaccinated *Control subjects:* Tuberculin negative, unvaccinated siblings of the vaccinated children	Matching to surveillance data	Not specified Strain: not specified		Medical records	Neonatal	Neonatal (< 1 year), young children (1–5 years)	Both
Child eligible for schools tuberculin testing, aged 13 years between 1984/85 and 1992/93 inclusive, attending a local school at age 13 years *Vaccinated:* Tuberculin negative	Medical records	Intradermal injection Strain: not specified		Schools medical service records	Neonatal	Not specified	Both
Children from 1 to 15 years old living in Dusseldorf region (either county cities or rural areas)	Matching to surveillance data	Intradermal injection Strain: not specified		Vaccination records	Neonatal	Neonatal (< 1 year)	Both
Children 1 month to 5 years in city of Ancona	Medical records, hospital data	Not specified Strain: not specified		Medical records	Neonatal	Neonatal (< 1 year), young children (1–5 years)	Both

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Study name	Author (year) Country/ region	Additional/ duplicate references	Years of recruitment	*n* cohort (*n* BCG vaccinated/*n* unvaccinated)	Source of population
Morocco children[116]	Gaud (1952) Morocco (Yacoub el Mansour)	Duplicate: [146]	1950–3	1601 (830/771)	General population
Swedish conscripts[113]	Dahlstrom (1951) Sweden	Additional: [147] Duplicate: [148]	1941–4	61,474 (36,235/25,239)	New miliary recruits to Swedish army
Norwegian deported[103]	Oeding (1946) Norway	None	1940–5	227 (62/165)	Norwegian deportees to Germany during WWII

9999, missing.

Population inclusion criteria	Follow-up method	BCG vaccination administration and type	Vaccination period	BCG vaccination ascertainment	Reason for BCG vaccination	Age at BCG vaccination	Gender
Children up to 20 years living in Yacoub el Mansour, testing negative for 10 UI Mantoux	Screening at 6 months follow-up (chest radiography)	Intradermal injection Strain: not specified		Research-related	Research	All ages (range 0–20 years)	Both
Tuberculin negative	Miliary medical records and dispensation records	Intradermal injection Strain: Sahlgrenska Sjukhuset, Gothenburg		Miliary medical records	Occupational	Adult (> 19 years)	Male
Vaccinated: Tuberculin negative	Medical records	Not specified Strain: not specified		Medical records	Not specified	All ages	Male

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Case population studies

Study name Additional/ duplicate references	Author (year)	Case-finding start and end date	Source of population	BCG vaccination ascertainment/ definition	BCG vaccination type	Age at vaccination/ age at outcome assessment
Malaysia 0–19 year olds[159]	WHO (1982) Malaysia	1977–9	0- to 19-year olds with notified case of tuberculosis in national records in 1977–9	Scar	Intradermal	Early childhood/ 0–19 years
Malaysia meningitis[159]	WHO (1982) Malaysia	1976–8	0- to 14-year-olds admitted to Government hospitals in Malaysia	Scar	Intradermal	Early childhood/ 0–14 years
Korea neonatal[159]	WHO (1982) Republic of Korea	1976	Children treated for tuberculosis in a large hospital	Scar	Intradermal assumed	Not reported but all in 0- to 4-year age group so assumed infant/ 0–4 years
Britain surveys[153] Additional[171,172]	Sutherland (1987) UK	1973 1978 1983	Tuberculin negative 15–24 years olds living in Britain at age 13 years	Information sought through local health and education authorities; BCG vaccination reported by clinician confirming details of notified case in survey returns	Intradermal	13 years/ 15–24 years
Birmingham schoolchildren 54–58[152] Data overlaps for 2 years with[172]	Springett (1959) UK	1954–8	Tuberculin-negative children in school in Birmingham at from 1954–8. Given liquid BCG vaccination (Copenhagen)	Not reported	Intradermal	13 years/ 13–18 years
		1956–62				Age 13 years in 1953–61/ 14–16 years in 1956–62
		1962–9				Age 13 in 1961–9/ 13–14 in 1962–9
Israel neonatal[162]	Zilber (1984) Israel	1956–79	Infants born in Israel 1956–79 whose tuberculosis began at age 0 to 12 years during this period with known vaccination status	Notification forms	Not reported	Neonatal/ 0–12 years
Canadian nurses[156]	Burril (1985) Canada	1969–79	Tuberculin-negative Canadian-born women in nursing and related assisting occupations in British Columbia	Recorded in case files	Not reported	At time of training/ >18 years

Number of cases	Case-definition	Number vaccinated/ unvaccinated	Population vaccination ascertainment	Total estimated population during study period (Vaccine coverage calculated or given%)	Total estimated vaccinated/ unvaccinated
719	Notified tuberculosis case	495/224	Vaccine coverage determined in national survey 1976–7	17,544,000 (85%)	14,919,000/ 2,625,000
20	Tuberculosis meningitis	9/11	Not reported	Not reported (83%)	Not reported/ not reported
53	Treated for tuberculosis	7/46	Not reported	Not reported (60%)	Not reported/ not reported
465	Notification of tuberculosis in target population with survey forms returned by clinician	NA/NA	Local authority returns to the health departments for school-children and students	NA (NA)	NA/NA
381		212/168.8		6,812,000 (83%)	5,630,000/ 1182000
313		168/145.4		7,030,000 (99%)	5,783,000/ 1,247,000
40	Notified tuberculosis	4/36	Participant figures	146,319 (67%)	98,140/ 48,179
115.6 (estimated notification in unvaccinated)	Notified tuberculosis	21/94.6	Participant figures	559,470 (66%)	371,414/ 188,056
79.4 (estimated notification in unvaccinated)	Notified tuberculosis	17/62.4	Participant figures	492,744 (80%)	395,315/ 97,429
270	Pulmonary and extrapulmonary tuberculosis at any stage of activity	164/106	Calculated from denominator data (published and unpublished) from the Central Bureau of Statistics of Israel	11,972,249 (71%)	8,552,917/ 3,419,332
22	Pulmonary (post primary, pleural, primary) and extrapulmonary (lymphadenitis, genitourinary, osteoarticular, other)	13/9	Survey of nurses employed at two hospitals randomly selected from the British Columbia register of hospitals applied to population data from statistics Canada and the registered Nurses Association of British Columbia for the population studied over the time period	152,807 (76%)	118,439/ 34,368

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Study name Additional/ duplicate references	Author (year)	Case-finding start and end date	Source of population	BCG vaccination ascertainment/ definition	BCG vaccination type	Age at vaccination/ age at outcome assessment
Brazil meningitis[166]	Martins (1985) Brazil	1983–3	0- to 4-year-olds	Not reported	Intradermal	Neonatal/ 0–4 years
South Asian adults[155]	Chaloner (2002) UK	1982–2000	Indian subcontinent new immigrants who had entered the districts of Blackburn, Hyndburn and Ribble Valley between 1 January 1982 and 31 December 1998 inclusive, with a Heaf grade 0–1 and to who BCG vaccination had been administered and still registered locally with a GP	Recorded on individual cards and filed	Not reported, because of dates and population, assumed intradermal	Adult aged 15–34 years (vaccination upon entry into UK)/>18 years
Quebec meningitis[157]	Frappier (1962) Canada	1949–56	0- to 10-year-olds	Medical records	Scarification (subcutaneous)	Neonatal/ 0–10 years
Taiwan meningitis[167]	Chan (2008) Taiwan, Province of China	2002–7	0- to 5-year-olds	Not reported	Not reported	Neonatal/0
Bydgoszcz children[160]	Krzyszkowska (1956) Poland	1950–3	0–14 years	Medical records	Intradermal	Neonatal/ 10–14 years
Singapore schoolchildren[165]	Chew (1974) Singapore	1972	Tuberculin-negative secondary schoolchildren	Screening of all students for presence of scar	Intradermal	Neonatal or preschool (<6 years) or primary school entry (6 years) or primary school departure (12–13 years)/0
France schoolchildren[168] Additional[173]	Schwoebel (1994) France	1990	Children <5 years residing in France with CSF sample taken between January 1 and 31 December 1990	BCG vaccination status was reported in collected from laboratories reporting case	Scarification method	Minimum 6 months before *M. tuberculosis* diagnosis/ 0–4 years
Manchester hospital[154]	Curtis (1984) England	1975–80	0- to 14-year-olds, born to Manchester residents in 1968–80, still present in the city in 1980	Hospital records	Intradermal	Neonatal/0

Number of cases	Case-definition	Number vaccinated/ unvaccinated	Population vaccination ascertainment	Total estimated population during study period (Vaccine coverage calculated or given%)	Total estimated vaccinated/ unvaccinated
Not reported	Bacteriologically confirmed tuberculosis meningitis	Not reported/not reported	Demographic data	Not reported (not reported)	Not reported/ not reported
2	One is sputum smear negative, culture positive and one is sputum smear and culture positive	2/0	NA	Expected number of cases was 16.1 yielding a standardised incidence ratio of 0.124 (0.015 to 0.448) (NA)	NA/NA
139	Bacteriologically/ cytologically confirmed death from tuberculosis meningitis (ICD-6)	5/133	Records	8,735,000 (24%)	2,058,000/ 6,632,100
12	Notified tuberculosis meningitis	8/4	Not reported	1,290,000 (97%)	1,251,300/ 38,700
583	'Full clinical investigation' confirming that cases presenting with abnormal chest radiograph pictures were in fact tuberculosis, no other details	23/560	Demographic records	50,208 (43%)	21,730/ 28,478
92	Active tuberculosis	41/51	Detailed records of BCG vaccination held by the school tuberculosis Section of the tuberculosis Control Unit	161,000 (75%)	120,750/ 40250
6	CSF sample culture positive for *M. tuberculosis* complex	2/4	BCG coverage based on unpublished data on vaccination coverage from the Department of Statistics at the Ministry of Health	3,900, 000 (80%)	3,100,000/ 800,000
65	Notified tuberculosis cases plus four found in hospital activity analysis	4 (St Mary's Hospital Manchester)/6 (St Mary's Hospital Manchester) +55 (other hospitals)	Name-counting on weekly returns and systematic 1 in 55 sampling of St Mary's Hospital birth register	674,000 person-years (NA)	High estimate: 152,800 person-years; low estimate: 113800 person-years

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Study name Additional/ duplicate references	Author (year)	Case-finding start and end date	Source of population	BCG vaccination ascertainment/ definition	BCG vaccination type	Age at vaccination/ age at outcome assessment
			0- to 14-year-olds, born to at St Mary's Hospital Manchester residents in 1968–80, still present in the city in 1980			Neonatal/0
Czechoslovakia meningitis[170]	Votjek (1960) Czechoslovakia	1954–8	0- to 4-year-olds (born 1954–8, Czech region)	Records	Not reported	Neonatal/0
			0- to 4-year-olds (born 1954–8, Slovak region)	Records	Not reported	Neonatal/0
Quebec pulmonary[158]	Frappier (1971) Canada	1956–61	0–29 years (non-American Indian, 'Eskimo' or immigrant)	Individual files in central BCG record system	Scarification (subcutaneous)	Neonatal or 5–9 years/0
Ireland surveys[167]	Kelly (1997) Ireland	1986	National Tuberculosis Surveys	Areas that have a neonatal vaccination policy and those that do not from National Tuberculosis Surveys of 1986	0	Neonatal/ all ages
		1991	National Tuberculosis Surveys	Areas that have a neonatal vaccination policy and those that do not from National Tuberculosis Surveys of 1991	0	Neonatal/ All ages
Cologne children[164]	Lotschert (1983) Germany	1967–76	0- to 15-year-olds	Medical records	Not reported	Neonatal/ 0–15 years
Hungary 4–14[163] Duplicate[174]	Lugosi (1985) Hungary	1964	Children born in 1950–60 with all form tuberculosis both BCG vaccinated and unvaccinated in 1964	Data on antituberculous measures (including BCG) has been provided by 20 departmental tuberculosis dispensaries based on principles standardised in 1953	Not reported but assumed intradermal owing to time of study	Neonatal + revaccination in those 3–20 years so maybe have some revaccination/ 4–14 years

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Number of cases	Case-definition	Number vaccinated/ unvaccinated	Population vaccination ascertainment	Total estimated population during study period (Vaccine coverage calculated or given%)	Total estimated vaccinated/ unvaccinated
10	Notified tuberculosis cases	4/6	21.9	NA (NA)	High estimate: 521,200 person-years; low estimate: 386,800 person-years
30	Notified tuberculosis meningitis	15/15	Not reported	793,976 (95%)	753,138/ 40,838
157	Notified tuberculosis meningitis	32/125	Not reported	487,665 (86%)	415,904/ 71,761
6345	Minimal tuberculosis or moderately advanced or advanced tuberculosis, miliary tuberculosis or primary infection or tuberculous pleurisy	546/5799	Records from individual files from central BCG record system	17,460.5 (38%)	6601.4/ 10,859.1
756	Not reported	536/220	Areas that have a neonatal vaccination policy and those that do not from National Tuberculosis Surveys of 1986 and 1991	3,496,871 (73%)	2,563,836/ 933,035
582	Not reported	371/211	Areas that have a neonatal vaccination policy and those that do not from National Tuberculosis Surveys of 1986 and 1994	3,523,399 (88%)	2,499,725/ 1,023,674
216	Tuberculosis disease (all types)	63/153	Demographic statistic estimations	164,700 (80%)	131,760/ 32,940
145	All forms of tuberculosis	56/89	Data on antituberculosis measures (including BCG) has been provided by 20 departmental tuberculosis dispensaries based on principles standardised in 1957	660,839 (76%)	499,250/ 161,589

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Cross-sectional studies

Study name	Author (year) Country/region	Additional/ duplicate references	Years of recruitment	Number BCG vaccinated/ number unvaccinated	Source of population	Population inclusion criteria
Contact studies						
Madrid contacts[175]	Castan Vidal (1991) Spain (Madrid)	None	9999	114/101 (109 index cases)	Single hospital	*Index cases*: recently diagnosed cases of sputum-positive pulmonary tuberculosis with positive bacilloscopy and culture *Contacts*: All close contacts of index cases < 15 years old
Rio de Janeiro contacts[179]	Kritski (1996) Brazil (Rio de Janeiro and six neighbouring municipalities)	None	1988– 92	153/65 (64 index cases)	Single hospital: Chest Service of the Federal University of Rio de Janeiro	*Index cases*: Multidrug resistant tuberculosis cases, the first in the household to be diagnosed with tuberculosis and HIV negative *Contacts:* People living in the same household as the index case during the entire previous 5 years. HIV negative
Bangkok contacts[188]	Padungchan (1986) Thailand (Bangkok)	None	1981– 4	1253/253 (971 index cases)	Single hospital: Central chest clinic	*Index cases*: Newly detected smear-positive pulmonary tuberculosis cases *Contacts*: Household child contacts, < 5 years old
Togo contacts[178]	Tidjani (1986) Togo (Lome)	None	9999–9999	875/523 (352 index cases)	Not specified	*Index cases*: newly detected smear positive pulmonary tuberculosis patients *Contacts*: ≤ 6 years old, household contact
Togo children[177]	Tidjani (1992) Togo (Lome)	None	1988–9	504/201 (201 index cases)	Single hospital: University of Lome hospital	*Index cases*: bacteriologically confirmed pulmonary tuberculosis case *Contacts*: immediate/close contacts of index cases – 6 years old not lost to follow-up and with complete examination results, with definite BCG vaccination status (unknowns excluded)
Irkutsk Russian[192]	Khadeeva (2003) Russian Federation (Irkutsk region)	None	2003	277/99 (unknown number of index cases)	Local surveillance: Irkutsk region	*Index cases*: tuberculosis cases *Contacts*: close relatives of infected cases
Egypt contacts[189]	Mahmoud (1986) Egypt (Bab-El-Shaaria and El-Hussin)	None	9999–9999	200/240 (137 index cases)	Multiple hospitals and chest dispensary	*Index cases*: Newly diagnosed pulmonary tuberculosis cases with positive sputum by direct smear and/or culture
General population studies						
Kenya[187]	Aluoch (1985) Kenya (Kirinyaga, Kitui, Siaya and Kwale)	None	1979– 82	971/1159	Multiple hospitals	Outpatients from four district hospitals aged ≥ 6 years, with main complaint of cough and/or sputum for 1 month or more or haemoptysis of any duration
Liege children[182]	Bassleer (1972) Belgium (Liege)	None	1950– 62	1085/4631	Multiple hospitals: tuberculosis dispensaries in Liege	Children examined in dispensaries in 1950 to 1965

BCG vaccination administration and type	Vaccination period	BCG vaccination ascertainment	Reason for BCG vaccination	Age at BCG vaccination	Gender
Assumed intradermal (BCG vaccination status assessed through scar) Strain: not specified	Not specified	Vaccination card, scar	Neonatal	Neonatal (< 1 year)	Both
Not specified Strain: not specified	Not specified	Scar	Not specified	Not specified	Both
Assumed intradermal (BCG vaccination status assessed through scar) Strain: Merieux	Not specified	Vaccination card, scar	Neonatal	Neonatal (< 1 year)	Both
Assumed intradermal (BCG vaccination status assessed through scar) Strain: Glaxo	Not specified	Parents of participant recall, scar	Neonatal	Neonatal (< 1 year)	Both
Assumed intradermal (BCG vaccination status assessed through scar Strain: not specified	Not specified	Parents of participant recall, scar	Neonatal/ childhood vaccination	Neonatal (< 1 year), young child (1–5 years)	Both
Assumed intradermal (BCG vaccination status assessed through scar Strain: not specified	1961–9999	Scar	Neonatal	Neonatal (< 1 year)	Both
Assumed intradermal (BCG vaccination status assessed through scar Strain: not specified	Not specified	Participant recall, scar	Not specified	Not specified	Both
Assumed intradermal (BCG vaccination status assessed through scar Strain: not specified	Not specified	Scar	Childhood vaccination	Neonatal (< 1 year), young child (1–5 years), older child (6–11 years), teen (12–18 years)	Both
Assumed intradermal (BCG vaccination status assessed through scar Strain: not specified	Not specified	Not specified	Not specified	Neonatal (< 1 year), young child (1–5 years), older child (6–11 years), teen (12–18 years), mean: 4 years	Both

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Study name	Author (year) Country/region	Additional/ duplicate references	Years of recruitment	Number BCG vaccinated/ number unvaccinated	Source of population	Population inclusion criteria
Surui Indians[180]	Basta (2006) Brazil (Rondonia)	None	2003	699/37	Population subgroup: Surui Indians	Willing participants in the survey
Naples classroom[185]	Biscione (1969) Italy (Naples)	Duplicate: [194]	1967	14/19	Schoolchildren	All children in one classroom where a high percentage of Mantoux positivity was detected in routine screening
Madras[186]	Chandra (1975) India (Madras)	Additional: [195]	1968–70	232/362	Single hospital	Children < 10 years of age recruited through the Employees State Insurance Hospital, all with some type of illness
Vaupes population[191]	Garcia (2004) Colombia (Mitú, Vaupes)	None	2001	14/958	165 households in town of Mitú	Part of random cluster sampling (20 clusters, 165 households visited, 972 participants selected)
Bas-Rhin[184]	Lotte (1988) France (Bas-Rhin Region)	None	1965– 84	3,104,656/ 1,159,744	General population: Bas-Rhin region	Children < 15 years
Madrid students[176]	Zapatero-Dominguez (1986) Spain (Madrid)	Duplicate: [196]	1969– 83	58,384/78,485	Students of the Madrid Complutense University	Any student who was observed, upon entry to the university, by the Chest Unit
Lebanese children[193]	Sleiman (2007) Lebanon	None	2004	2325/1946	Schoolchildren	Children from selected schools in Lebanon aged 3–19 years without chronic disease, undergoing any immunosuppressive treatment, no symptoms of viral illness that could be early signs of measles and would interfere with PPD reading, no allergic diseases
Opstine Zvezdara[183]	Horvat-Grubac (1963) Yugoslavia (Opstine Zvezdara)	None	1959– 61	3/1	Local surveillance	Families with tuberculosis
Cape Town children[190]	Mahomed (2006) South Africa (Cape Town)	None	1999–2002	2766/48	Multiple hospitals and local surveillance	Children who were < 2 years of age when diagnosed with tuberculosis; born in Cape Town from January 1999 to June 2000 and those born between January 2001 and June 2002; listed in tuberculosis registry and at health facilities as having tuberculosis after review of medical records by study clinicians
Tohoku outpatients[181]	Ebina (1959) Japan (north-east/Tohoku)	None	1949– 53	2147/1990	Single hospital: (Research Institute for Tuberculosis and Leprosy, Tohoku University)	BCG vaccinated and unvaccinated persons who, because of symptoms suggestive of tuberculosis, attended the outpatient clinic or treated in the hospital; between 14 and 25 years of age and residing in the north-east district of Japan

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BCG vaccination administration and type	Vaccination period	BCG vaccination ascertainment	Reason for BCG vaccination	Age at BCG vaccination	Gender
Assumed intradermal (BCG vaccination status assessed through scar Strain: not specified	Not specified	Scar	Not specified	Not specified	Both
Not specified Strain: not specified	1961–2	Not specified	Neonatal	Older child (6–11 years)	Male
Intradermal injection Strain: not specified	Not specified	Not specified	Neonatal	Neonatal (< 1 year)	Both
Assumed intradermal (BCG vaccination status assessed through scar Strain: not specified	Not specified	Scar	Neonatal	Neonatal (< 1 year)	Both
Intradermal injection Strain: not specified	Not specified	Review from regional register	Neonatal	Neonatal (< 1 year), young child (1–5 years), older child (6–11 years)	Both
Assumed intradermal (BCG vaccination status assessed through scar Strain: not specified	Not specified	Vaccination card, Scar	Not specified	Older child (6–11 years), teen (12–18 years)	Both
Assumed intradermal (BCG vaccination status assessed through scar Strain: not specified	Not specified	Scar	Neonatal	Not specified	Both
Not specified Strain: not specified	Not specified	Not specified	Neonatal	Neonatal (< 1 year), young child (1–5 years)	Both
Intradermal injection Strain: Statens, Tokyo	Not specified	Medical records, Parents of participant recall	Neonatal	Neonatal (< 1 year)	Both
Intradermal injection Strain: not specified	Not specified	Not specified	Not specified	Not specified	Both

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Outbreak studies

Study name	Author (year) Country/ Region	Additional/ duplicate references	Years of outbreak and subsequent investigation	Number of tuberculosis cases vaccinated/ unvaccinated	Number BCG vaccinated/ Number unvaccinated	Source of population	Inclusion criteria
Danish school[203]	Hyge (1957) Denmark (Copenhagen)	[204, 205]	1943	0/41	133/105	Single school	School girls in a Danish state school at the time of a tuberculosis epidemic caused by the teacher source case
Cork girls school[197]	Bredin (1991) Ireland (Cork)		1986–90	4/2	342/262	Girls' school	Girls at a girls' school in Cork, Ireland
Cork toddler[198]	Gaensbauer (2009) Ireland (Cork)		2007	0/18	64/204	Two child care centres in Cork, Ireland	Children attending two child care centres where the source cases were two tuberculosis diseased carers
Community C[200]	Long (2004) Canada (AB)		1991–2000	1/17	2/30	Community C First Nations outbreak	Paediatric contacts of index cases
Community I[200]	Long (2004) Canada (AB)		1991–2000	10/3	18/9	Community I First Nation reserve	Paediatric contacts of index cases
Donegal school[199]	Shannon (1991) Ireland (Donegal)		1986	6/9	909/251	Secondary school	Pupils attending, or recently left, a secondary school in Donegal Ireland
Stockholm dental school[201]	Bergqvist (1947) Sweden (Stockholm)		1945–6	10/4	44/14	New students entering Stockholm Dentistry school in 1944	Tuberculin negative dentist school students attending same classes as initial case in outbreak
Grade 7 students[202]	Hertzberg (1947) Norway (Oslo)		1941–6	2/77	233/141	Seventh grade students	Seventh grade students offered vaccination

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BCG vaccination administration and type	Vaccination policy	Vaccination period	BCG vaccination ascertainment	Reason for BCG vaccination	Age at BCG vaccination	Gender
Not reported (not reported)	Not reported	1942	Not reported	Not specified	Teen (12–18 years)	Female
Intradermal injection (not reported)	Neonatal BCG vaccination was discontinued in Ireland in December 1972	Not specified	Scar/signed community care records	Neonatal	Neonatal (< 1 year)	Female
Not reported (not reported)	Not reported	Not specified	Not reported	Neonatal	Neonatal (< 1 year)	Both
Not reported (not reported)	BCG vaccination is offered to Inuit and on-reserve First Nations children born to mothers who tested negative for HIV prenatally	Not specified	Not reported	Neonatal	Neonatal (< 1 year)	Both
not reported (not reported)	BCG vaccination is offered to Inuit and on-reserve First Nations children born to mothers who tested negative for HIV prenatally	Not specified	Not reported	Neonatal	Neonatal (< 1 year)	Both
Intradermal injection (not reported)	Policy of Community Care Area to give neonatal BCG vaccination	Not specified	Vaccination card/scar	Neonatal/ childhood	Neonatal (< 1 year), young child (1–5 years), older child (6–11 years)	Both
Not reported (not reported)	Not reported	Not specified	Not reported	Not specified	Not specified	Both
Not reported (not reported)	Not reported	1941–6	Vaccination at school so records held there	School offers vaccination in grade 7	Teen (12–18 years)	Both

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Appendix 4

Quality assessment results

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Clinical trials

Study name	Author	Country	Year started	Was the allocation sequence adequately generated?	Was treatment allocation adequately concealed?	Was knowledge of the allocated intervention prevented during the study?	Were incomplete outcome data adequately addressed?	Are reports of the study free from the suggestion of selective outcome reporting?	Was ascertainment of cases comparable?	Was diagnosis detection bias prevented?
Native American[5]	Aronson	USA	1935	No	Unclear	Yes	Unclear	Yes	Yes	Yes
Turtle and Rosebud infants[45]	Aronson	USA	1938	No	Unclear	No	Yes	Yes	Yes	Yes
Illinois mentally handicapped[50]	Bettag	USA	1947	Unclear	Unclear	No	Yes	Yes	Yes	No
African gold miners[54]	Coetzee	South Africa	1965	No	Unclear	No	Yes	Yes	Yes	Yes
Saskatchewan infants[13]	Ferguson	Canada	1933	Unclear	Unclear	No	Yes	Yes	Yes	Yes
Madanapalle[53]	Frimodt-Moller	India	1950	Unclear	Unclear	No	No	Unclear	Unclear	Yes
NY infants randomised[12]	Levine	USA	1933	No	No	No	Unclear	Yes	Yes	Yes
MRC[14]	MRC	UK	1950	No	Unclear	No	Unclear	Yes	Yes	Yes
Agra[51]	Mehrotra	India		Unclear	Unclear	No	Unclear	Yes	Unclear	Yes
Bombay infants[52]	Mehta	India		Unclear	Unclear	No	Unclear	Yes	Yes	Yes
Georgia/Alabama[15]	Palmer	USA	1950	No	No	No	Yes	Yes	Yes	Unclear
Puerto Rico children[15]	Palmer	USA	1949	No	No	No	Unclear	Yes	Yes	No
Chicago nurses[47]	Rosenthal	USA	1940	No	Unclear	Unclear	Unclear	Yes	Yes	Yes
Chicago medical students[46]	Rosenthal	USA	1939	Unclear	Unclear	Unclear	Unclear	Yes	Unclear	No
Chicago Infants TT HH[48]	Rosenthal	USA	1941	No	Yes	No	Yes	Yes	Yes	Yes
Chicago Infants CCH[48]	Rosenthal	USA	1937	No	Unclear	No	Yes	Yes	Yes	Yes
Ida B Wells housing project[44]	Rosenthal	USA	1942	No	Unclear	Unclear	Unclear	Yes	Yes	Yes
US mental Health patients[44]	Rosenthal	USA	1944	No	Unclear	No	Unclear	Yes	Unclear	No
Georgia (school)[49]	Shaw	USA	1947	No	No	No	Unclear	Yes	Yes	No
Chingleput[28]	TBPT	India	1968	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Haiti[55]	Vandiviere	Haiti	1965	Unclear	Yes	Yes	Yes	Yes	Yes	Yes

Case–control studies

Study name	Author	Country	Year started	Were vaccination definitions the same for cases and control subjects?	Was disease status blinded to BCG assessors?	Were control sampled from the same population that gave rise to the cases?	Were cases and control subjects determined independently of BCG vaccination status?	Was this a matched study?	If a matched study design was a matched analysis performed?	Were study results adjusted for SES?
Saudi Arabia[77]	Al-Kassimi	Saudi Arabia	1991	Yes	No	Yes	Yes	No		No
Lucknow children[60]	Awasthi	India	1995	Yes	Unclear	Yes	Yes	No		Yes
Delhi[57]	Bhattacharjee	India	1989	Yes	Unclear	Yes	Unclear	Yes	Yes	No
Madagascar children[79]	Boileau	Madagascar	1992	Yes	Unclear	Yes	Yes	Yes	No	No
Brazil[67]	Camargos	Brazil	1975	Yes	No	Yes	Unclear	Yes	Yes	Yes
Bangalore children[56]	Chadha	Bangalore		Yes	Unclear	Yes	Unclear	Yes	No	Yes
Thailand[66]	Chavalittemrong	Thailand	1980	Yes	Unclear	Yes	Unclear	No		No
Canada 1975[63]	Houston	Canada	1975	Yes	Unclear	Yes	Yes	Yes	Yes	Yes
Lucknow paediatric[61]	Kumar	India		Yes	No	Yes	Yes	No		Yes
Korea[71]	Kwong	Repiblic of Korea	1979	No	No	Yes	Yes	Yes	No	No
Mexico[78]	Martinez-Gonzalez	Mexico	1991	Yes	Unclear	Yes	Yes	Yes	No	Yes
Argentina[72]	Miceli	Argentina	1981	Yes	Unclear	Yes	Yes	No		No
Dehli paediatric[58]	Mittal	India	1993	Yes	No	Yes	Yes	No		No
Papua New Guinea children[69]	Murtagh	Papua New Guinea	1975	Yes	No	Yes	Yes	No		No
Myanmar[74]	Myint	Myanmar	1983	Yes	Unclear	Yes	Yes	Yes	No	Yes
Birmingham UK[33]	Packe	UK	1965	Yes	Unclear	Yes	Yes	Yes	Yes	No
Nepal[75]	Pust	Nepal	1983	No	No	Yes	Unclear	Yes	No	No
Indonesia[73]	Putrali	Indonesia	1981	Yes	Unclear	Yes	Unclear	Yes	No	No
Asian children in UK[32]	Rodrigues	UK		Yes	Unclear	Yes	Yes	Yes	Yes	Yes
Cali children[70]	Shapiro	Colombia	1977	Yes	Unclear	Yes	Yes	Yes	Yes	No
Bangkok children[65]	Sirinavin	Thailand	1987	Yes	Unclear	Yes	Yes	Yes	Yes	Yes
Osaka children[76]	Takamatsu	Japan	1988	Unclear	Unclear	Yes	Yes	Yes	No	Yes
India[59]	Thilothammal	India	1990	Yes	Unclear	Yes	Unclear	Yes	No	No
São Paulo[68]	Wunsch Filho	Argentina	1981	Yes	Unclear	Yes	Yes	Yes	Yes	Yes
Canada[64]	Young	Canada	1979	Yes	Unclear	Yes	Unclear	No		No
Nagpur hospital[62]	Zodpey	India	1994	Unclear	Unclear	Yes	Yes	Yes	Yes	Yes

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Cohort studies

Study name	Author	Country	Year started	Was case ascertainment blinded to vaccination status?	Were methods of case ascertainment identical for vaccinated and unvaccinated groups?	Were losses to follow-up similar in each group?	Was diagnosis detection bias prevented?	Were study results adjusted for SES?
Brazil REVAC[6]	Barreto	Brazil	1996	No	Yes	Unclear	Yes	Yes
US physicians[95]	Barrett-Connor	USA	1974	No	Yes	Unclear	No	No
Jordan[119]	Batieha	Jordan	1980	No	Yes	Unclear	No	No
Dutch nurses[112]	Bergsma	Netherlands	1939	No	Yes	Unclear	Yes	No
Norway[101]	Borgen	Norway	1947	No	Yes	No	Yes	No
Edinburgh 1977 contacts[97]	Capewell	UK	1977	No	Yes	Unclear	No	No
Edinburgh[96]	Capewell	UK	1985	No	Yes	Unclear	No	No
Philadelphia nurses[92]	Chakravarty	USA	1950	No	Yes	Unclear	Yes	No
Dublin nurses[115]	Counihan	Ireland	1949	No	Yes	Yes	No	No
Hesse 23 districts[106]	Daelen	Germany	1947	Unclear	Unclear	Unclear	No	No
Swedish conscripts[113]	Dahlstrom	Sweden	1941	No	Yes	Yes	No	No
Boston nurses[89]	DeFriez	USA	1947	No	Yes	Unclear	No	No
Lyon students[108]	Despierres	France	1956	No	Yes	No	Yes	No
Hamburg children[105]	Ehrengut	Germany		Unclear	Unclear	Unclear	Unclear	No
Morocco children[116]	Gaud	Morocco	1950	No	Yes	Yes	Yes	No
Chicago medical students[90]	Geiseler	USA	1938	No	Yes	Yes	No	No
French children[109]	Gernez-Rieux	France	1948	No	Yes	Yes	Yes	No
Uruguay infants[114]	Gomez	Uruguay	1943	No	Yes	Unclear	No	No
Oslo nurses[150]	Heimbeck	Norway	1927	No	Yes	Unclear	No	No
UK contacts[99]	Horne	UK	1973	No	Yes	Unclear	Yes	No
Seoul contacts[120]	Jin	Republic of Korea	1984	Yes	Yes	Unclear	Yes	No

Study name	Author	Country	Year started	Was case ascertainment blinded to vaccination status?	Were methods of case ascertainment identical for vaccinated and unvaccinated groups?	Were losses to follow-up similar in each group?	Was diagnosis detection bias prevented?	Were study results adjusted for SES?
Virginia infants[94]	Kendig	USA	1948	No	Yes	Unclear	No	No
Richmond infants[93]	Kendig	USA	1949	No	Yes	Unclear	Yes	No
New York infants[91]	Kereszturi	USA	1927	No	Yes	Unclear	No	No
Rzeszow children[118]	Kubit	Poland	1965	No	Yes	Unclear	No	No
Bangui contacts[121]	Lanckriet	Bangui	1989	Yes	Yes	Unclear	Yes	No
Siblings cohort[107]	Liebknecht	Germany	1949	No	Yes	Unclear	No	No
Ancona children[111]	Mariotti	Italy	1938	No	Yes	Unclear	No	No
Norwegian deported[103]	Oeding	Norway	1940	No	Yes	Unclear	No	No
Bornholm[151]	Olsen	Denmark	1936	No	Yes	Unclear	No	No
Karonga[24]	Ponnighaus	Malawi	1979	Unclear	Yes	Unclear	No	Yes
Edinburgh contacts[98]	Rubilar	UK	1982	Unclear	Unclear	Unclear	Yes	No
Bougie schoolchildren[117]	Sarrouy	Algeria	1950	No	Yes	Unclear	Yes	No
Dusseldorf children[149]	Trub	Germany	1954	No	Yes	Unclear	No	No
Norway[102]	Tverdal	Norway	1956	Unclear	Yes	Yes	Unclear	No
Strasbourg students[110]	Vaucher	France	1947	No	Yes	Unclear	Yes	No
Medical students UK[100]	Verney	UK	1949	No	Unclear	Unclear	No	No
Trysil Norway[104]	Anon.	Norway	1927	No	Yes	Unclear	No	No

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Case population studies

Study name	Author	Were cases and population the same in terms of *time*?	Were cases and population the same in terms of *geography*?	Were cases and population the same in terms of *age*?	Was case ascertainment blinded to vaccination status?	Was disease status blinded to BCG assessors?	Were methods of case ascertainment same for vaccinated and unvaccinated?
Malaysia 0- to 19-year-olds[159]	WHO	Yes	Yes	Yes	No	No	Yes
Malaysia meningitis[159]	WHO	Yes	Yes	Yes	No	No	Yes
Korea 1976[159]	WHO	Yes	Yes	Yes	Unclear	Unclear	Yes
Britain survey[153]	Sutherland	Yes	Yes	Yes	No	No	Yes
France case population[168]	Schwoebel	Yes	Yes	Yes	Yes	No	Yes
Birmingham schoolchildren 54–58[152]	Springett	Yes	Yes	Yes	No	Yes	Yes
Israel neonatal[162]	Zilber	Yes	Yes	Yes	Unclear	Unclear	Yes
Canadian nurses[156]	Burril	Yes	Yes	Yes	Unclear	No	Yes
Brazil meningitis[166]	Martins	Yes	Yes	Yes	Unclear	Unclear	Unclear
South Asian adults[155]	Chaloner	Yes	No	Yes	Unclear	Unclear	Yes
Quebec meningitis[157]	Frappier	Yes	Yes	Yes	Yes	Yes	Yes
Taiwan meningitis[169]	Chan	Yes	Yes	Unclear	Unclear	Unclear	Yes
Bydgoszcz children[160]	Krzyszkowska	Yes	Yes	Yes	No	No	Unclear
Singapore schoolchildren[165]	Chew	Yes	Yes	Yes	Unclear	No	Unclear
France schoolchildren[168]	Schwoebel	Yes	Yes	Yes	Unclear	Unclear	Yes
Manchester hospital[154]	Curtis	Yes	Yes	Yes	Unclear	Unclear	Yes
Czechoslovakia meningitis[170]	Votjek	Yes	Yes	Yes	Unclear	Unclear	Yes
Quebec pulmonary[158]	Frappier	Yes	Yes	Yes	Yes	Yes	Yes
Ireland survey[167]	Kelly	Yes	Yes	Yes	No	Yes	Yes
Cologne children[164]	Lotschert	Yes	Yes	Yes	No	No	Unclear
Hungary 4- to 14-year-olds[163]	Lugosi	Yes	Yes	Yes	Unclear	Unclear	Yes

Cross-sectional studies

Study name	Author	Country	Year started	Were cases (and control subjects) ascertainment blinded to vaccination status?	Was disease status blinded to BCG assessors?	Were cases and control subjects ascertained independently of vaccine status?	Were study results adjusted for SES?
Kenya[187]	Aluoch	Kenya	1979	Yes	Unclear	Yes	No
Liege children[182]	Bassleer	Belgium	1950	Unclear	Unclear	Yes	No
Surui Indians[180]	Basta	Brazil	2003	Yes	Unclear	Yes	No
Naples classroom[185]	Biscione	Italy	1967	Yes	No	Yes	No
Madrid contacts[175]	Castan Vidal	Spain		Yes	Unclear	Yes	No
Madras[186]	Chandra	India	1968	Yes	Unclear	Unclear	No
Tohoku outpatients[181]	Ebina	Japan	1949	Unclear	Unclear	Yes	No
Vaupes population[191]	Garcia	Colombia	2001	Yes	No	Yes	No
Opstine Zvezdara[183]	Horvat-Grubac	Yugoslavia	1959	Unclear	Unclear	Yes	No
Rio de Janeiro contacts[179]	Kritski	Brazil	1988	Yes	Unclear	Yes	Yes
Egypt contacts[189]	Mahmoud	Egypt		Yes	Unclear	Yes	No
Cape Town children[190]	Mahomed	South Africa	1999	Yes	Unclear	Unclear	No
Bangkok contacts[188]	Padungchan	Thailand	1981	Yes	Unclear	Yes	No
Lebanese children[197]	Sleiman	Lebanon	2004	Yes	Unclear	Yes	No
Togo contacts[178]	Tidjani	Togo		Yes	Unclear	Yes	No
Togo children[177]	Tidjani	Togo	1988	Yes	Yes	Yes	No
Irkutsk Russian[192]	Khadeeva	Russian Federation	2003	Yes	Unclear	Yes	No
Madrid students[176]	Zapatero-Dominguez	Spain	1969	Yes	Unclear	Yes	No

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Study name	Author	Country	Was follow-up independent of vaccination status?	Was case ascertainment blinded to vaccination status?	Were losses to follow-up similar in each group?	Were methods of ascertainment of cases identical for vaccinated and unvaccinated groups?	Were data reported for all pre-specified subgroup analyses?	Were vaccination definitions the same for everyone in the study?	Was disease status blinded to BCG assessors?	Were control subjects selected from the same population as the cases?	Were cases and control subjects ascertained independent of vaccine status?
Cork girls school outbreak[197]	Bredin	Ireland				Yes	Yes				
Cork toddler outbreak[198]	Gaensbauer	Ireland						Yes	Unclear		Yes
Community I Canada outbreak[200]	Long	Canada						Yes	Unclear		Yes
Donegal school outbreak[199]	Shannon	Ireland				Yes	Yes				
Stockholm Dental School outbreak[201]	Bergqvist	Sweden						Yes	Unclear		Yes
Danish school outbreak[203]	Hyge	Denmark	Yes	Unclear	Yes						
Community C Canada outbreak[200]	Long	Canada	Yes	Yes	Yes						
Grade 7 students[202]	Hertzberg	Norway	Yes	Unclear	Years						

Appendix 5

List of excluded studies

Of the 847 full-text articles identified for potential inclusion into the review, 636 were excluded. The reasons for exclusion for these studies are found in *Table 32*.

Unable to obtain papers

1. Anon. Prophylaxis by means of BCG in doctors' families. *Ann Inst Pasteur* 1962;**49**:5.
2. Anon. Review of BCG vaccination programmes. Preliminary Report by the Director-General. (Executive Board Twenty-Fourth Session, Geneva, 1 and 2 June 1959. Annex 3.) Official Records of the World Health Organization 1959;**96**:19–50.
3. Alonso AE. Value of BCG vaccine in the prophylaxis of childhood tuberculosis. *Pediatr Panama* 1972;**1**:544–97.
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TABLE 32 Reasons for exclusion of 636 references identified in title and abstract screening for inclusion

Reason	Number of papers excluded on this basis
Unable to obtain papers	48
Not a primary study	77
Inappropriate study type	229
Study did not include BCG vaccinated and unvaccinated participants	74
Study did not report outcome data on tuberculosis disease and/or tuberculosis mortality	63
Study outcome was tuberculosis infection	21
Study did not report individual-level data to construct a 2 × 2 table	25
Study participants were only tuberculosis patients	16
Study included revaccinated participants	30
Animal studies	21
BCG vaccination studied was orally administered	32
Total	*636*

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Inappropriate study type

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Appendix 6

Results for other tuberculosis outcomes and stratifications

Efficacy

Randomised controlled trials

Stratified analysis by 20° latitude, ordered by year study started

Pulmonary tuberculosis

See *Figure 121*.

All tuberculosis disease outcomes

See *Figure 122*.

Combined tuberculosis meningitis and/or miliary tuberculosis

See *Figure 123*.

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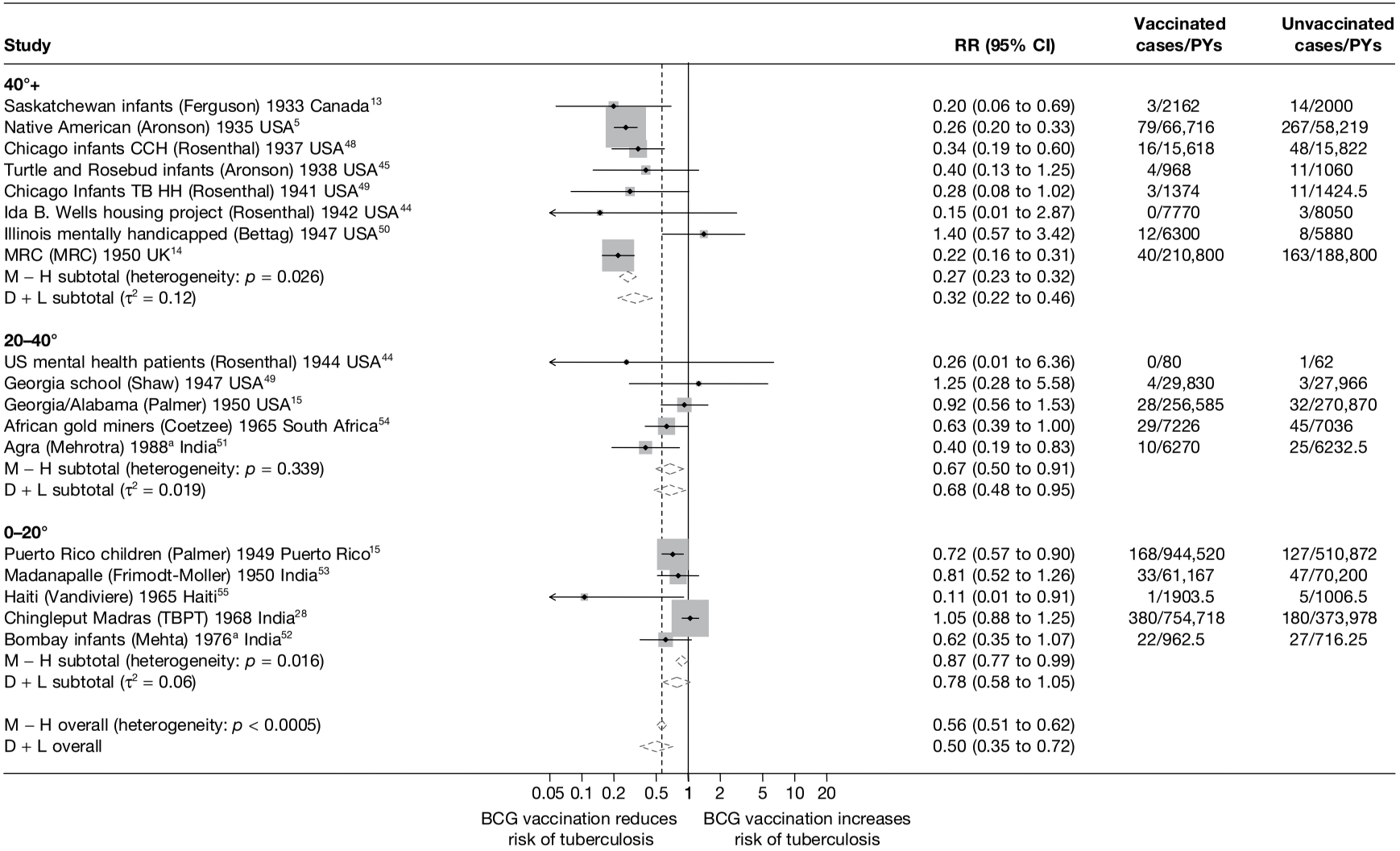

FIGURE 121 Rate ratios (with 95% CI) comparing the incidence of pulmonary tuberculosis among BCG vaccinated individuals with that in unvaccinated individuals for the longest duration of follow-up (see *Table 3*) in RCTs, stratified by latitude of study location (20° bands), ordered by year of study start. a, Date of study publication was used if study start date was not available. CCH, Cook County Hospital; D+L, DerSimonian and Laird method; M–H, Mantel–Haenszel method; TB HH, tuberculosis households; TBPT, Tuberculosis Prevention Trial.

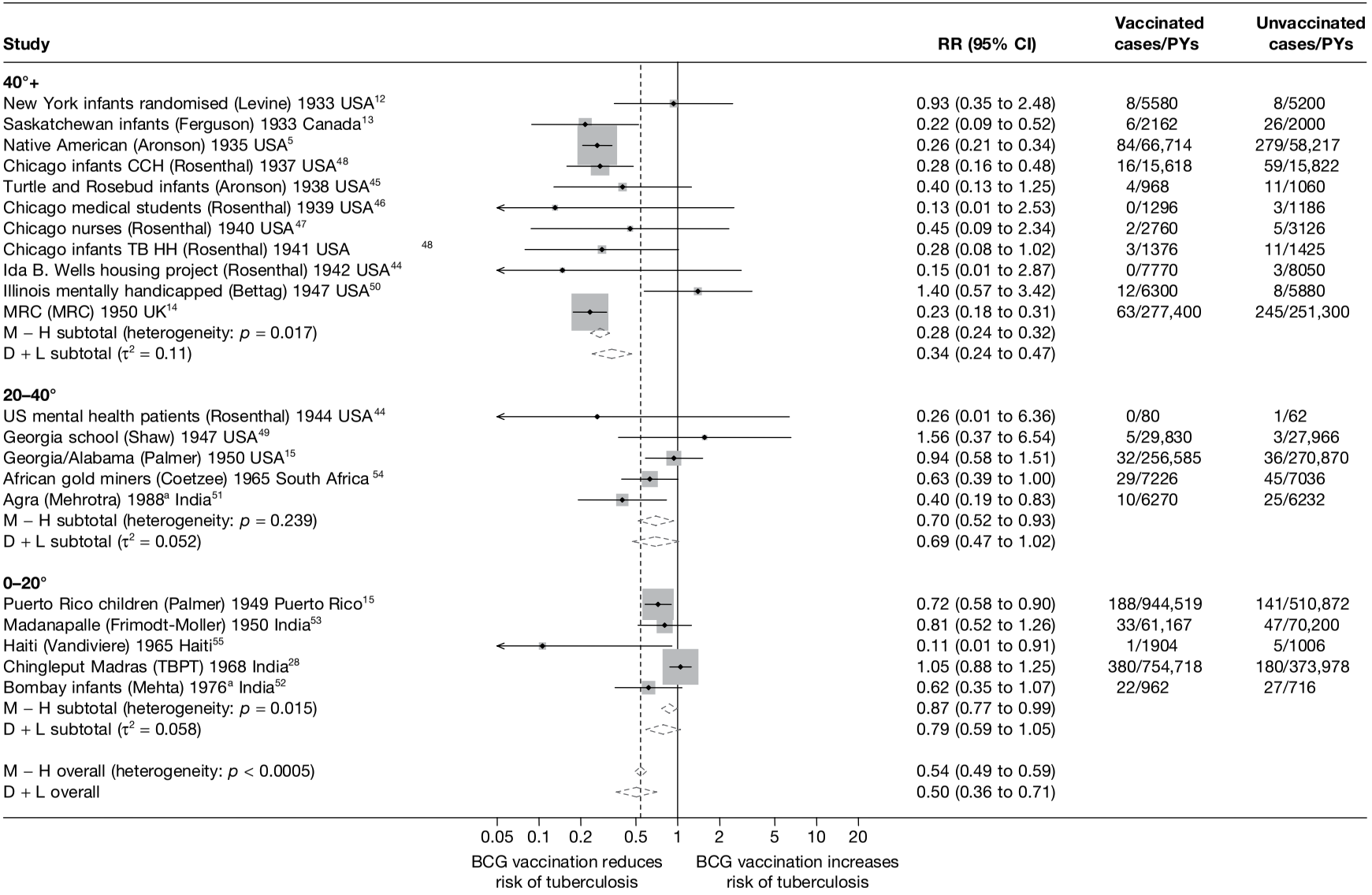

FIGURE 122 Rate ratios (with 95% CI) comparing the incidence of all tuberculosis disease outcomes among BCG vaccinated individuals with that in unvaccinated individuals for the longest duration of follow-up (see *Table 3*) in RCTs, stratified by latitude of study location (20° bands), ordered by year of study start. a, Date of study publication was used if study start date was not available. CCH, Cook County Hospital; D+L, DerSimonian and Laird method; M–H, Mantel–Haenszel method; TB HH, tuberculosis households; TBPT, Tuberculosis Prevention Trial.

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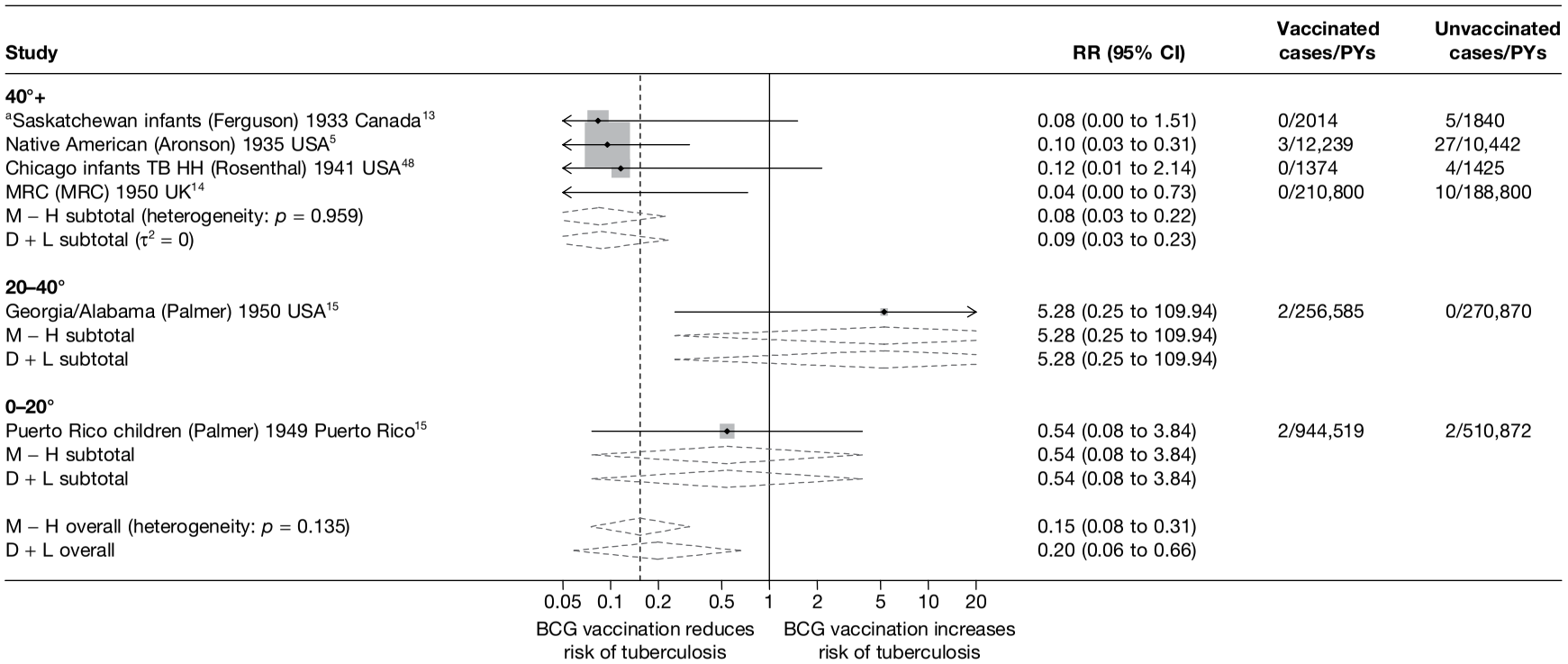

FIGURE 123 Rate ratios (with 95% CI) comparing the incidence of tuberculosis meningitis and/or miliary tuberculosis among BCG vaccinated individuals with that in unvaccinated individuals for the longest duration of follow-up (see *Table 3*) in RCTs, stratified by latitude of study location (20° bands), ordered by year of study start. a, The outcome is miliary tuberculosis only. D+L, DerSimonian and Laird method; M–H, Mantel–Haenszel method; TB HH, tuberculosis households.

Meningitis tuberculosis

Unstratified analyses are ordered by year trial started

See *Figure 124*.

Stratified analysis by 10° latitude, ordered by year study started

See *Figure 125*.

Stratified analysis by 20° latitude, ordered by year study started

See *Figure 126*.

Stratified analysis by age at vaccination, ordered by year study started

See *Figure 127*.

Stratified analysis by risk of diagnostic detection bias, ordered by year study started

See *Figure 128*.

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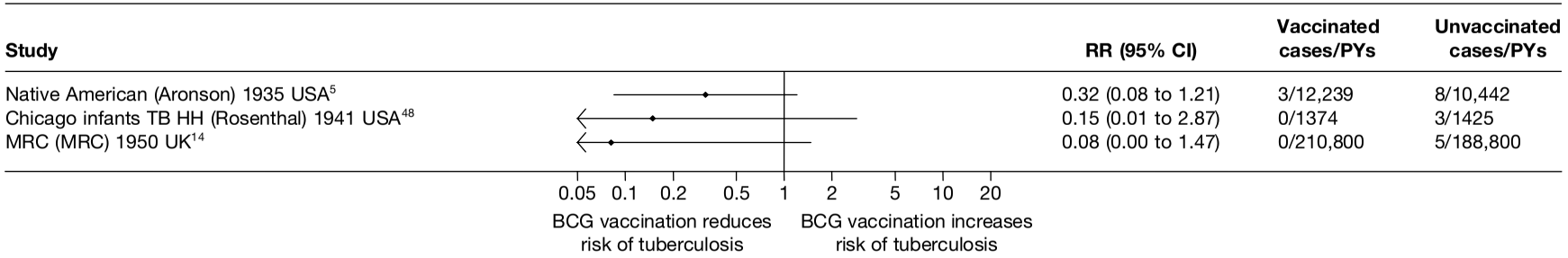

FIGURE 124 Rate ratios (with 95% CI) comparing the incidence of tuberculosis meningitis among BCG vaccinated individuals with that in unvaccinated individuals for the longest duration of follow-up (see *Table 3*) in RCTs ordered by year of study start. TB HH, tuberculosis households.

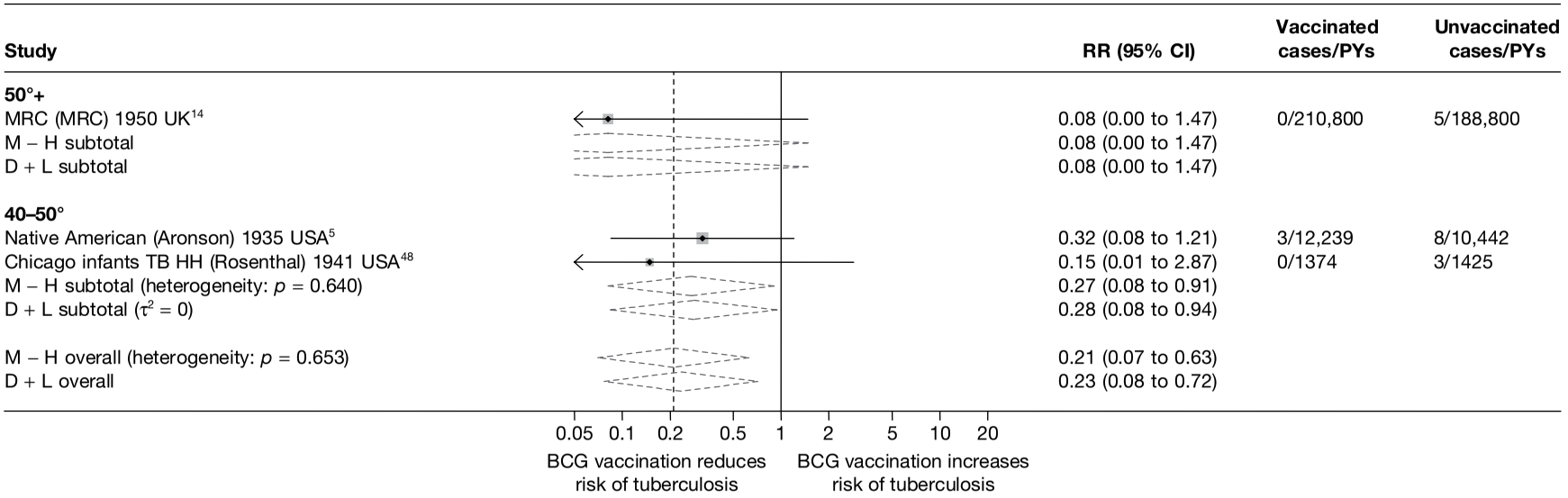

FIGURE 125 Rate ratios (with 95% CI) comparing the incidence of tuberculosis meningitis and/or miliary tuberculosis among BCG vaccinated individuals with that in unvaccinated individuals for the longest duration of follow-up (see *Table 3*) in RCTs, stratified by latitude of study location (20° bands), ordered by year of study start. D+L, DerSimonian and Laird method; M–H, Mantel–Haenszel method; TB HH, tuberculosis households.

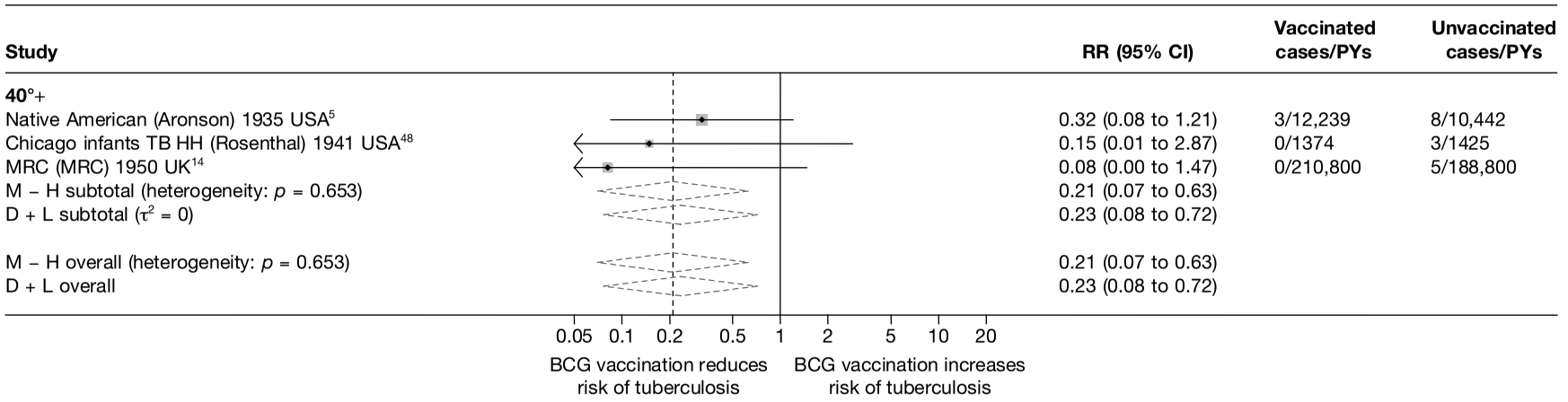

FIGURE 126 Rate ratios (with 95% CI) comparing the incidence of tuberculosis meningitis and/or miliary tuberculosis among BCG vaccinated individuals with that in unvaccinated individuals for the longest duration of follow-up (see *Table 3*) in RTCs, stratified by latitude of study location (20° bands), ordered by year of study start. D+L, DerSimonian and Laird method; M–H, Mantel–Haenszel method; TB HH, tuberculosis households.

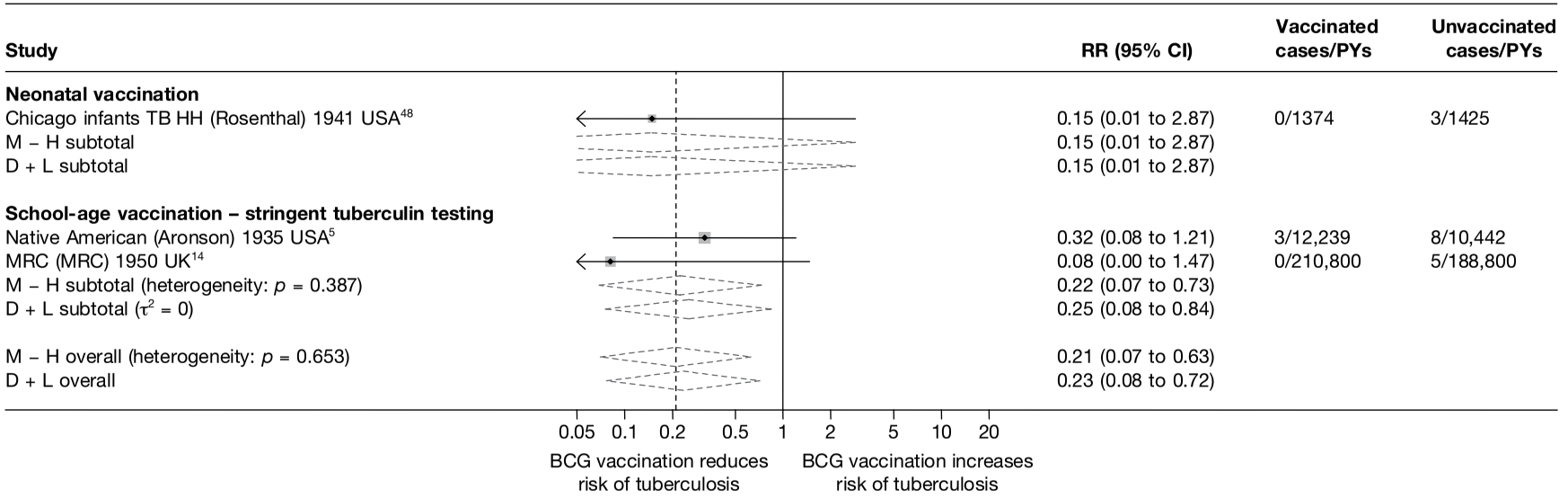

FIGURE 127 Rate ratios (with 95% CI) comparing the incidence of tuberculosis meningitis among BCG vaccinated individuals with that in unvaccinated individuals for the longest duration of follow-up (see *Table 3*) in RCTs, stratified by age at vaccination, ordered by year of study start. D+L, DerSimonian and Laird method; M–H, Mantel–Haenszel method; TB HH, tuberculosis households.

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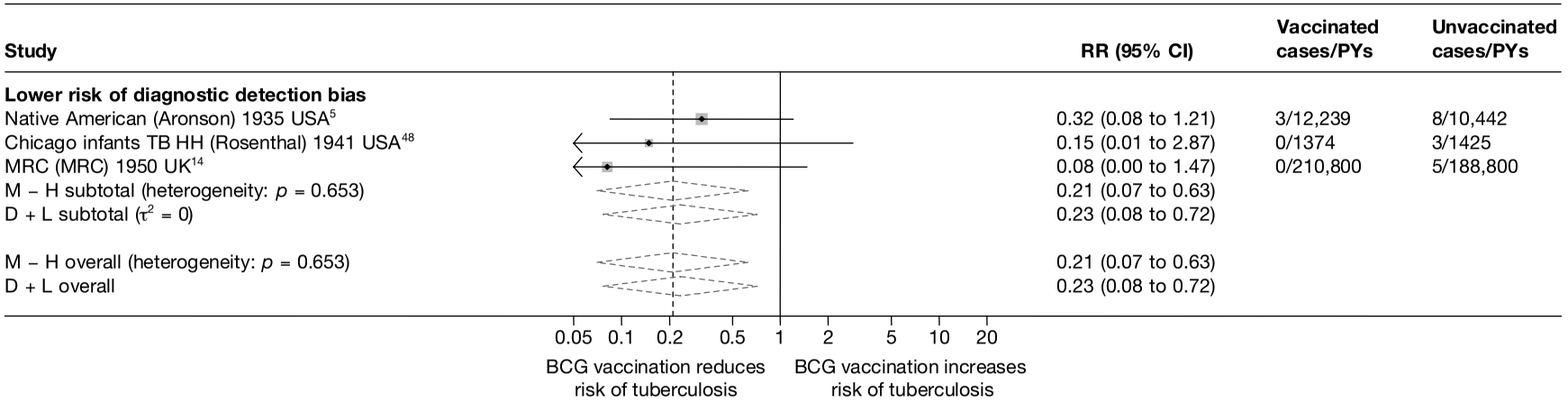

FIGURE 128 Rate ratios (with 95% CI) comparing the incidence of tuberculosis meningitis among BCG vaccinated individuals with that in unvaccinated individuals for the longest duration of follow-up (see *Table 3*) in RCTs, stratified by risk of diagnostic detection bias[a] and ordered by year of study start. a, Diagnostic detection bias occurs if the assessor of BCG outcome is not blinded to vaccination status. D+L, DerSimonian and Laird method; M–H, Mantel–Haenszel method; TB HH, tuberculosis households.

Miliary tuberculosis

Unstratified analyses are ordered by year trial started

See *Figure 129*.

Stratified analysis by 10° latitude, ordered by year study started

See *Figure 130*.

Stratified analysis by 20° latitude, ordered by year study started

See *Figure 131*.

Stratified analysis by age at vaccination, ordered by year study started

See *Figure 132*.

Stratified analysis by risk of diagnostic detection bias, ordered by year study started

See *Figure 133*.

Stratified analysis by 20° latitude, ordered by year study started

Extrapulmonary tuberculosis

See *Figure 134*.

Tuberculosis mortality

See *Figure 135*.

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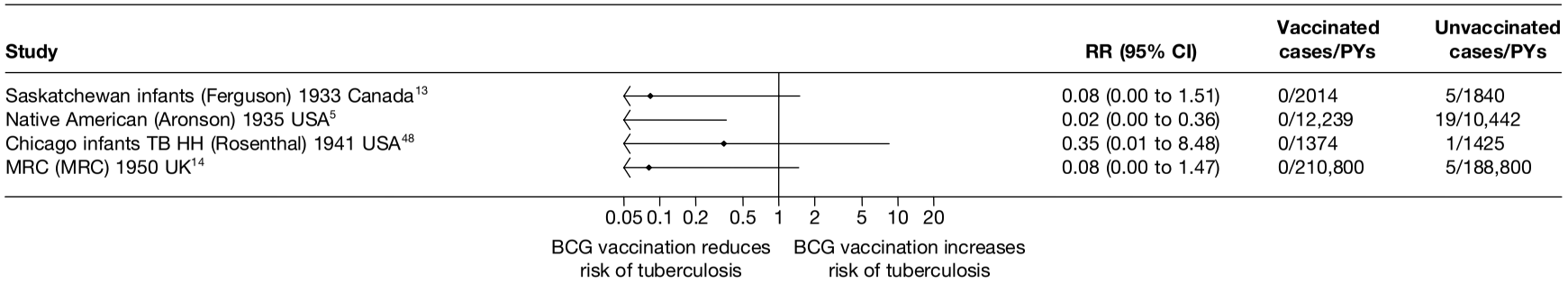

FIGURE 129 Rate ratios (with 95% CI) comparing the incidence of miliary tuberculosis among BCG vaccinated individuals with that in unvaccinated individuals for the longest duration of follow-up (see *Table 3*) in RCTs, ordered by year of study start. TB HH, tuberculosis households.

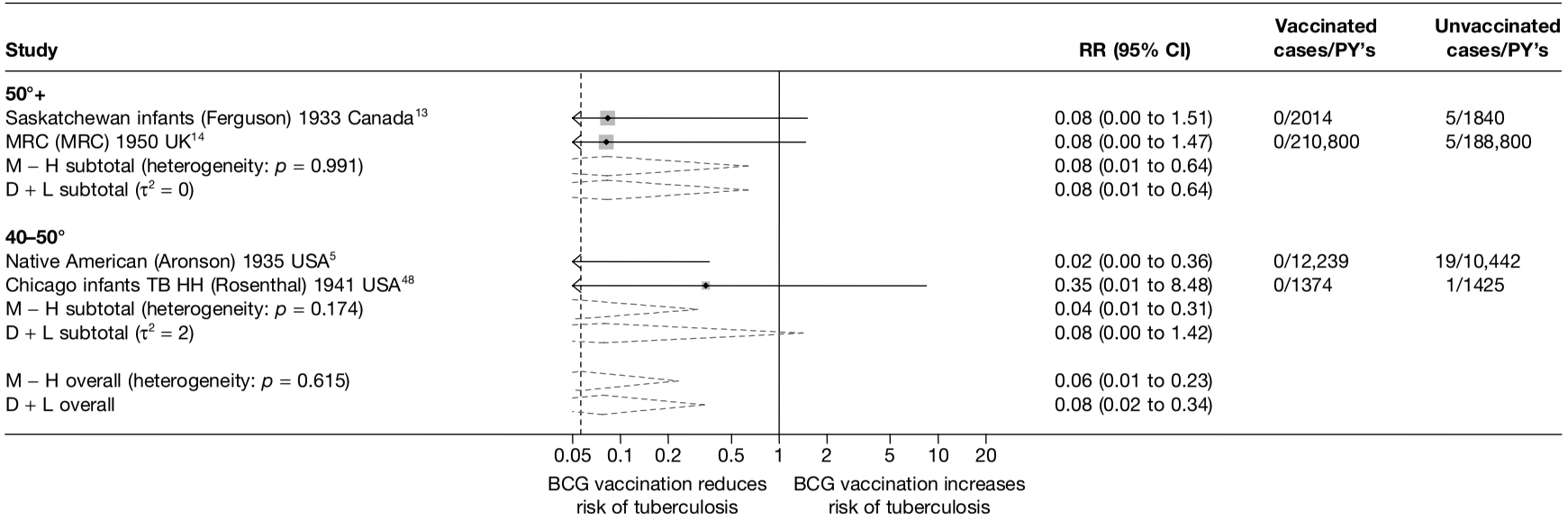

FIGURE 130 Rate ratios (with 95% CI) comparing the incidence of miliary tuberculosis among BCG vaccinated individuals with that in unvaccinated individuals for the longest duration of follow-up (see *Table 3*) in RCTs, stratified by latitude of study location (10° bands), ordered by year of study start. D+L, DerSimonian and Laird method; M–H, Mantel–Haenszel method; TB HH, tuberculosis households.

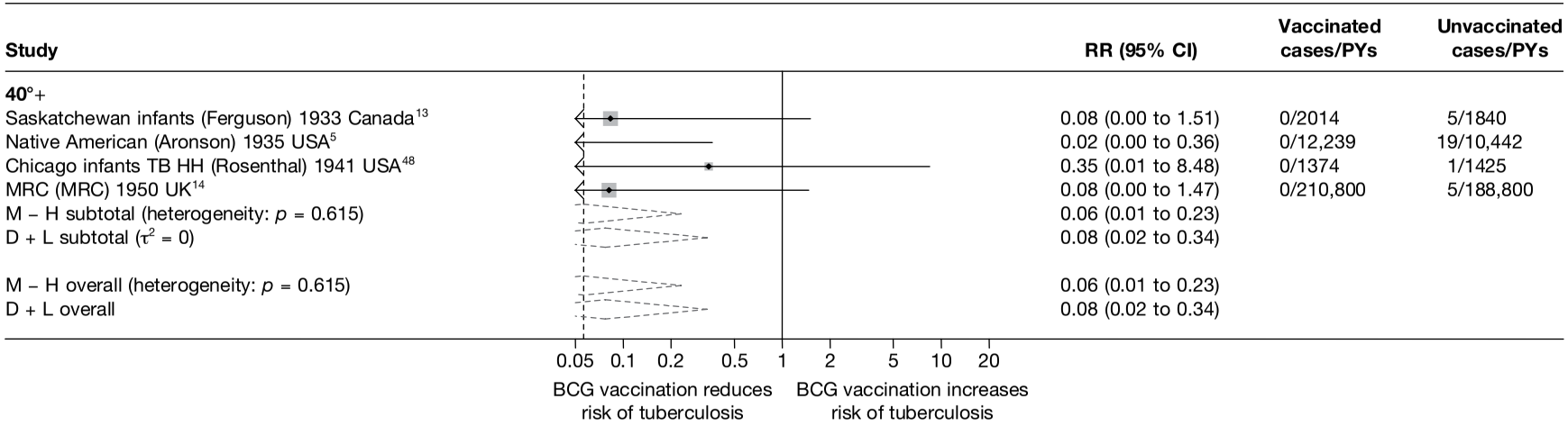

FIGURE 131 Rate ratios (with 95% CI) comparing the incidence of miliary tuberculosis among BCG vaccinated individuals with that in unvaccinated individuals for the longest duration of follow-up (see *Table 3*) in RCTs, stratified by latitude of study location (20° bands), ordered by year of study start. D + L, DerSimonian and Laird method; M – H, Mantel–Haenszel method; TB HH, tuberculosis households.

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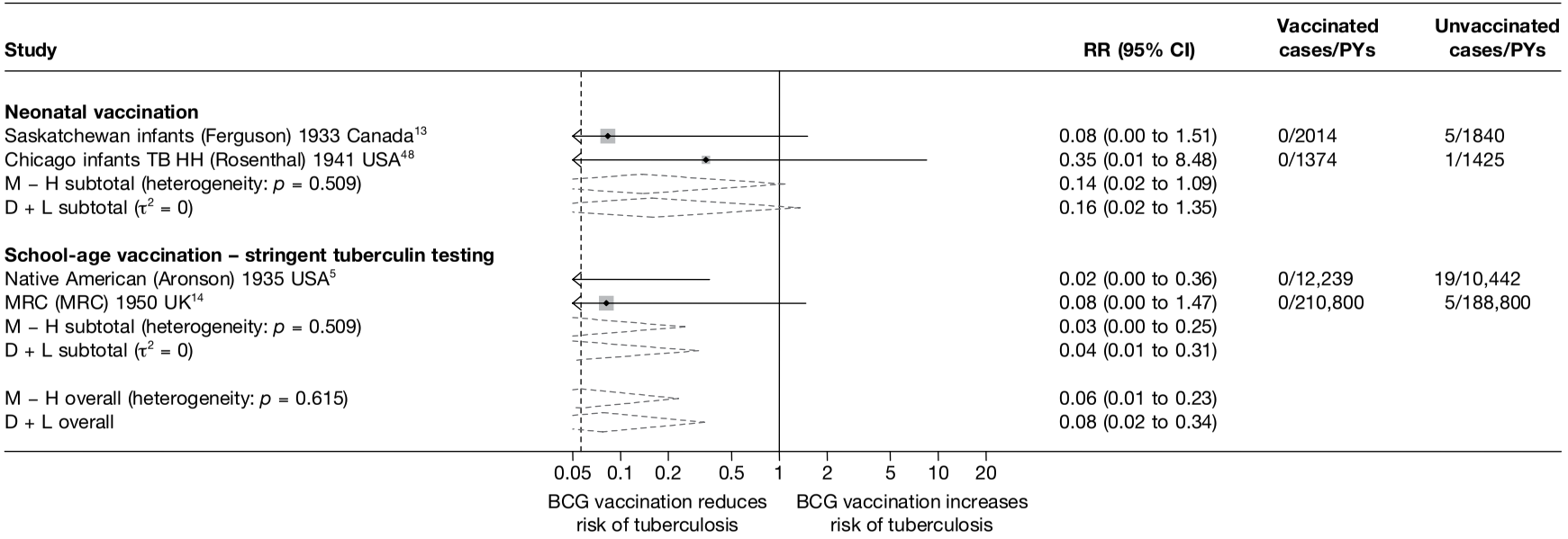

FIGURE 132 Rate ratios (with 95% CI) comparing the incidence miliary tuberculosis among BCG vaccinated individuals with that in unvaccinated individuals for the longest duration of follow-up (see *Table 3*) in RCTs, stratified by age at vaccination, ordered by year of study start. D+L, DerSimonian and Laird method; M–H, Mantel–Haenszel method; TB HH, tuberculosis households.

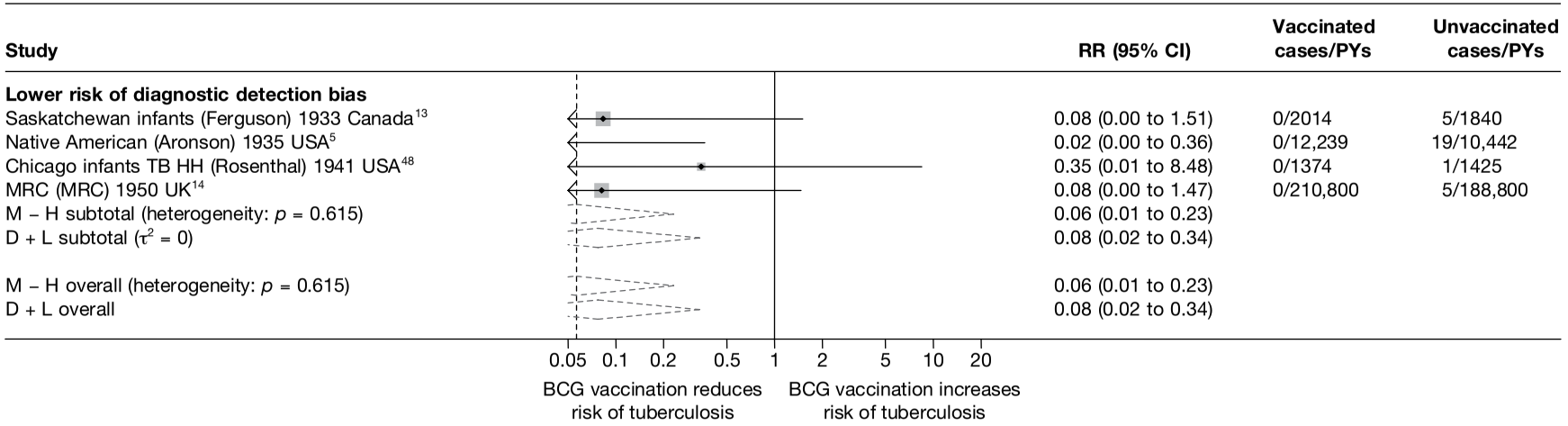

FIGURE 133 Rate ratios (with 95% CI) comparing the incidence of miliary tuberculosis among BCG vaccinated individuals with that in unvaccinated individuals for the longest duration of follow-up (see *Table 3*) in RCTs, stratified by risk of diagnostic detection bias[a] and ordered by year of study start a, Diagnostic detection bias occurs if the assessor of BCG outcome is not blinded to vaccination status. D+L, DerSimonian and Laird method; M–H, Mantel–Haenszel method; TB HH, tuberculosis households.

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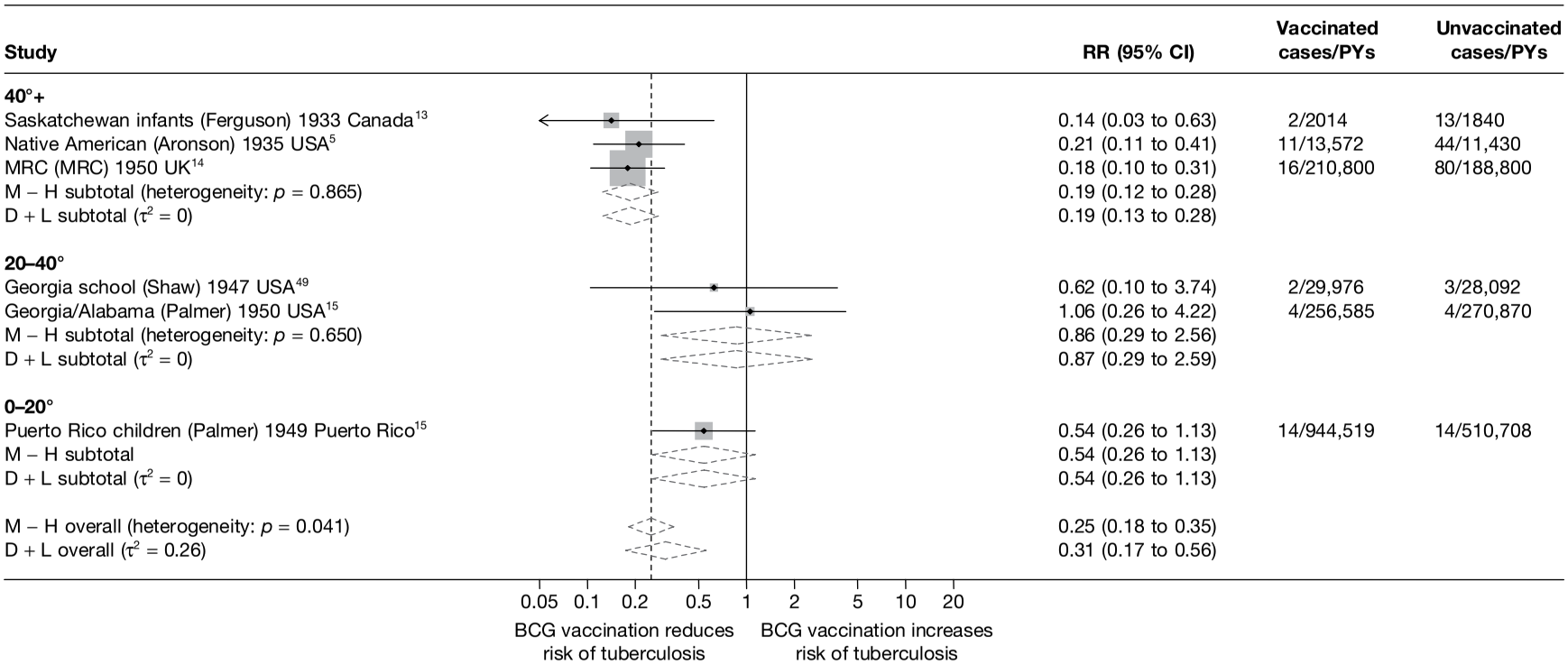

FIGURE 134 Rate ratios (with 95% CI) comparing the incidence of extrapulmonary tuberculosis among BCG vaccinated individuals with that in unvaccinated individuals for the longest duration of follow-up (see *Table 3*) in RCTs, stratified by latitude of study location (20° bands), ordered by year of study start. D+L, DerSimonian and Laird method; M–H, Mantel–Haenszel method.

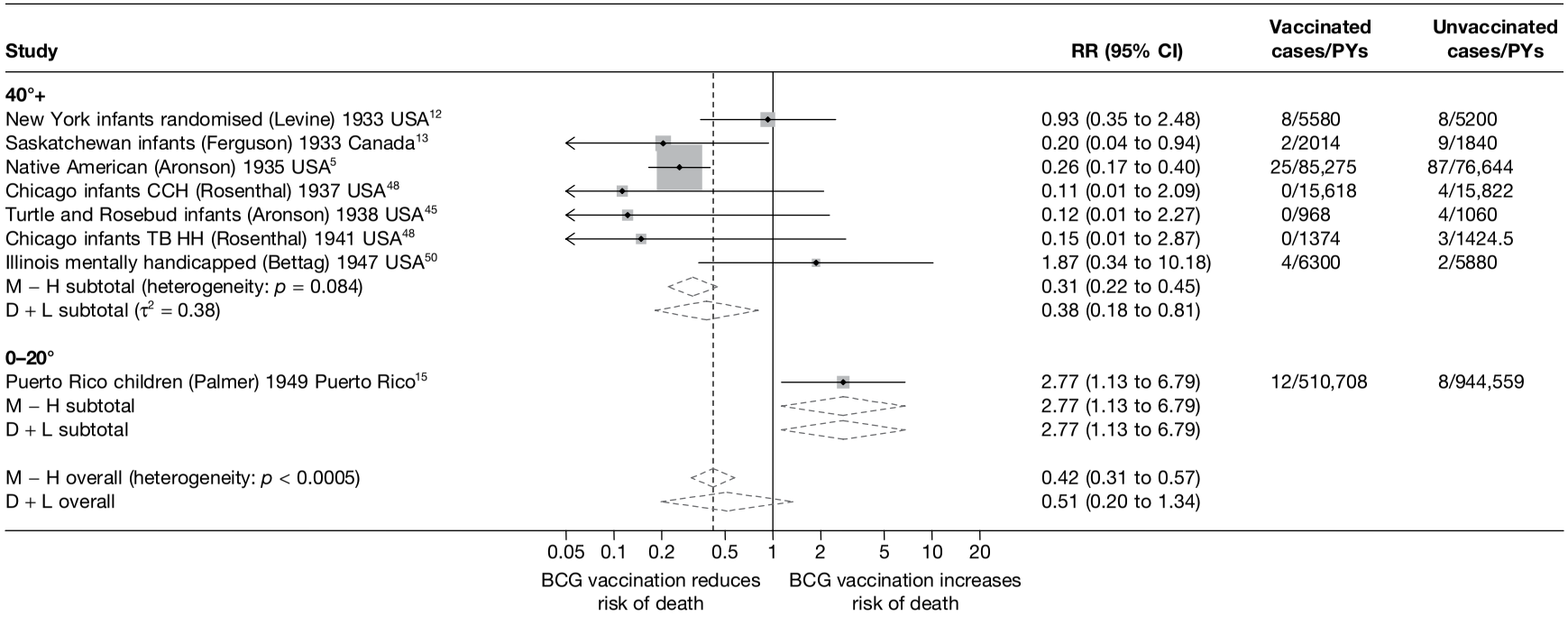

FIGURE 135 Rate ratios (with 95% CI) comparing the incidence of tuberculosis mortality among BCG vaccinated individuals with that in unvaccinated individuals for the longest duration of follow-up (see *Table 3*), in RCTs stratified by latitude of study location (20° bands), ordered by year of study start. CCH, Cook County Hospital; D+L, DerSimonian and Laird method; M–H, Mantel–Haenszel method; TB HH, tuberculosis households.

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Observational studies

Pulmonary tuberculosis

Stratified analysis by 20° latitude, ordered by year study started

Case–control studies

See *Figure 136*.

Cohort studies

See *Figure 137*.

Case population studies

See *Figure 138*.

Cross-sectional studies

See *Figure 139*.

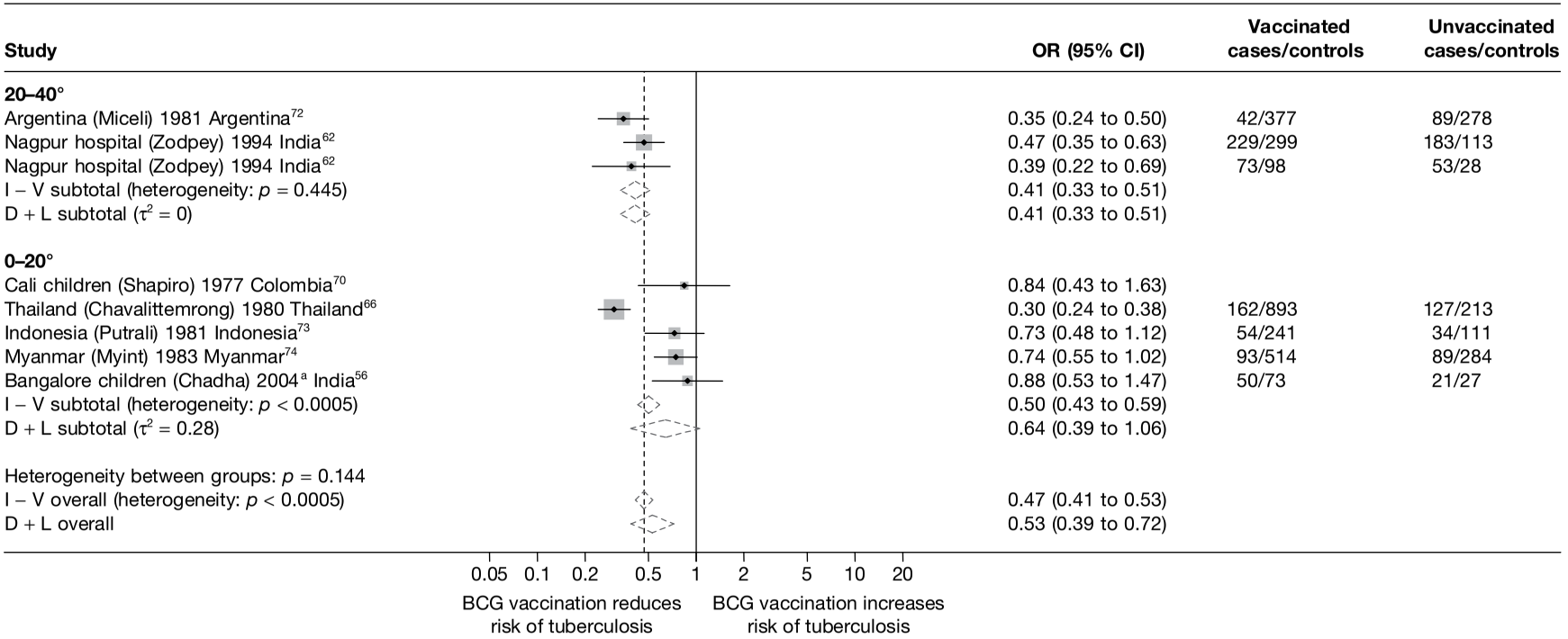

FIGURE 136 Odds ratios (with 95% CI) comparing the BCG vaccination status of pulmonary tuberculosis cases and control subjects in case–control studies, stratified by latitude of study location (20° bands), ordered by year of study start. a, Date of study publication was used if study start date was not available. D+L, DerSimonian and Laird method; I–V, inverse variance method.

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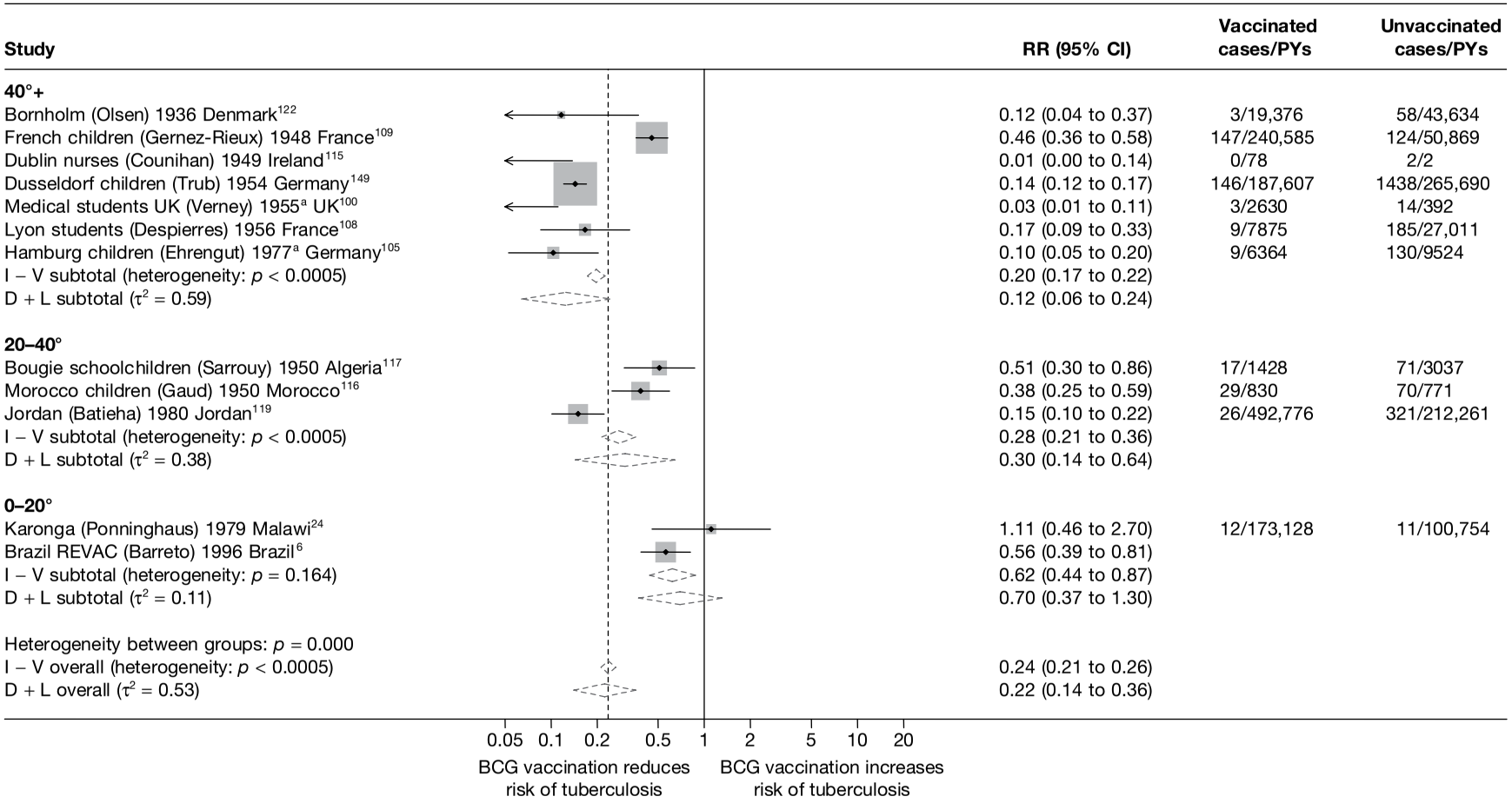

FIGURE 137 Rate ratios (with 95% CI) comparing the incidence of pulmonary tuberculosis among BCG vaccinated individuals with that in unvaccinated individuals for the longest duration of follow-up (see *Table 4*) in cohort studies, stratified by latitude of study location (20° bands), ordered by year of study start. a, Date of study publication was used if study start date was not available. D+L, DerSimonian and Laird method; I–V, inverse variance method.

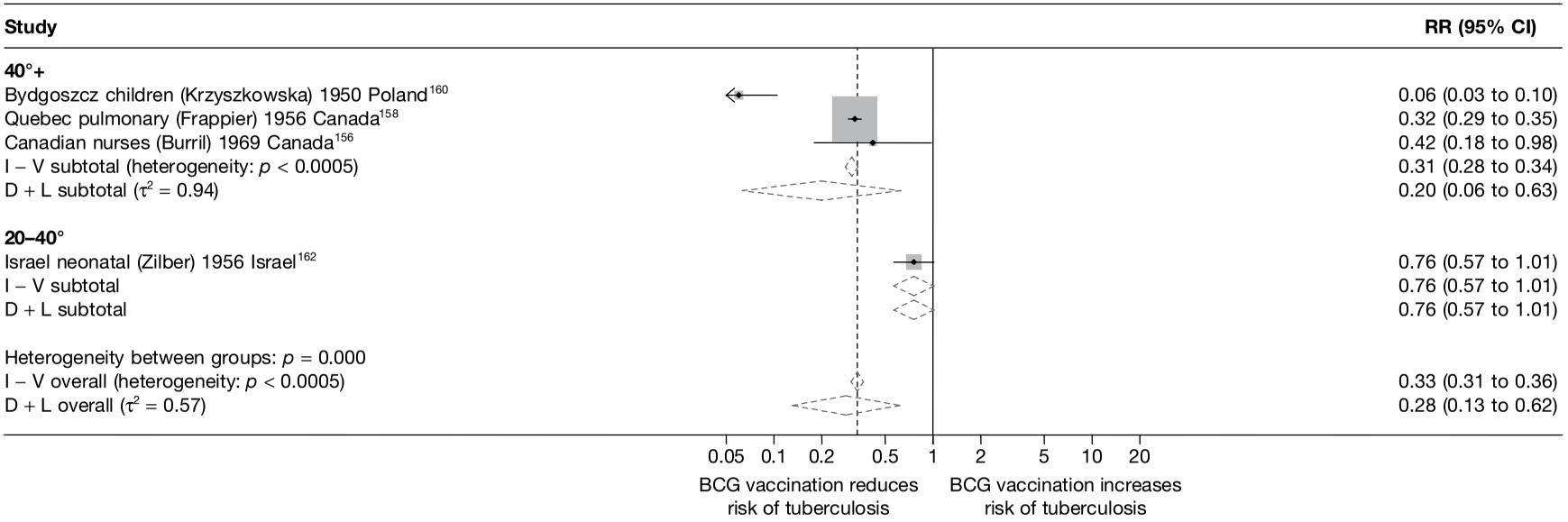

FIGURE 138 Rate ratios (with 95% CI) comparing the incidence of pulmonary tuberculosis among BCG vaccinated individuals with that in unvaccinated individuals for the longest duration of follow-up (see *Table 5*) in case population studies, stratified by latitude of study location (20° bands), ordered by year of study start. D + L, DerSimonian and Laird method; I–V, inverse variance method.

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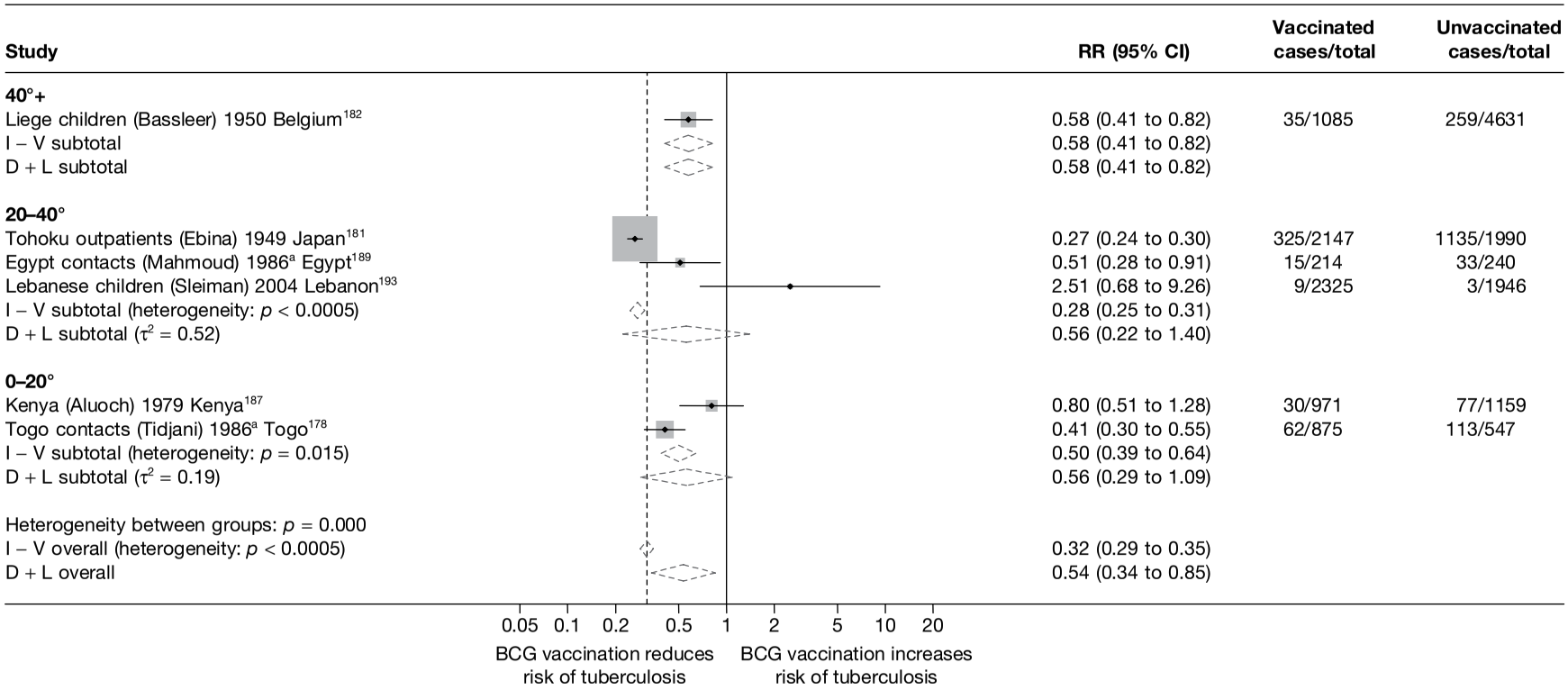

FIGURE 139 Risk ratios (with 95% CI) comparing the prevalence of pulmonary tuberculosis among BCG vaccinated individuals with that in unvaccinated in cross-sectional studies, stratified by latitude of study location (20° bands), ordered by year of study start. a, Date of study publication was used if study start date was not available. D+L, DerSimonian and Laird method; I–V, inverse variance method.

All tuberculosis disease outcomes

Stratified analysis by 20° latitude, ordered by year study started

Case–control studies

See *Figure 140*.

Cohort studies

See *Figure 141*.

Case population studies

See *Figure 142*.

Cross-sectional studies

See *Figure 143*.

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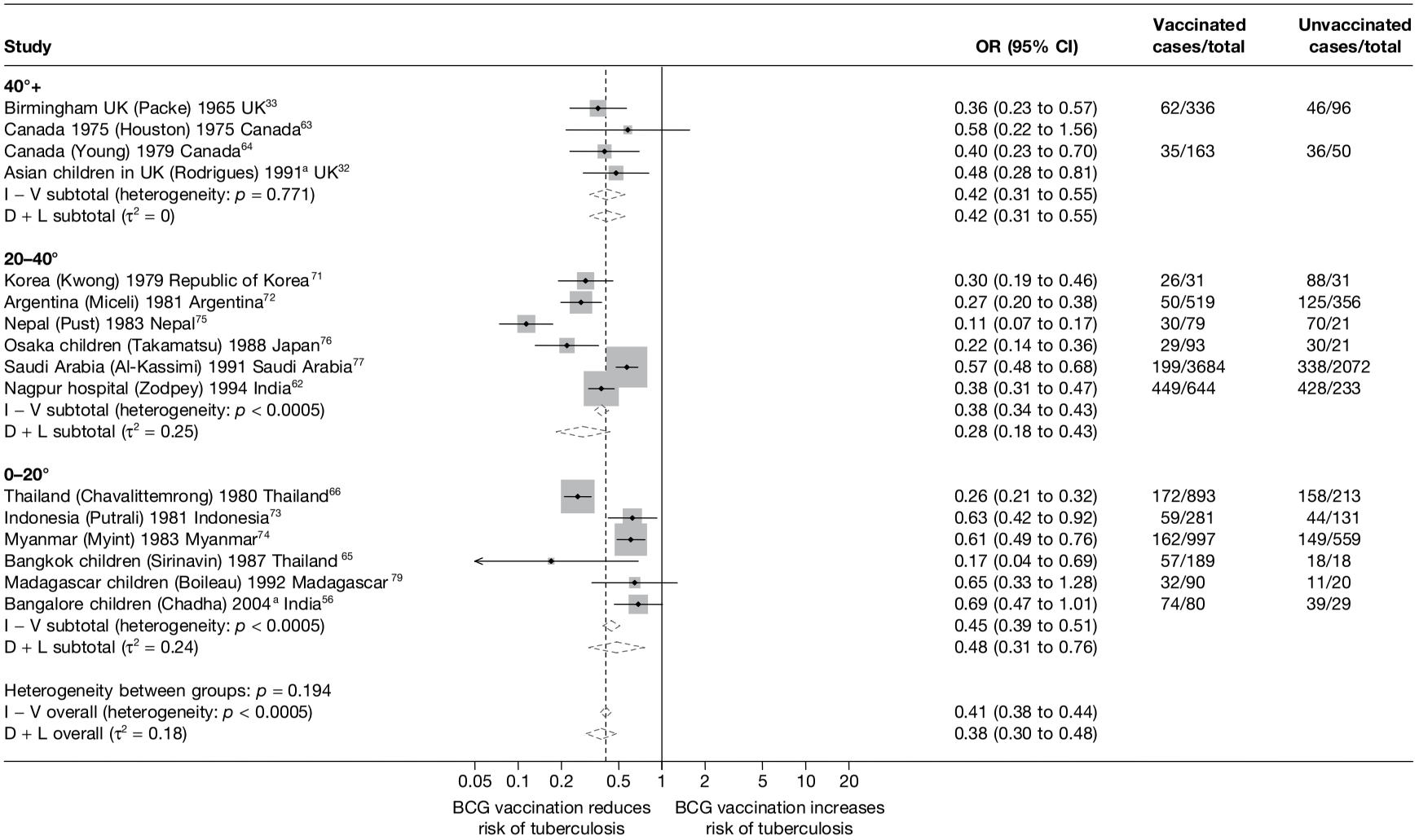

FIGURE 140 Odds ratios (with 95% CI) comparing the BCG vaccination status of all tuberculosis outcome cases and control subjects in case–control studies, stratified by latitude of study location (20° bands), ordered by year of study start. a, Date of study publication was used if study start date was not available. D+L, DerSimonian and Laird method; I–V, inverse variance method.

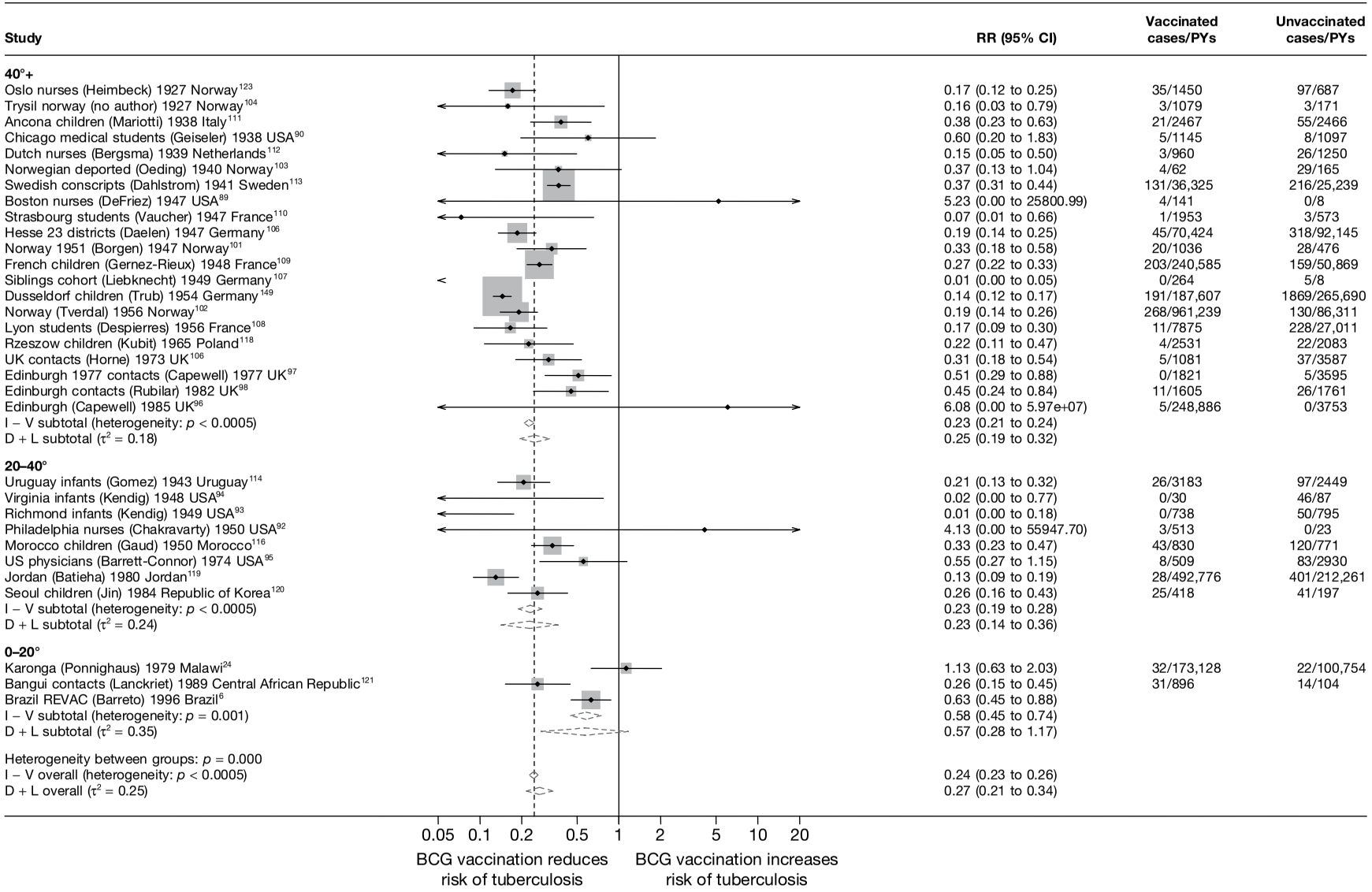

FIGURE 141 Rate ratios (with 95% CI) comparing the incidence of all tuberculosis disease outcomes among BCG vaccinated individuals with that in unvaccinated individuals for the longest duration of follow-up (see *Table 4*) in cohort studies, stratified by latitude of study location (20° bands), ordered by year of study start. D + L, DerSimonian and Laird method; I – V, inverse variance method.

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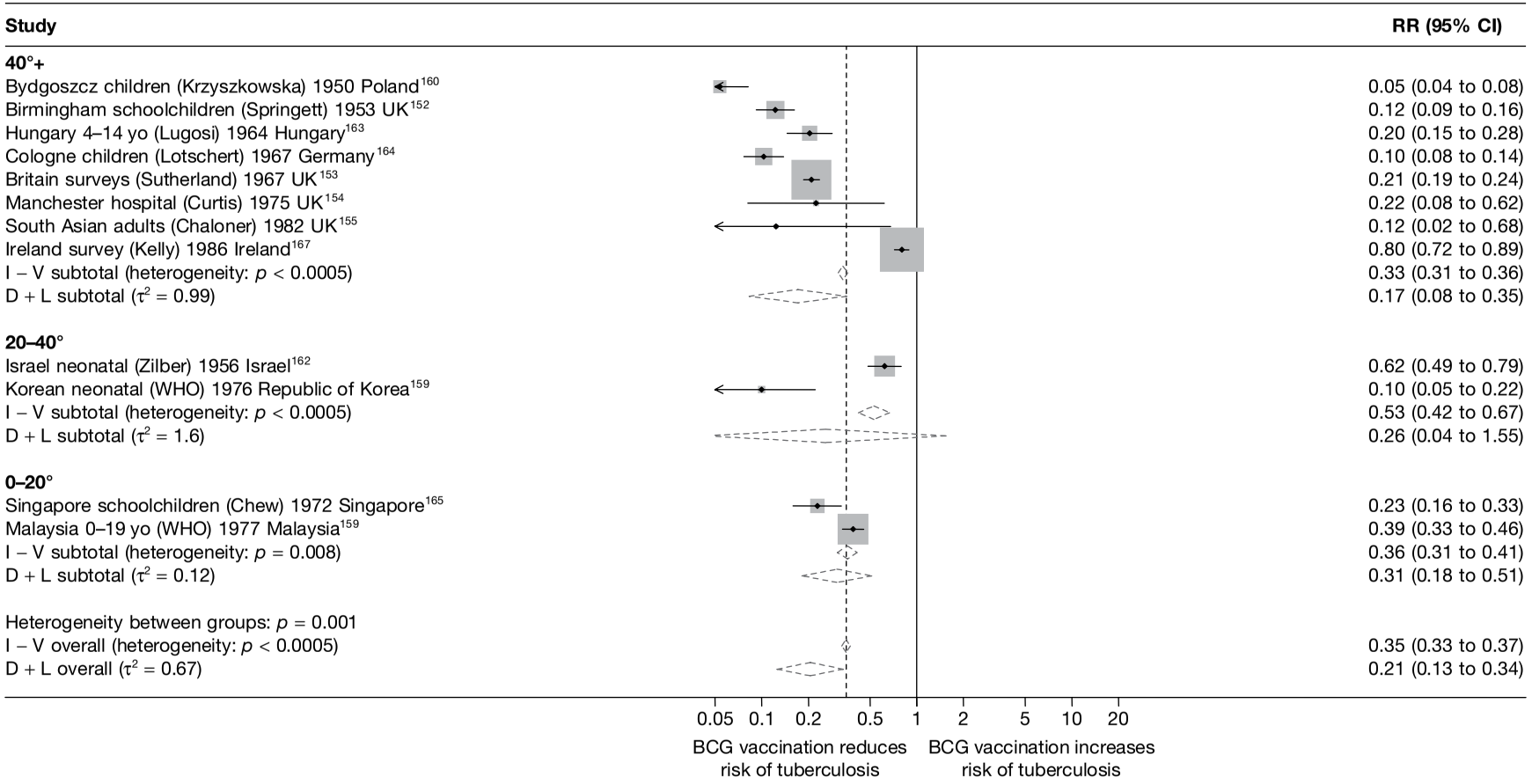

FIGURE 142 Rate ratios (with 95% CI) comparing the incidence of all tuberculosis disease outcomes among BCG vaccinated individuals with that in unvaccinated individuals for the longest duration of follow-up (see *Table 5*) in case population studies, stratified by latitude of study location (20° bands), ordered by year of study start. D+L, DerSimonian and Laird method; I–V, inverse variance method.

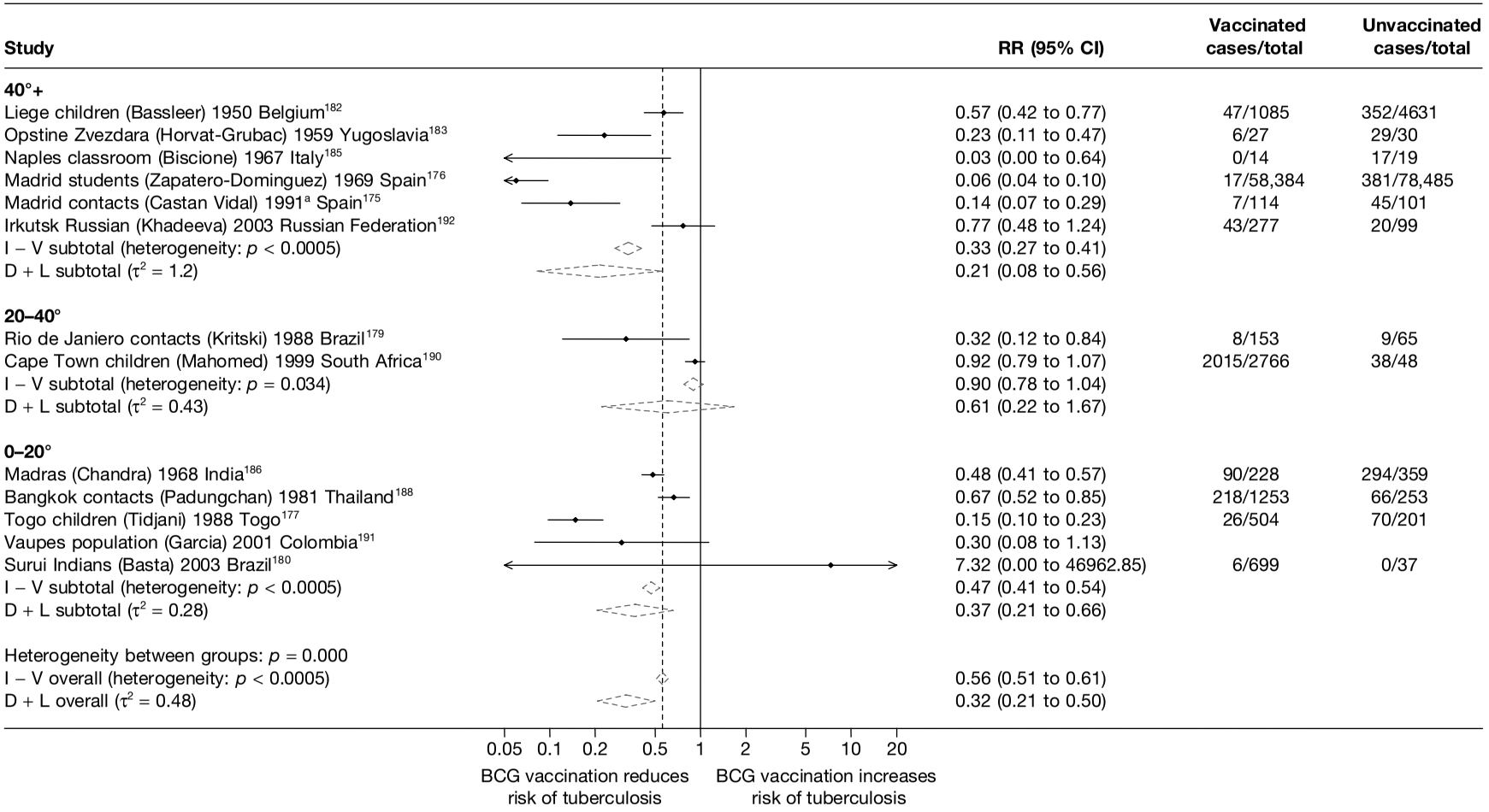

FIGURE 143 Risk ratios (with 95% CI) comparing the prevalence of all tuberculosis disease outcomes among BCG vaccinated individuals with that in unvaccinated individuals, in cross-sectional studies, stratified by latitude of study location (20° bands), ordered by year of study start. a, Date of study publication was used if study start date was not available. D + L, DerSimonian and Laird method; I – V, inverse variance method.

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Combined tuberculosis meningitis and/or miliary tuberculosis

Stratified analysis by 20° latitude, ordered by year study started

Case–control studies

See *Figure 144*.

Cohort studies

See *Figure 145*.

Case population studies

See *Figure 146*.

Cross-sectional studies

See *Figure 147*.

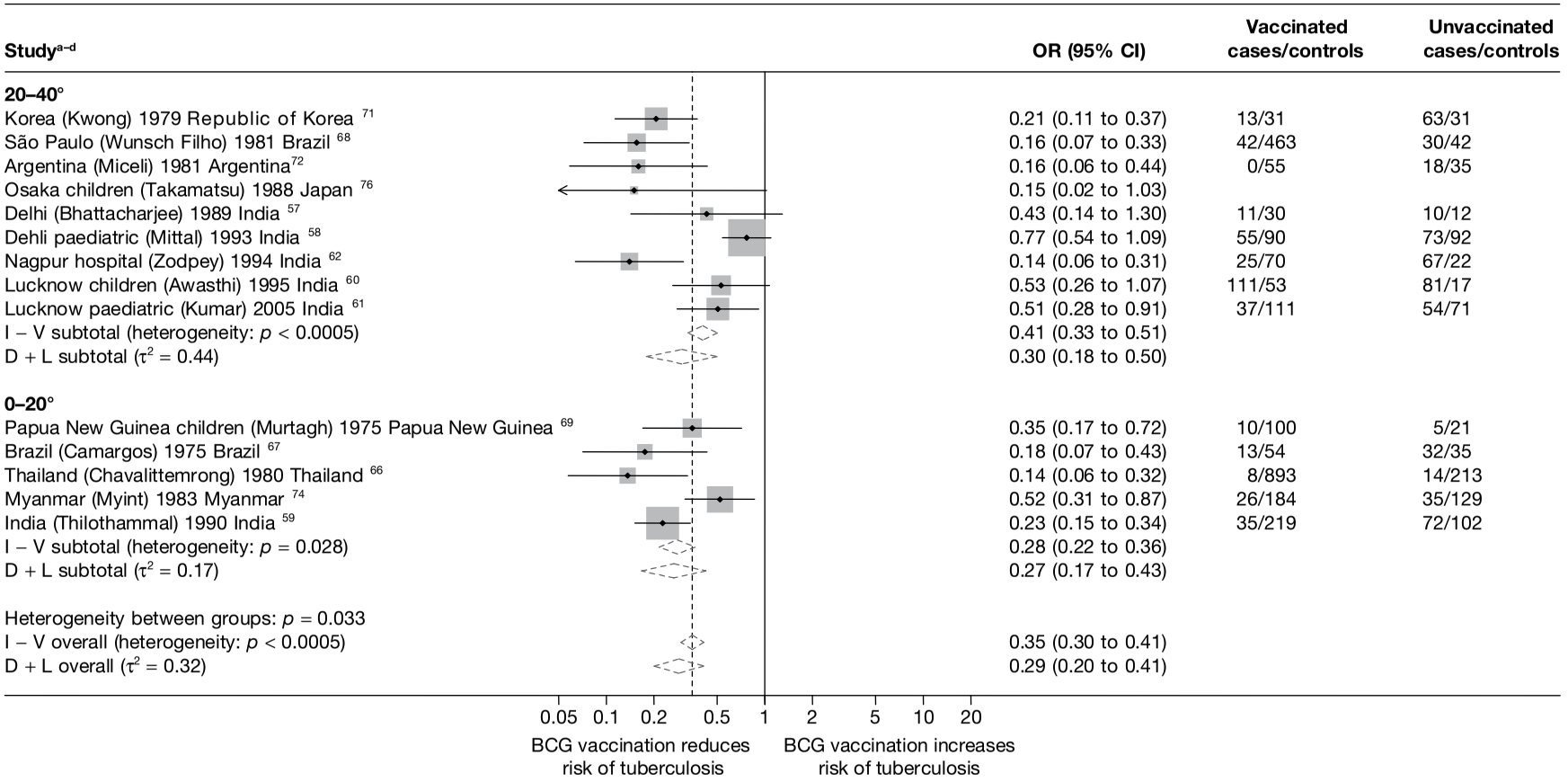

FIGURE 144 Odds ratios (with 95% CI) comparing the BCG vaccination status of meningeal and/or miliary tuberculosis cases and control subjects in case–control studies, stratified by latitude of study location (20° bands), ordered by year of study start. a, Date of study publication was used if study start date was not available; b, Combined tuberculosis meningitis and miliary tuberculosis outcomes; c, Meningeal tuberculosis outcome only; d, Miliary tuberculosis outcome only. D+L, DerSimonian and Laird method; I–V, inverse variance method.

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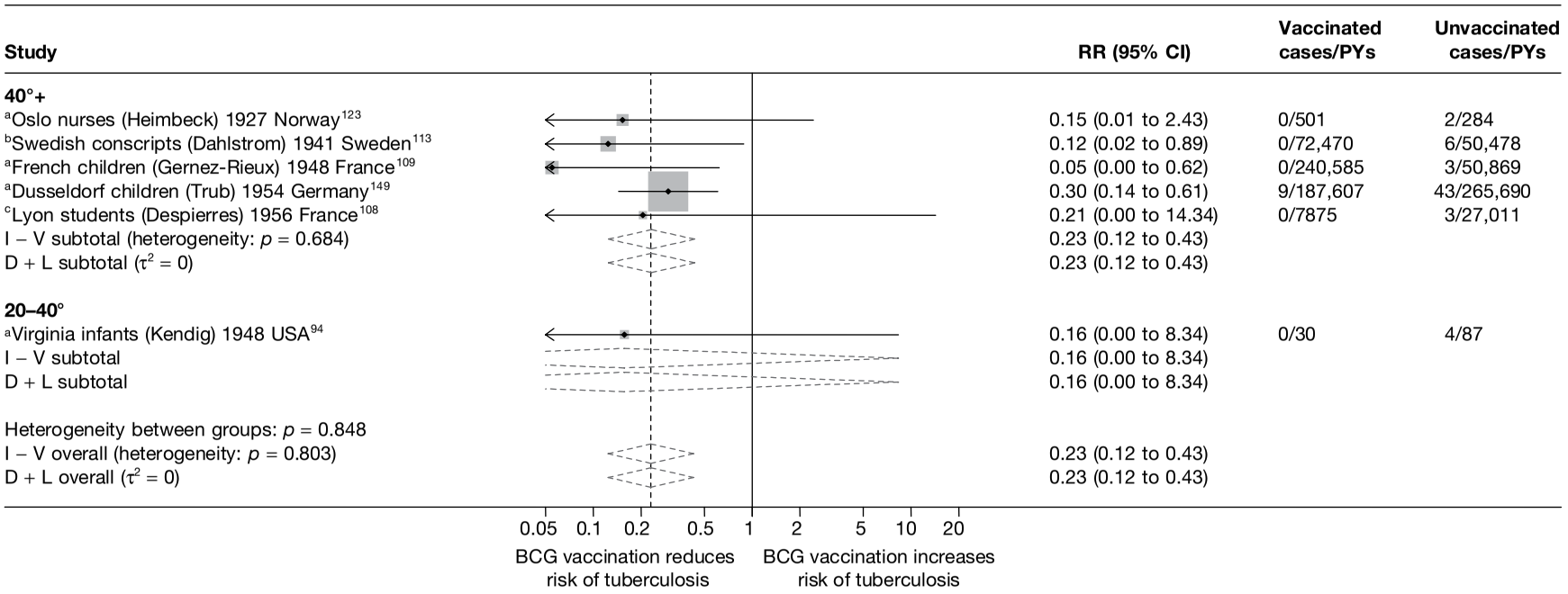

FIGURE 145 Rate ratios (with 95% CI) comparing the incidence of meningeal and/or miliary tuberculosis outcomes among BCG vaccinated individuals with that in unvaccinated individuals for the longest duration of follow-up (see *Table 4*) in cohort studies, stratified by latitude of study location (20° bands), ordered by year of study start. a, Meningeal tuberculosis outcome only; b, Combined tuberculosis meningitis and miliary tuberculosis outcomes; c, Miliary tuberculosis outcome only. D+L, DerSimonian and Laird method; I–V, inverse variance method.

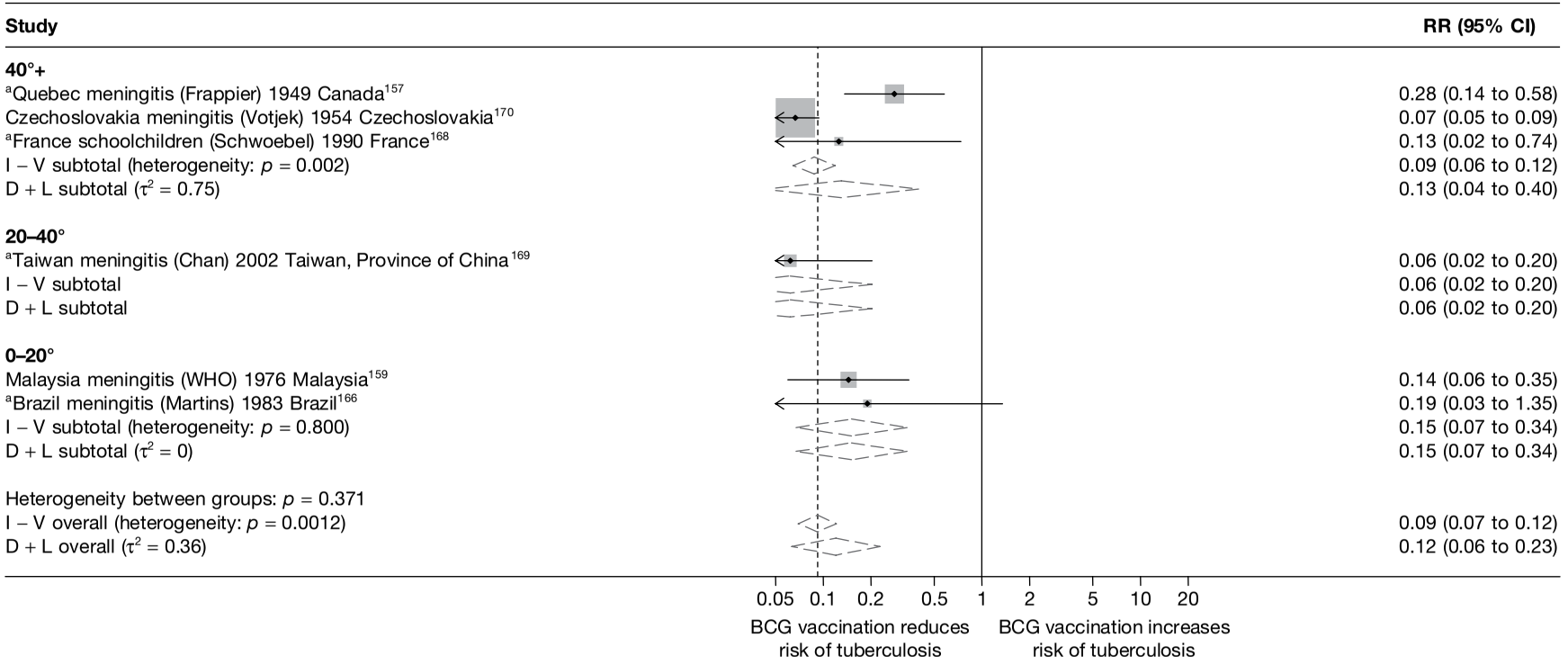

FIGURE 146 Rate ratios (with 95% CI) comparing the incidence of meningeal and/or miliary tuberculosis among BCG vaccinated individuals with that in unvaccinated individuals for the longest duration of follow-up (see *Table 5*) in case population studies, stratified by latitude of study location (20° bands), ordered by year of study start. a, Meningeal tuberculosis outcome only. D+L, DerSimonian and Laird method; I–V, inverse variance method.

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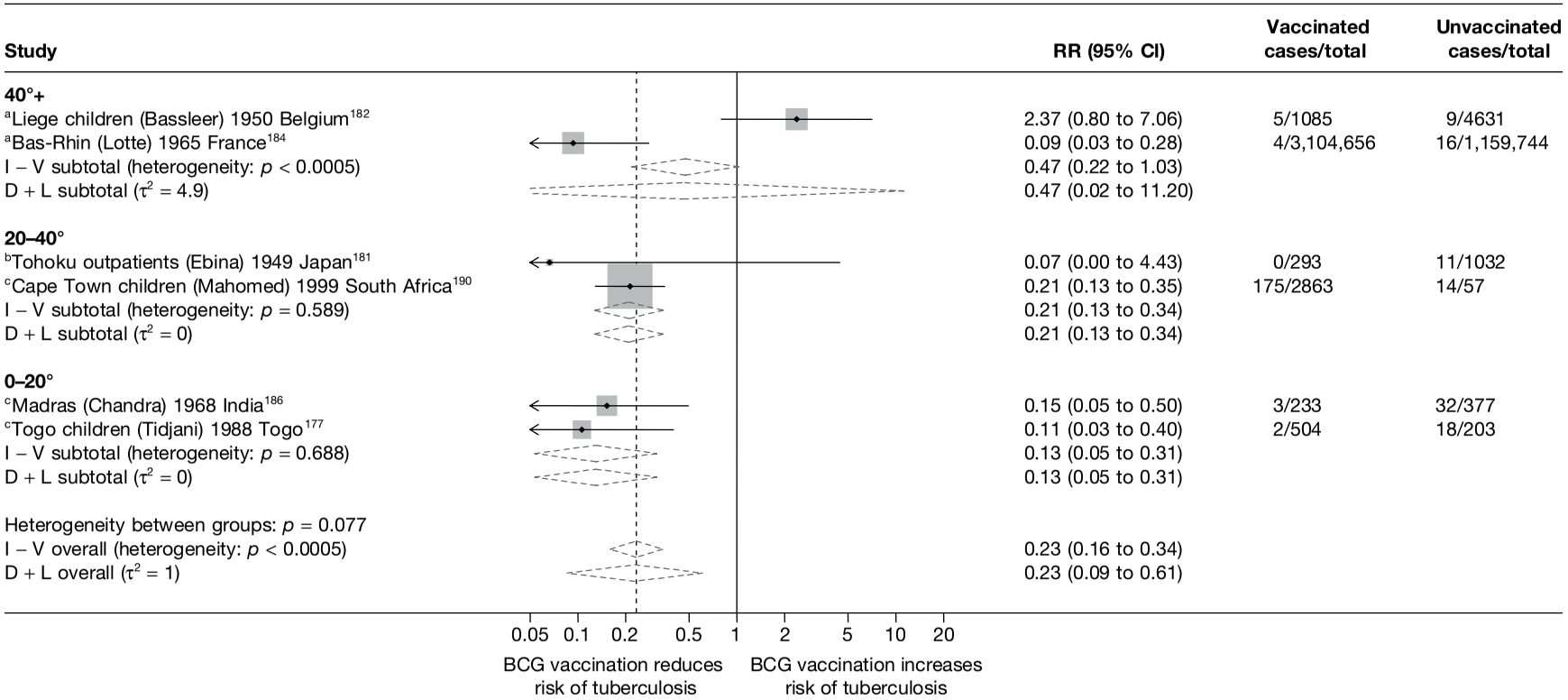

FIGURE 147 Risk ratios (with 95% CI) comparing the prevalence of meningeal and/or miliary tuberculosis among BCG vaccinated individuals with that in unvaccinated individuals, in cross-sectional studies, stratified of study location (20° bands), ordered by year of study start. a, Meningeal tuberculosis outcome only; b, Miliary tuberculosis outcome only; c, Combined tuberculosis meningitis and miliary tuberculosis outcomes. D+L, DerSimonian and Laird method; I–V, inverse variance method.

Tuberculosis meningitis

Case–control studies

Unstratified analyses are ordered by year trial started

See *Figure 148*.

Stratified analysis by 10° latitude, ordered by year study started

See *Figure 149*.

Stratified analysis by 20° latitude, ordered by year study started

See *Figure 150*.

Stratified analysis by age at vaccination, ordered by year study started

See *Figure 151*.

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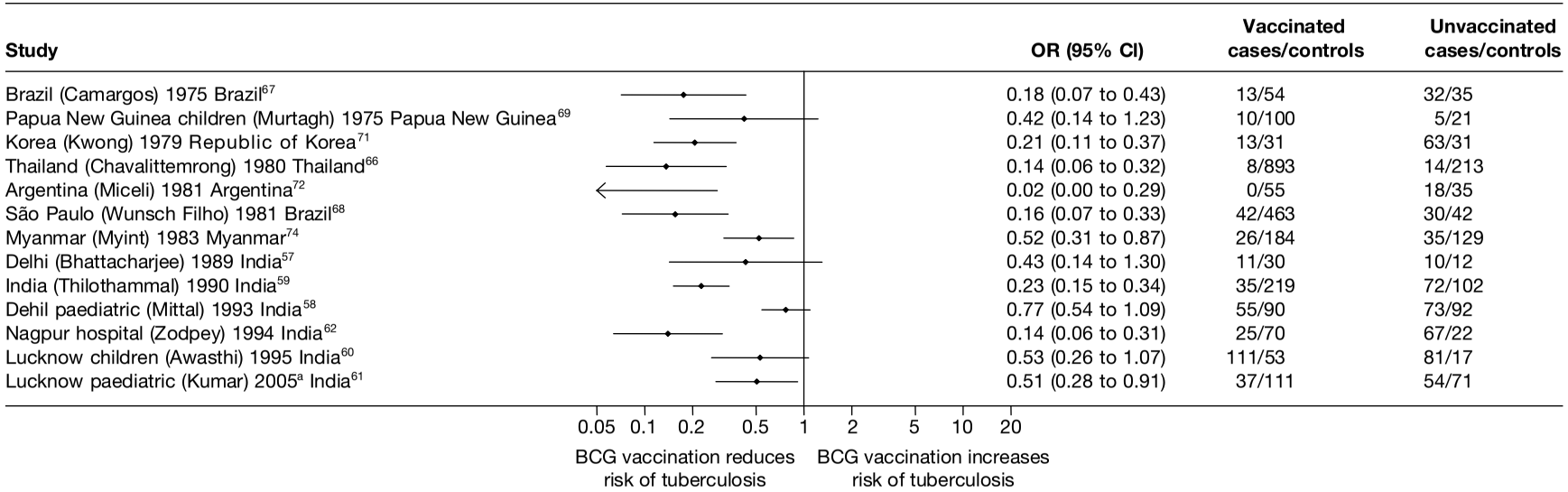

FIGURE 148 Odds ratios (with 95% CI) comparing the BCG vaccination status of meningeal tuberculosis cases and control subjects in case–control studies, ordered by year of study start. a, Date of study publication was used if study start date was not available. D + L, DerSimonian and Laird method; I–V, inverse variance method.

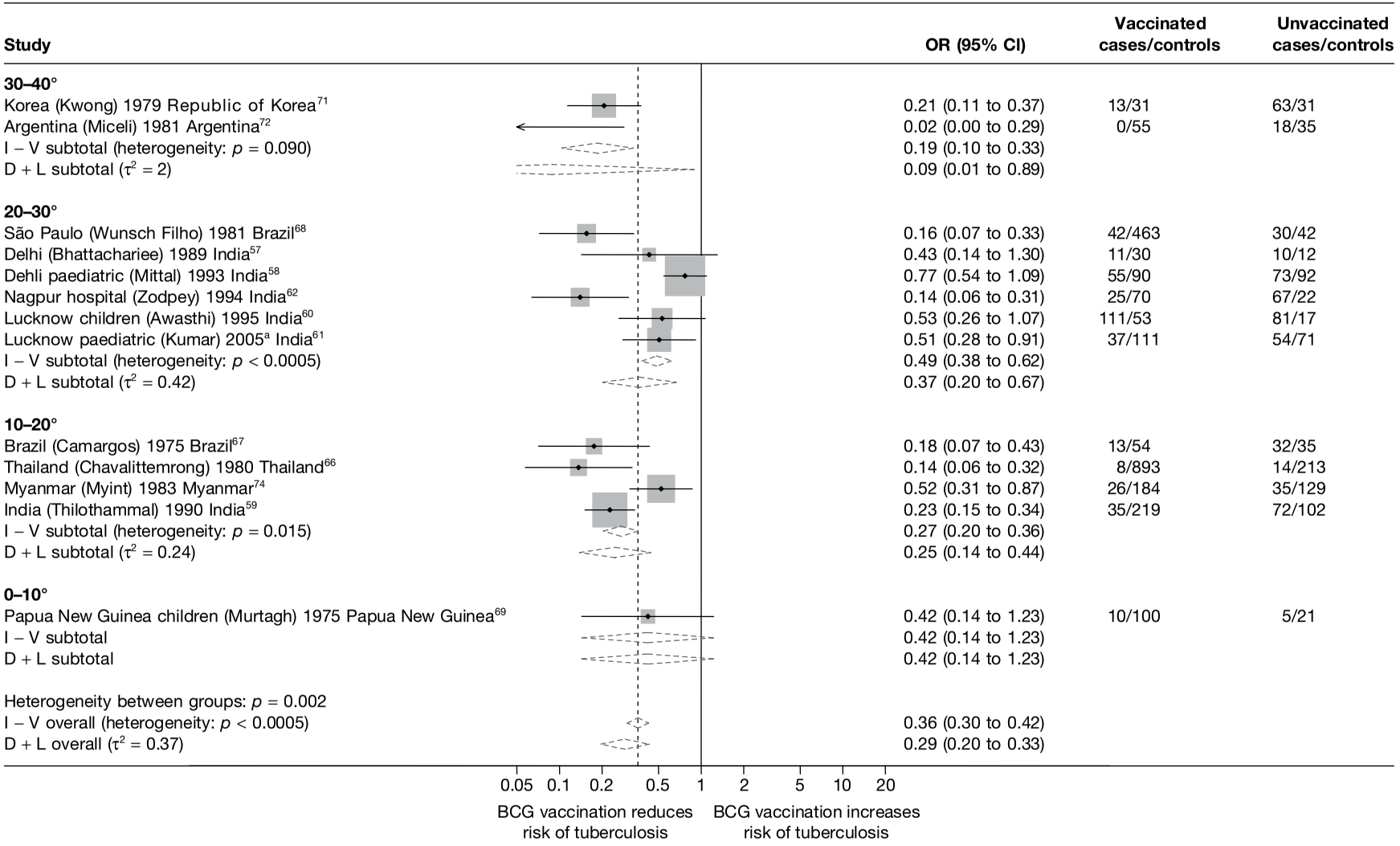

FIGURE 149 Odds ratios (with 95% CI) comparing the BCG vaccination status of meningeal tuberculosis cases and control subjects in case–control studies, stratified by latitude of study location (10° bands), ordered by year of study start. a. Date of study publication was used if study start date was not available. D+L, DerSimonian and Laird method; I–V, inverse variance method.

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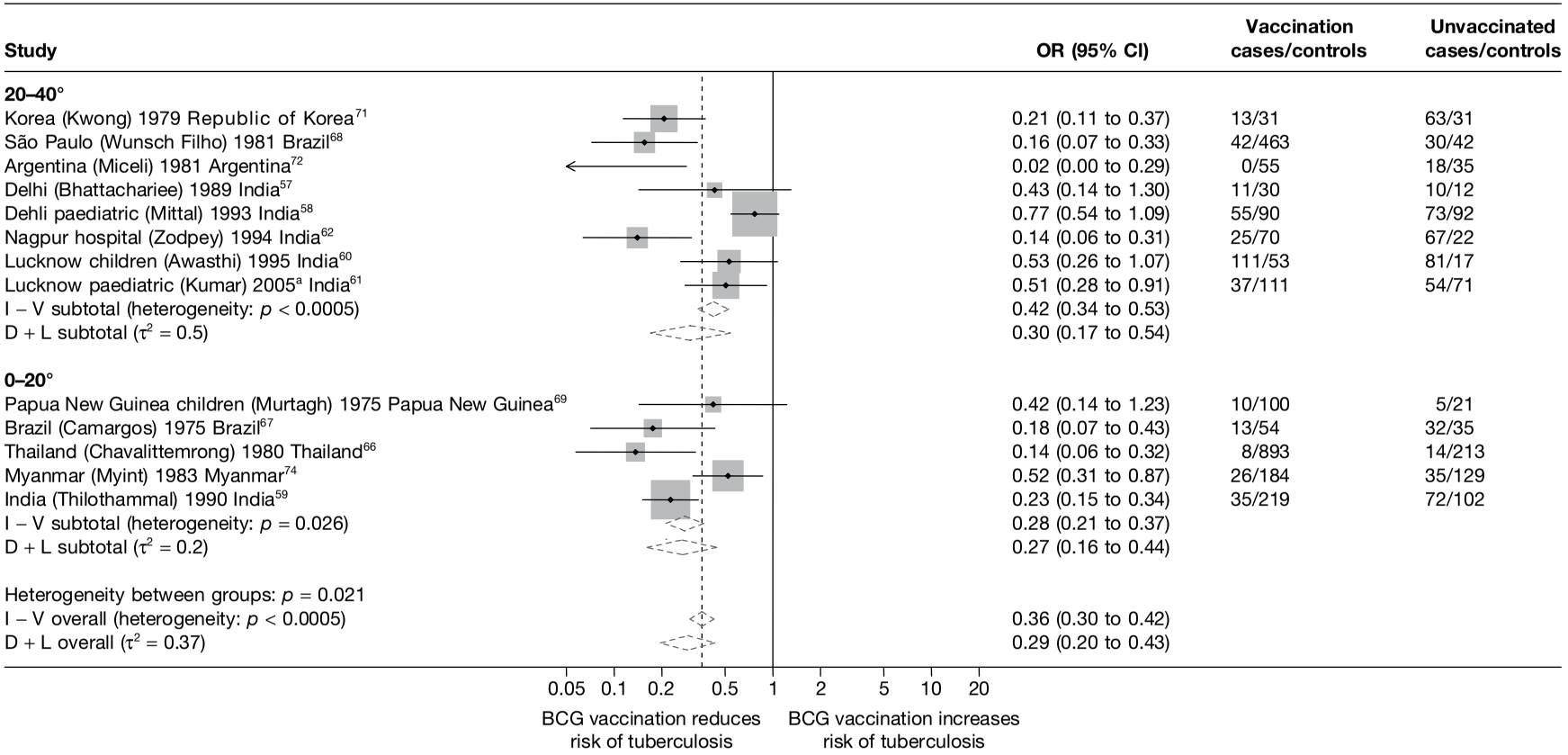

FIGURE 150 Odds ratios (with 95% CI) comparing the BCG vaccination status of meningeal tuberculosis cases and control subjects in case–control studies, stratified by latitude of study location (20° bands), ordered by year of study start. a, Date of study publication was used if study start date was not available. D+L, DerSimonian and Laird method; I–V, inverse variance method.

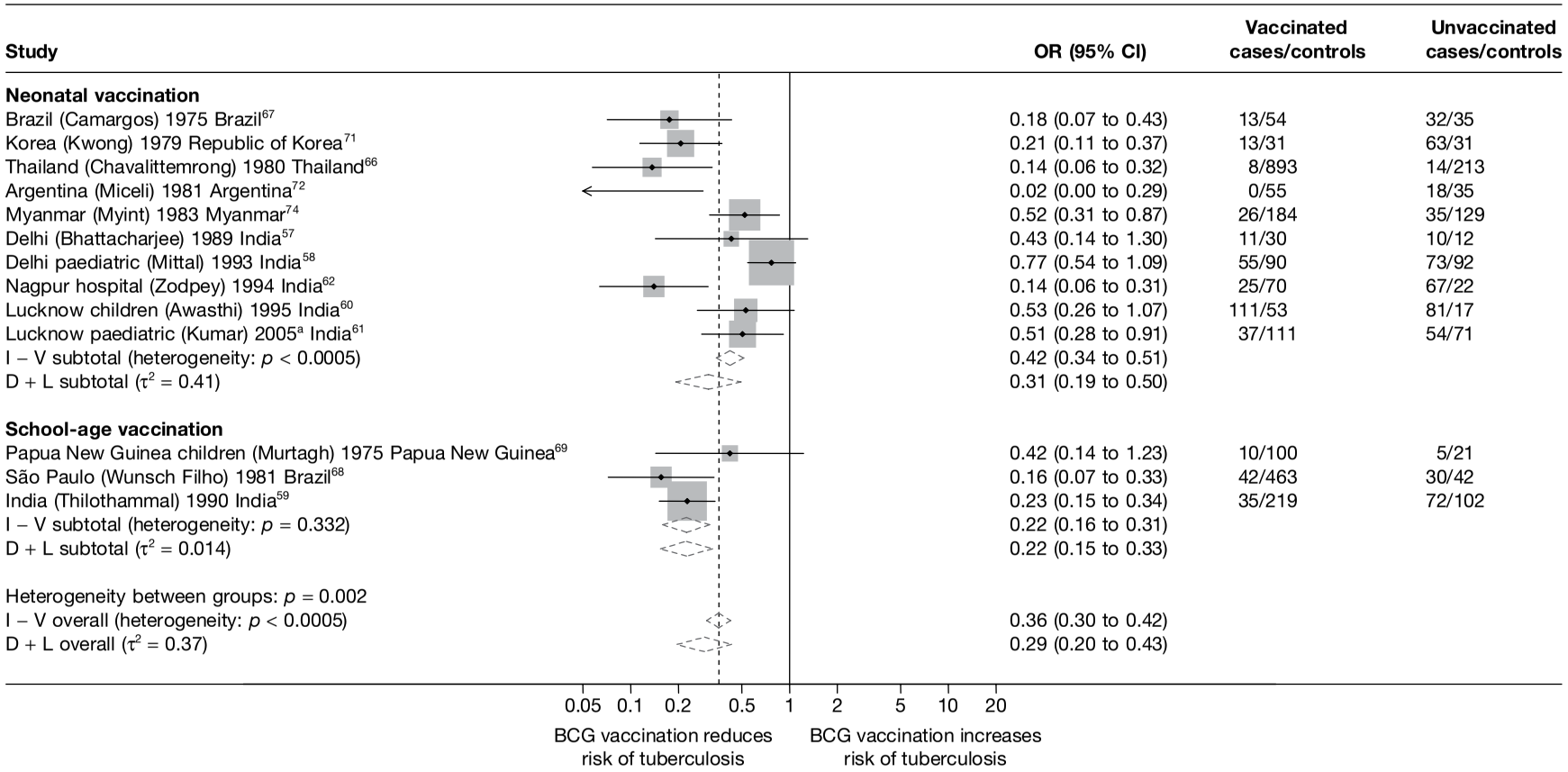

FIGURE 151 Odds ratios (with 95% CI) comparing the BCG vaccination status of meningeal tuberculosis cases and control subjects in case–control studies, stratified by age at vaccination, ordered by year of study start. a, Date of study publication was used if study start date was not available. D+L, DerSimonian and Laird method; I–V, inverse variance method.

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Cohort studies

Unstratified analyses are ordered by year trial started

See *Figure 152*.

Stratified analysis by 10° latitude, ordered by year study started

See *Figure 153*.

Stratified analysis by 20° latitude, ordered by year study started

See *Figure 154*.

Stratified analysis by age at vaccination, ordered by year study started

See *Figure 155*.

Stratified analysis by cohort study design, ordered by year study started

See *Figure 156*.

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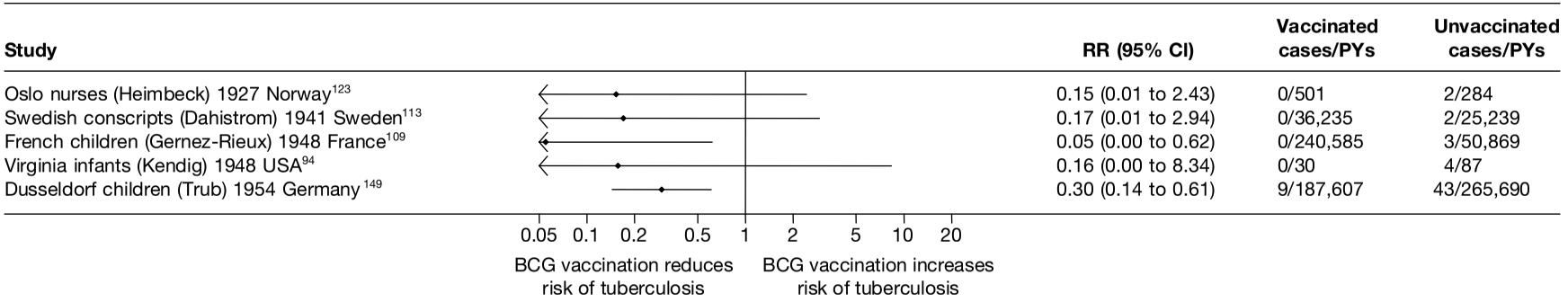

FIGURE 152 Rate ratios (with 95% CI) comparing the incidence of meningeal tuberculosis outcomes among BCG vaccinated individuals with that in unvaccinated individuals for the longest duration of follow-up (see *Table 4*) in cohort studies, ordered by year of study start. D + L, DerSimonian and Laird method; I–V, inverse variance method.

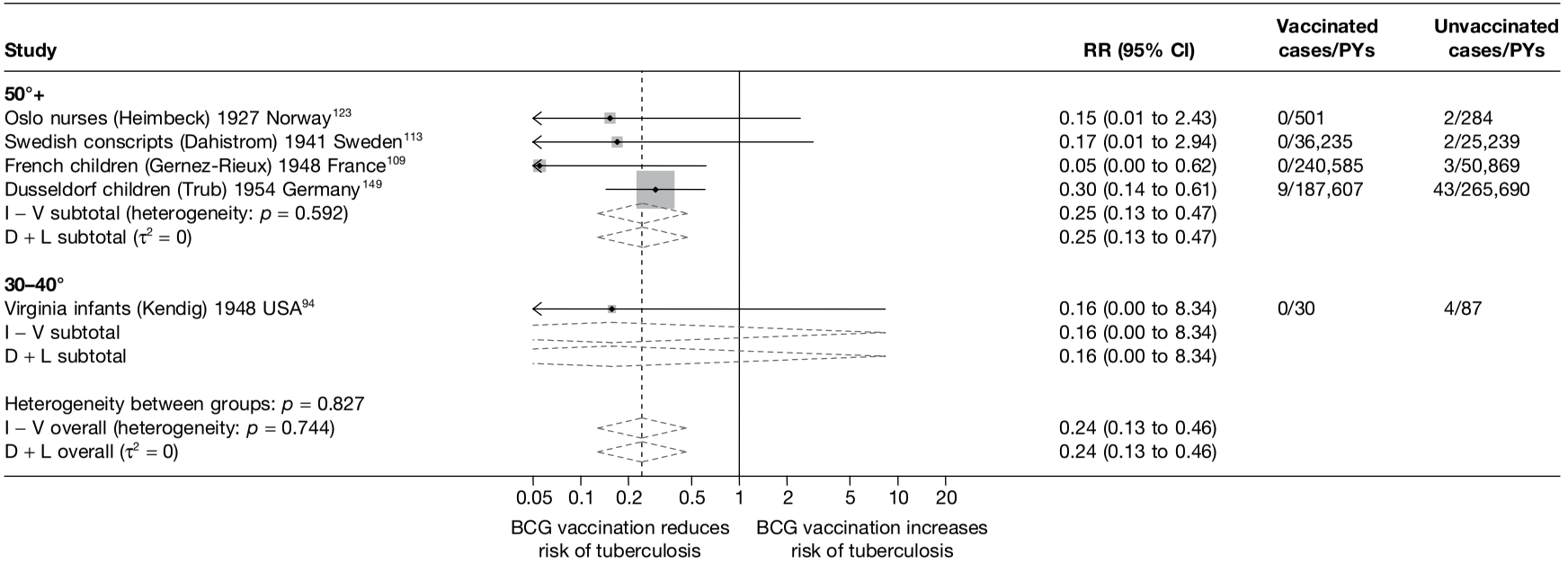

FIGURE 153 Rate ratios (with 95% CI) comparing the incidence of meningeal tuberculosis outcomes among BCG vaccinated individuals with that in unvaccinated individuals for the longest duration of follow-up (see *Table 4*) in cohort studies, stratified by latitude of study location (10° bands), ordered by year of study start. D + L, DerSimonian and Laird method; I–V, inverse variance method.

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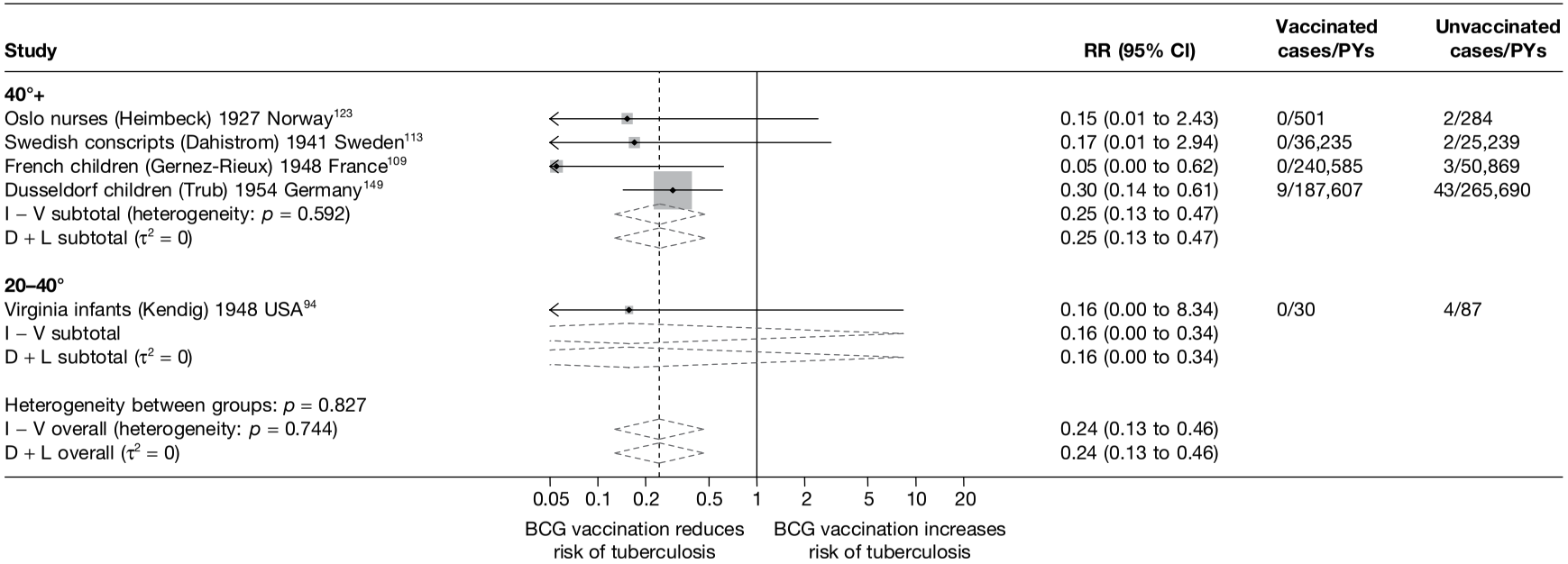

FIGURE 154 Rate ratios (with 95% CI) comparing the incidence of meningeal tuberculosis outcomes among BCG vaccinated individuals with that in unvaccinated individuals for the longest duration of follow-up (see *Table 4*) in cohort studies, stratified by latitude of study location (20° bands), ordered by year of study start. D+L, DerSimonian and Laird method; I–V, inverse variance method.

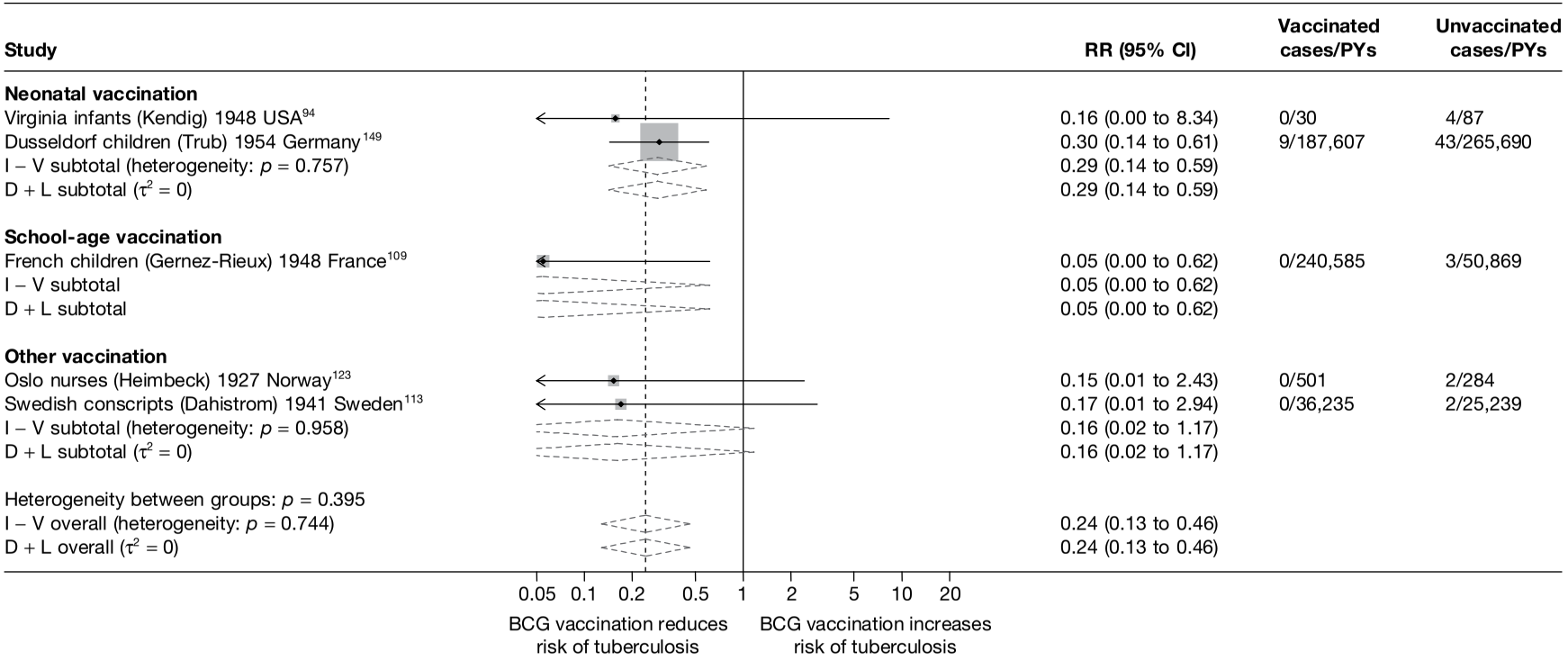

FIGURE 155 Rate ratios (with 95% CI) comparing the incidence of meningeal tuberculosis outcomes among BCG vaccinated individuals with that in unvaccinated individuals for the longest duration of follow-up (see *Table 4*) in cohort studies, stratified by age at vaccination, ordered by year of study start. D+L, DerSimonian and Laird method; I–V, inverse variance method.

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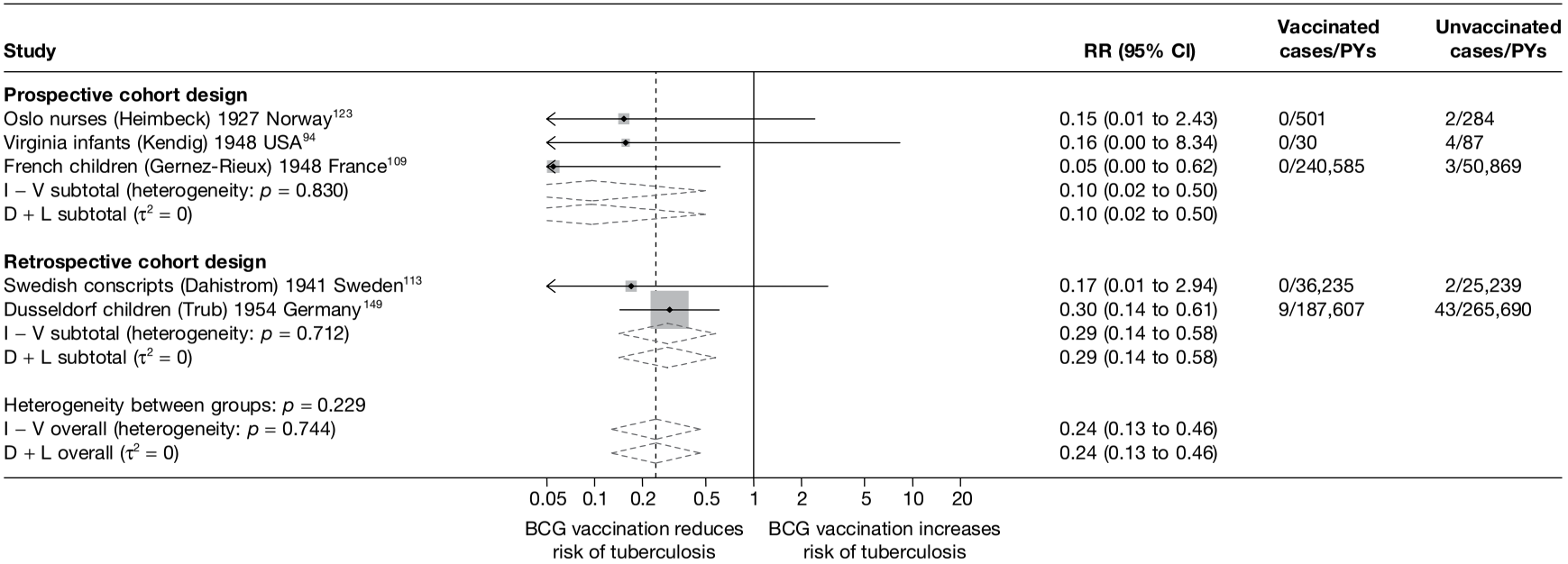

FIGURE 156 Rate ratios (with 95% CI) comparing the incidence of meningeal tuberculosis outcomes among BCG vaccinated individuals with that in unvaccinated individuals for the longest duration of follow-up (see *Table 4*) in cohort studies, stratified cohort study design, ordered by year of study start. D+L, DerSimonian and Laird method; I–V, inverse variance method.

Cross-sectional studies

Unstratified analyses are ordered by year trial started

See *Figure 157*.

Stratified analysis by 10° latitude, ordered by year study started

See *Figure 158*.

Stratified analysis by 20° latitude, ordered by year study started

See *Figure 159*.

Stratified analysis by age at vaccination, ordered by year study started

See *Figure 160*.

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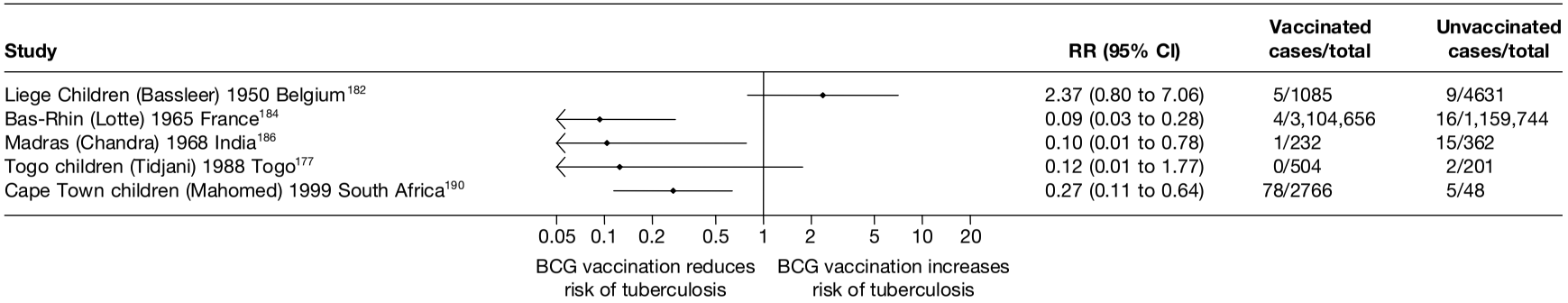

FIGURE 157 Risk ratios (with 95% CI) comparing the prevalence of meningeal tuberculosis among BCG vaccinated individuals with that in unvaccinated individuals, in cross-sectional studies ordered by year of study start. D+L, DerSimonian and Laird method; I–V, inverse variance method.

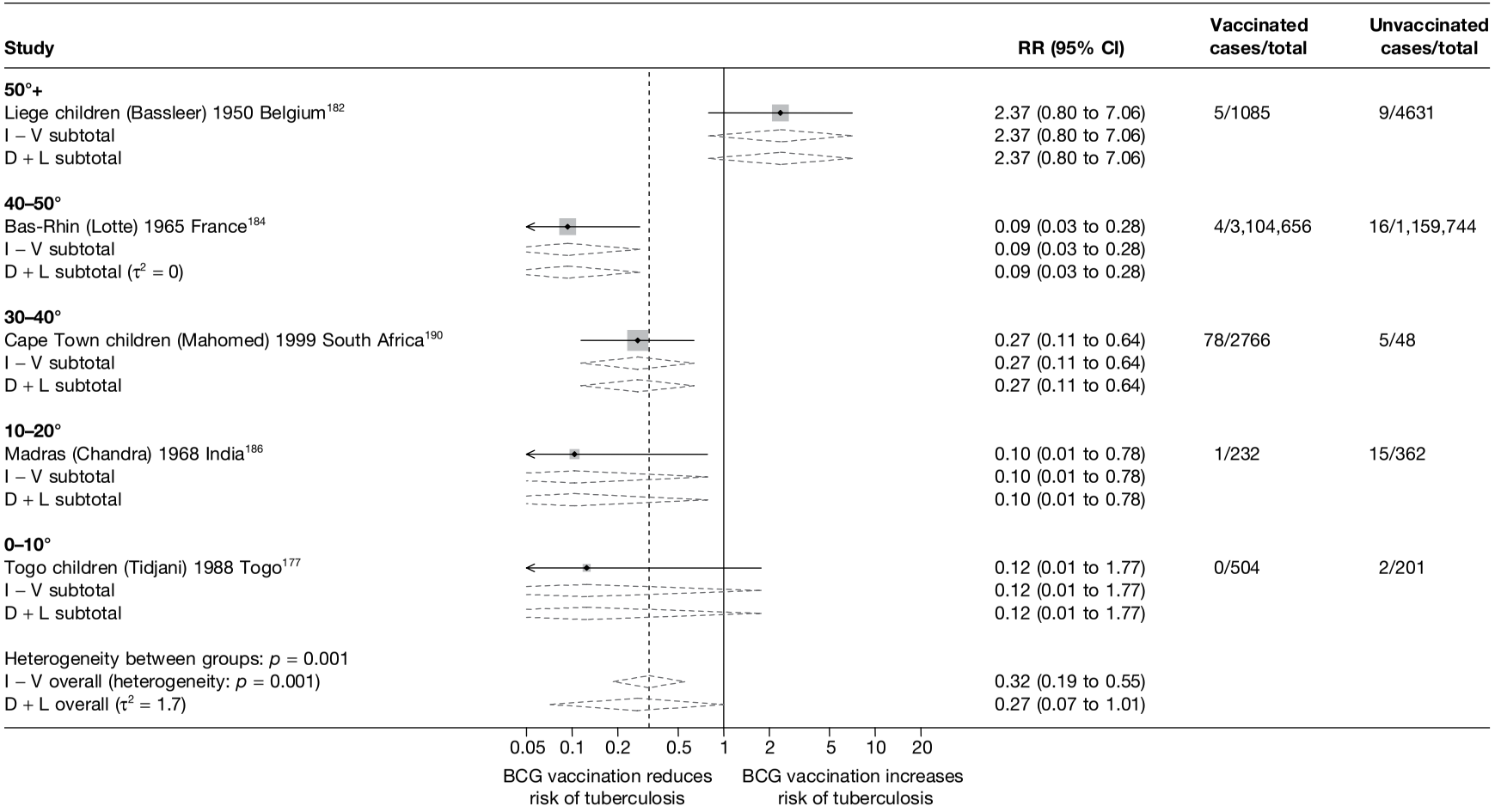

FIGURE 158 Risk ratios (with 95% CI) comparing the prevalence of meningeal tuberculosis among BCG vaccinated individuals with that in unvaccinated individuals, in cross-sectional studies, stratified by latitude of study location (10° bands), ordered by year of study start. D + L, DerSimonian and Laird method; I – V, inverse variance method.

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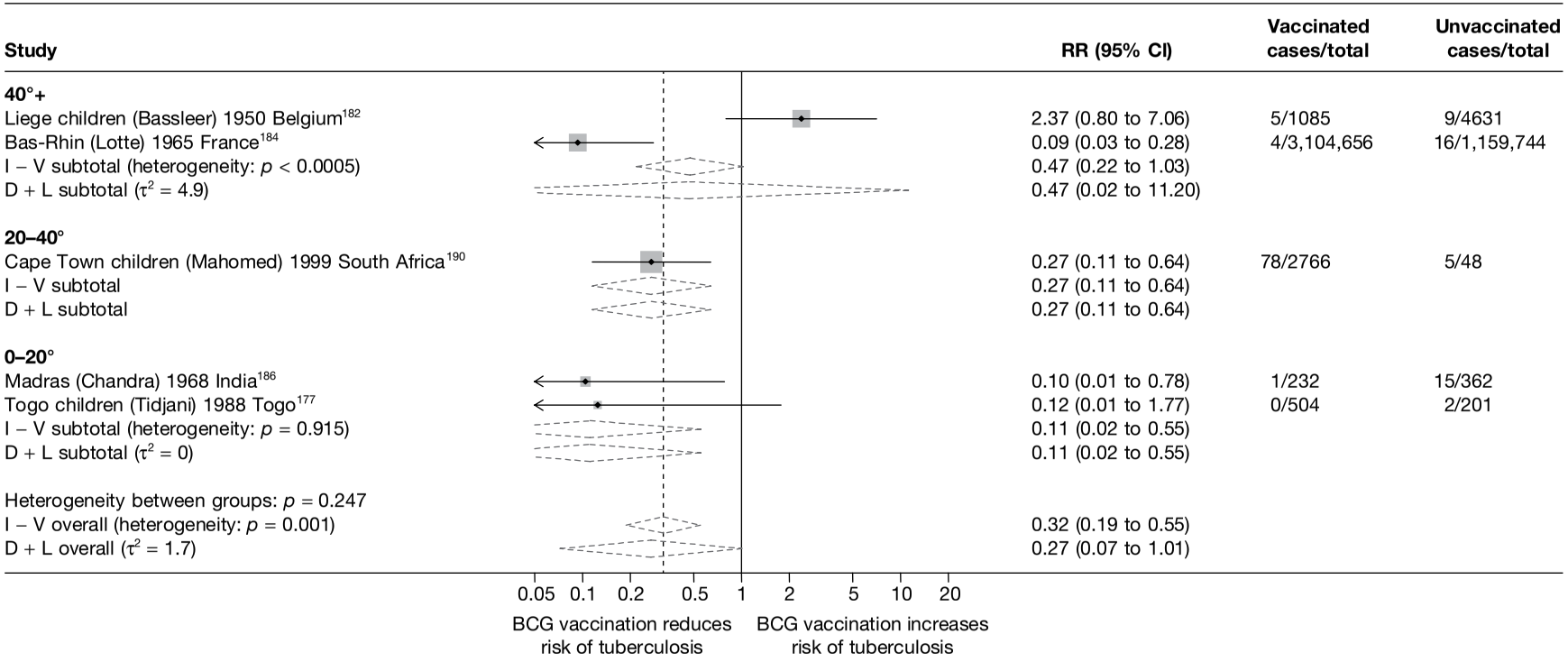

FIGURE 159 Risk ratios (with 95% CI) comparing the prevalence of meningeal tuberculosis among BCG vaccinated individuals with that in unvaccinated individuals, in cross-sectional studies, stratified by latitude of study location (20° bands), ordered by year of study start. D + L, DerSimonian and Laird method; I – V, inverse variance method.

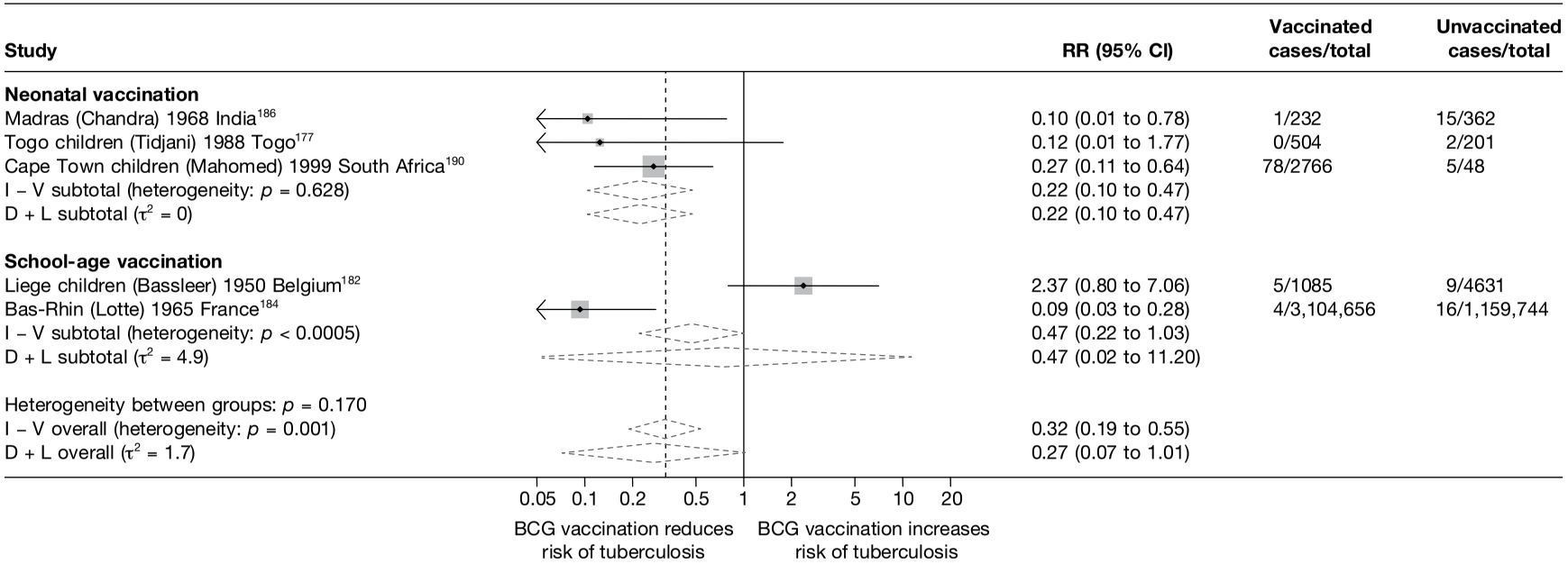

FIGURE 160 Risk ratios (with 95% CI) comparing the prevalence of meningeal tuberculosis among BCG vaccinated individuals with that in unvaccinated individuals, in cross-sectional studies, stratified by age at vaccination, ordered by year of study start. D+L, DerSimonian and Laird method; I–V, inverse variance method.

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Miliary tuberculosis

Case–control studies

Unstratified analyses are ordered by year trial started

See *Figure 161*.

Stratified analysis by 10° latitude, ordered by year study started

See *Figure 162*.

Stratified analysis by 20° latitude, ordered by year study started

See *Figure 163*.

Stratified analysis by age at vaccination, ordered by year study started

See *Figure 164*.

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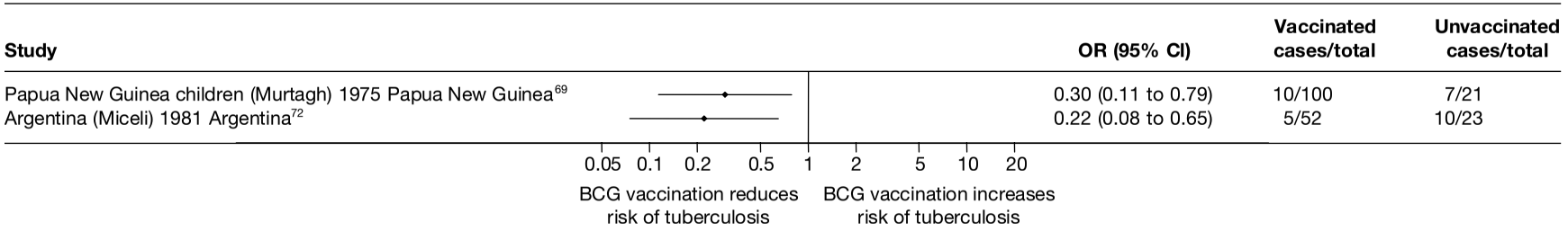

FIGURE 161 Odds ratios (with 95% CI) comparing the BCG vaccination status of miliary tuberculosis cases and control subjects in case–control studies, ordered by year of study start. D+L, DerSimonian and Laird method; I–V, inverse variance method.

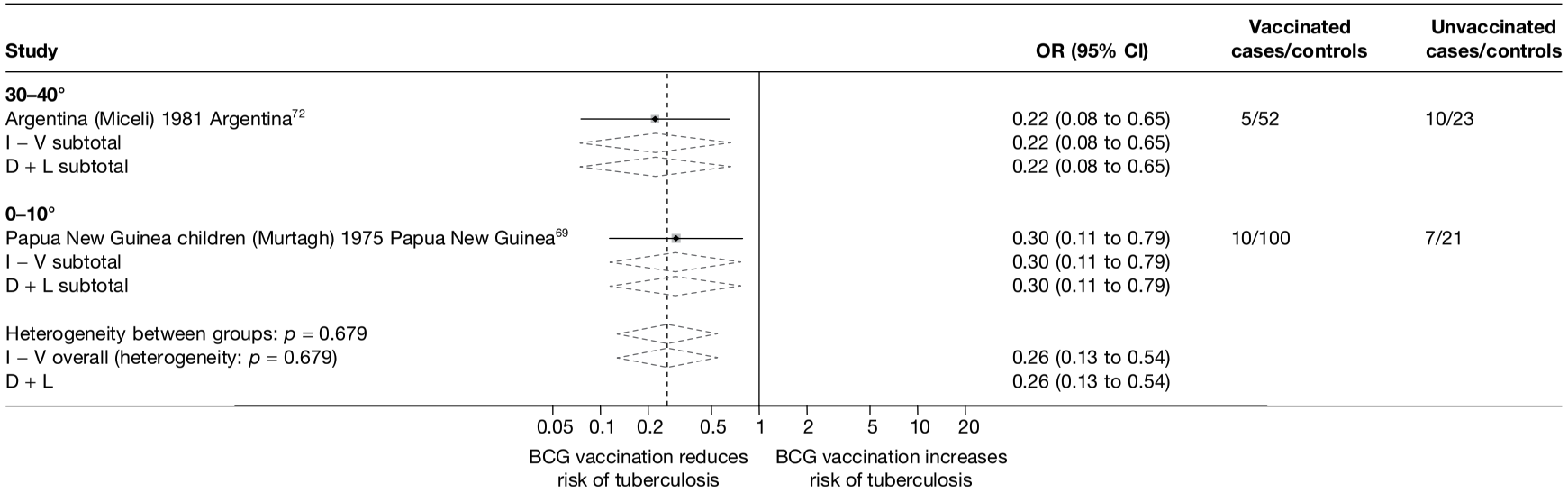

FIGURE 162 Odds ratios (with 95% CI) comparing the BCG vaccination status of miliary tuberculosis cases and control subjects in case–control studies, stratified by latitude of study location (10° bands), ordered by year of study start. D+L, DerSimonian and Laird method; I–V, inverse variance method.

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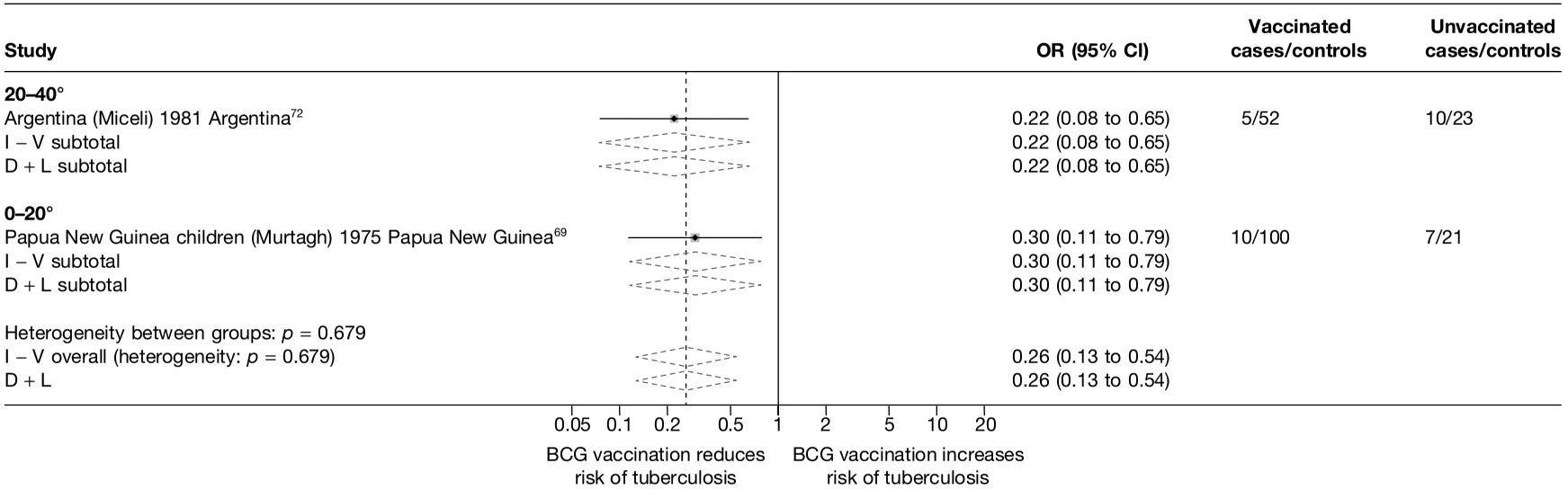

FIGURE 163 Odds ratios (with 95% CI) comparing the BCG vaccination status of miliary tuberculosis cases and control subjects in case–control studies, stratified by latitude of study location (20° bands), ordered by year of study start. D + L, DerSimonian and Laird method; I – V, inverse variance method.

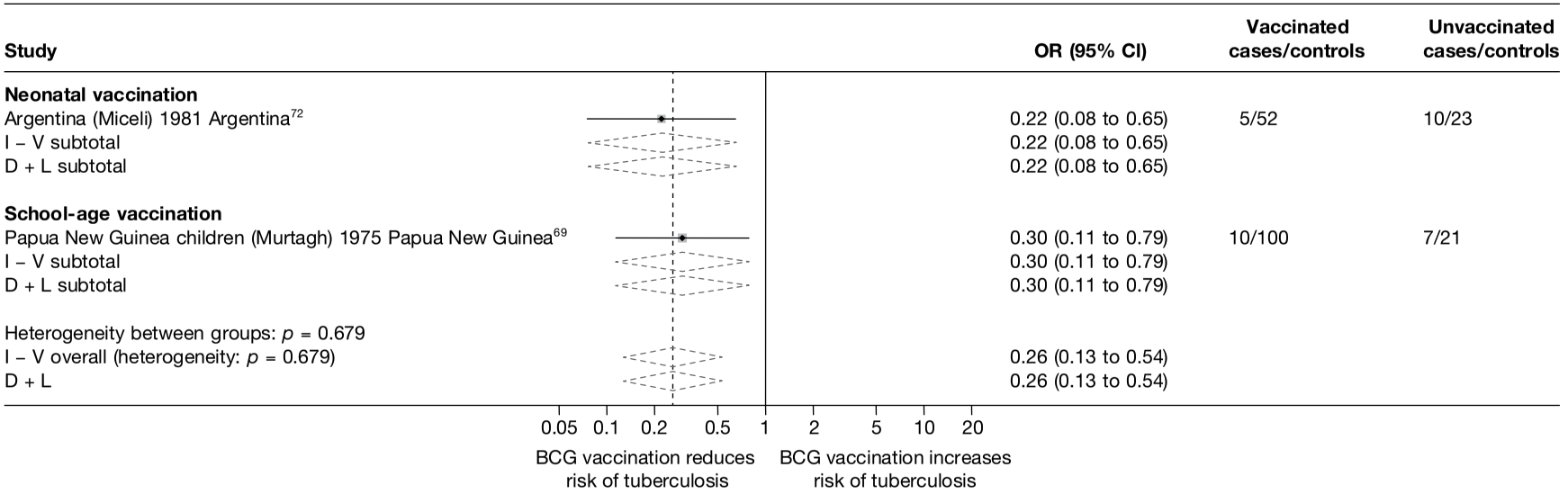

FIGURE 164 Odds ratios (with 95% CI) comparing the BCG vaccination status of miliary tuberculosis cases and control subjects in case–control studies, stratified by age at vaccination, ordered by year of study start. D+L, DerSimonian and Laird method; I–V, inverse variance method.

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Cohort studies

Unstratified analyses are ordered by year trial started

See *Figure 165*.

Stratified analysis by 10° latitude, ordered by year study started

See *Figure 166*.

Stratified analysis by 20° latitude, ordered by year study started

See *Figure 167*.

Stratified analysis by age at vaccination, ordered by year study started

See *Figure 168*.

Stratified analysis by cohort study design, ordered by year study started

See *Figure 169*.

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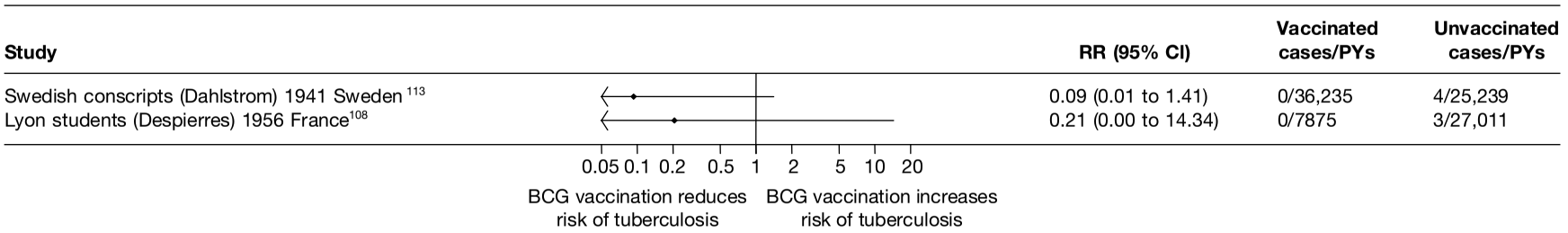

FIGURE 165 Rate ratios (with 95% CI) comparing the incidence of miliary tuberculosis outcomes among BCG vaccinated individuals with that in unvaccinated individuals for the longest duration of follow-up (see *Table 4*) in cohort studies, ordered by year of study start. D+L, DerSimonian and Laird method; I–V, inverse variance method.

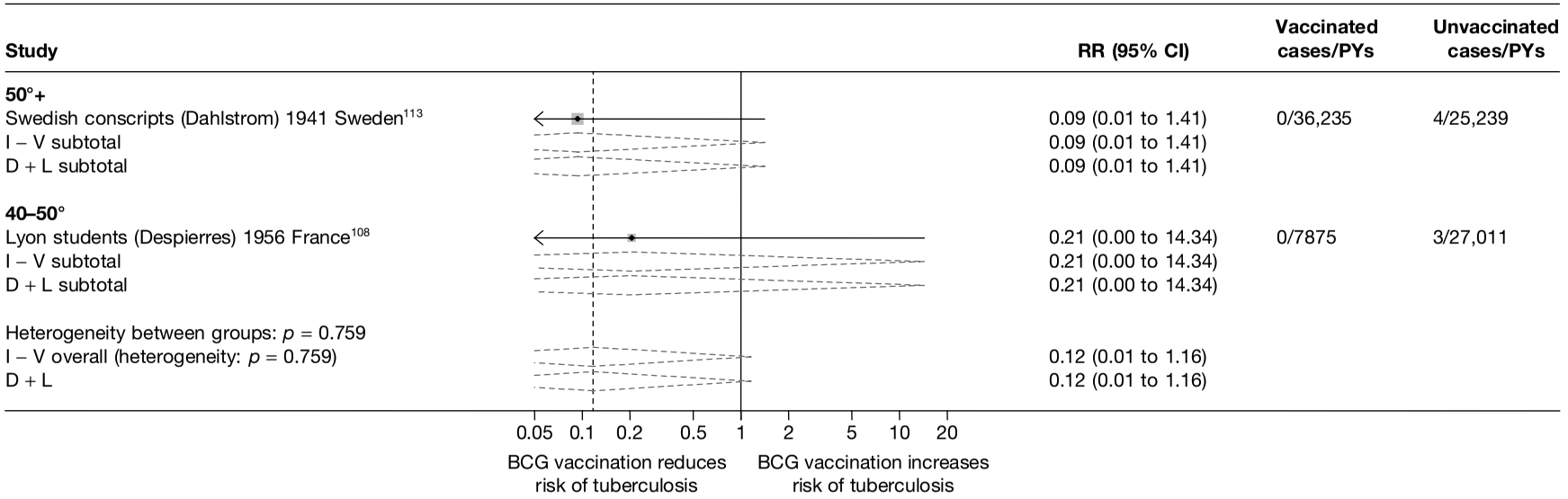

FIGURE 166 Rate ratios (with 95% CI) comparing the incidence of miliary tuberculosis outcomes among BCG vaccinated individuals with that in unvaccinated individuals for the longest duration of follow-up (see *Table 4*) in cohort studies, stratified by latitude of study location (10° bands), ordered by year of study start. D+L, DerSimonian and Laird method; I–V, inverse variance method.

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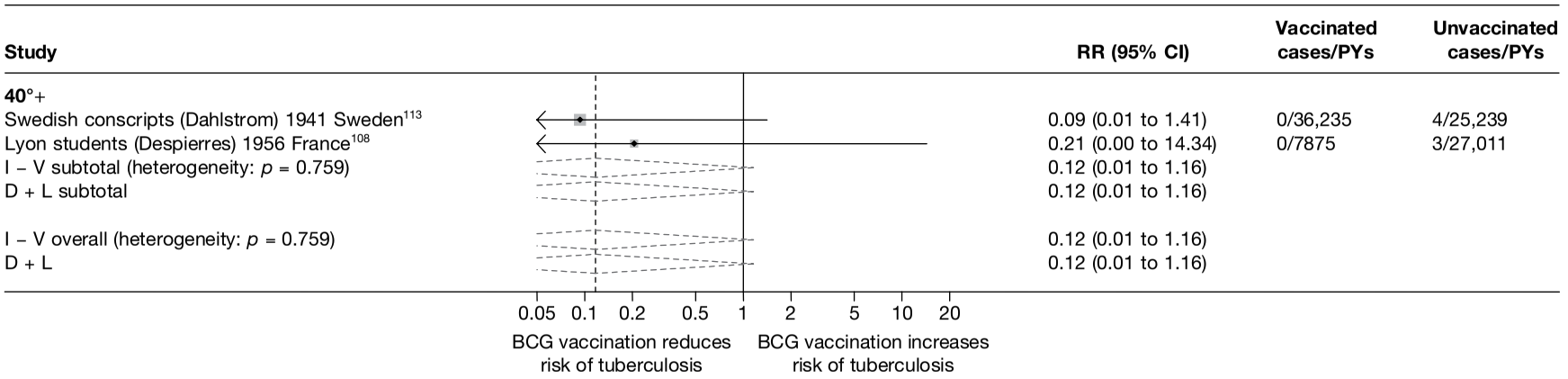

FIGURE 167 Rate ratios (with 95% CI) comparing the incidence of miliary tuberculosis outcomes among BCG vaccinated individuals with that in unvaccinated individuals for the longest duration of follow-up (see *Table 4*) in cohort studies, stratified by latitude of study location (20° bands), ordered by year of study start. D+L, DerSimonian and Laird method; I–V, inverse variance method.

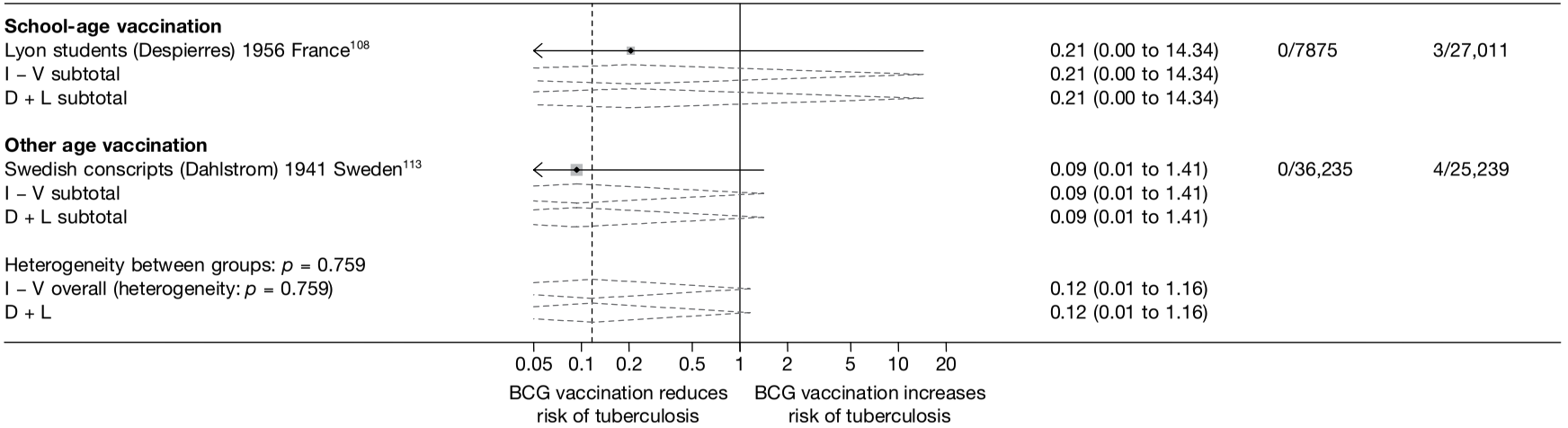

FIGURE 168 Rate ratios (with 95% CI) comparing the incidence of miliary tuberculosis outcomes among BCG vaccinated individuals with that in unvaccinated individuals for the longest duration of follow-up (see *Table 4*) in cohort studies, stratified by age at vaccination, ordered by year of study start. D+L, DerSimonian and Laird method; I–V, inverse variance method.

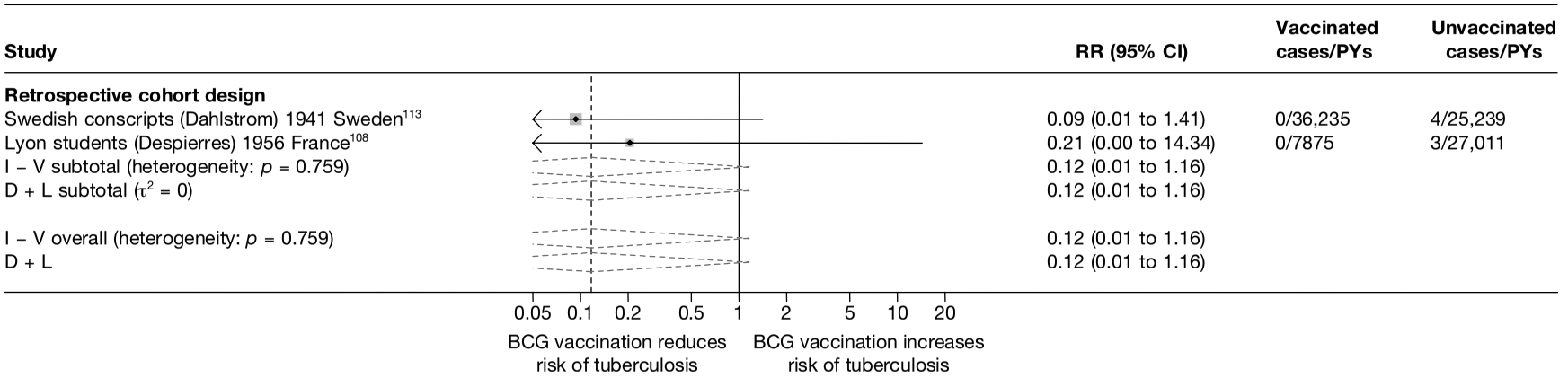

FIGURE 169 Rate ratios (with 95% CI) comparing the incidence of miliary tuberculosis outcomes among BCG vaccinated individuals with that in unvaccinated individuals for the longest duration of follow-up (see *Table 4*) in cohort studies, stratified cohort study design, ordered by year of study start. D+L, DerSimonian and Laird method; I–V, inverse variance method.

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Cross-sectional studies

Unstratified analyses are ordered by year trial started

See *Figure 170*.

Stratified analysis by 10° latitude, ordered by year study started

See *Figure 171*.

Stratified analysis by 20° latitude, ordered by year study started

See *Figure 172*.

Stratified analysis by age at vaccination, ordered by year study started

See *Figure 173*.

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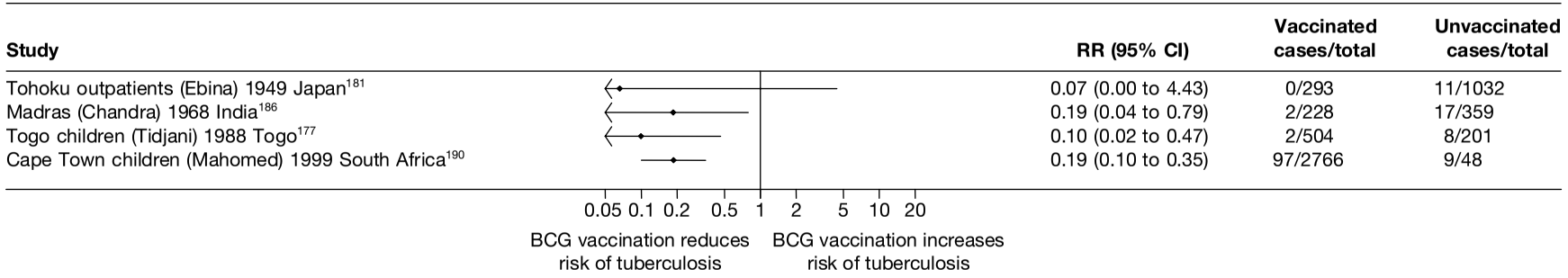

FIGURE 170 Risk ratios (with 95% CI) comparing the prevalence of miliary tuberculosis among BCG vaccinated individuals with that in unvaccinated individuals, in cross-sectional studies ordered by year of study start. D + L, DerSimonian and Laird method; I–V, inverse variance method.

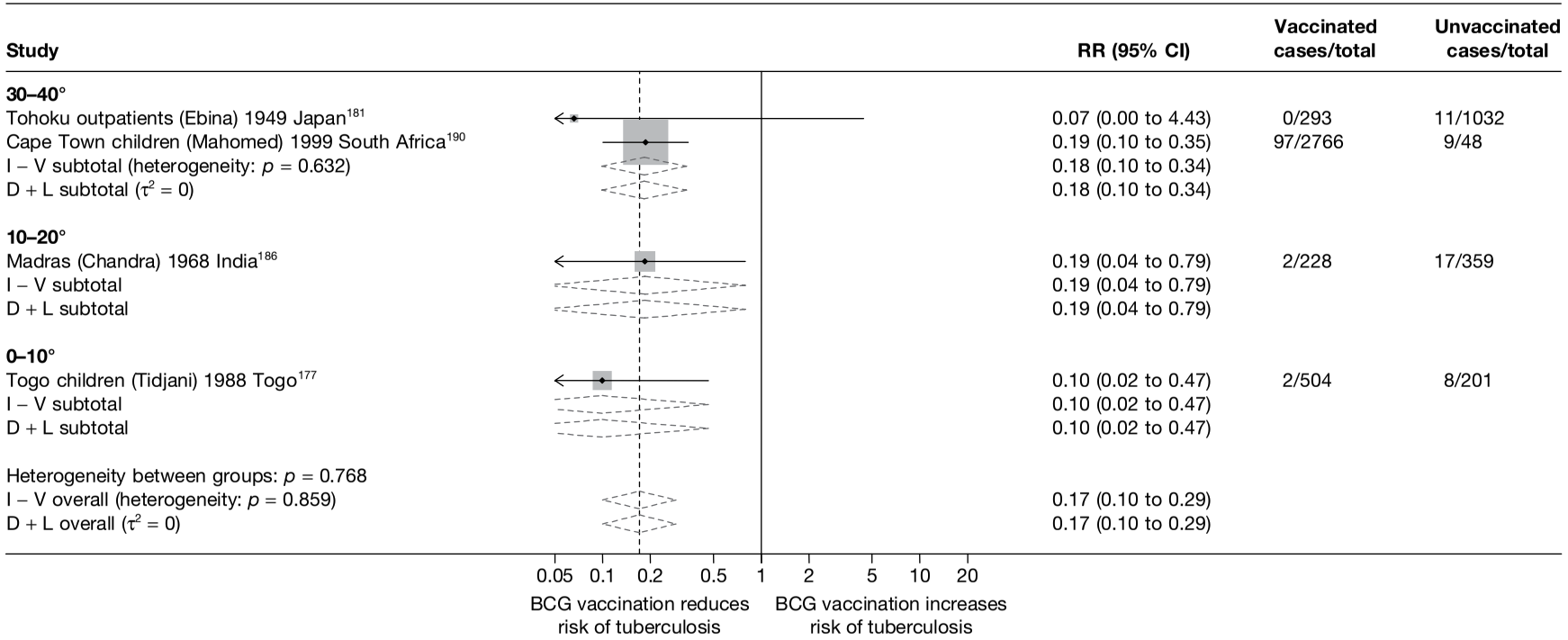

FIGURE 171 Risk ratios (with 95% CI) comparing the prevalence of miliary tuberculosis among BCG vaccinated individuals with that in unvaccinated individuals, in cross-sectional studies, stratified by latitude of study location (10° bands), ordered by year of study start. D + L, DerSimonian and Laird method; I–V, inverse variance method.

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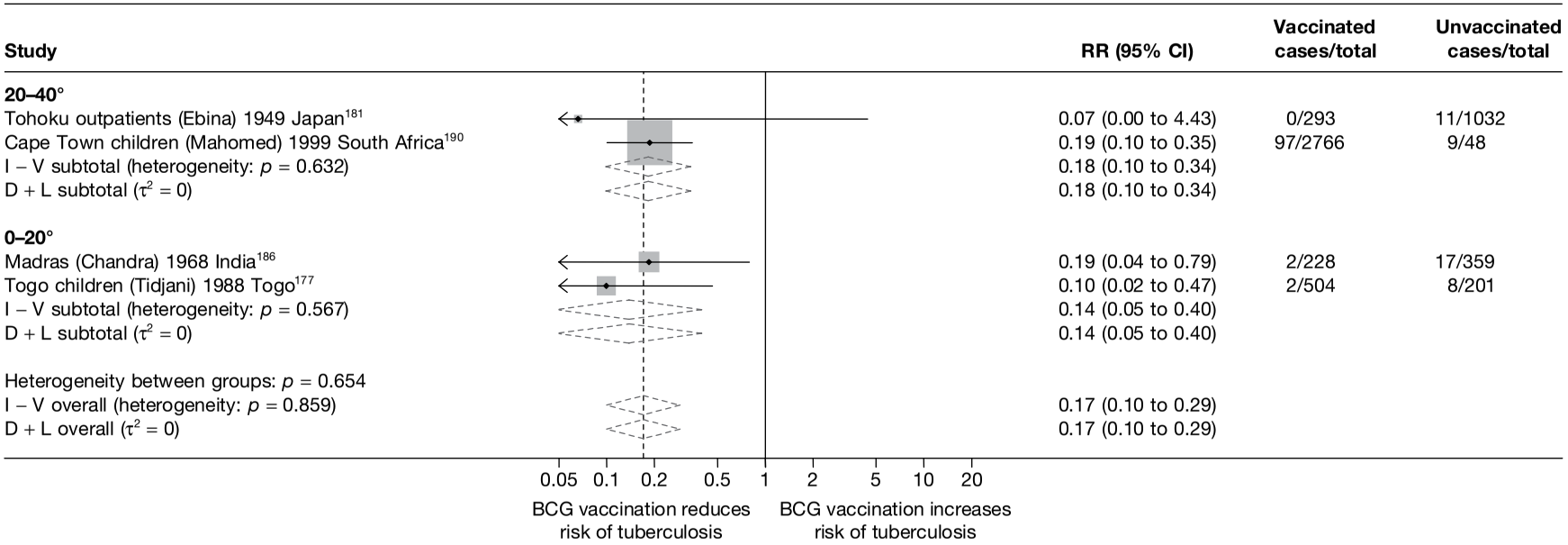

FIGURE 172 Risk ratios (with 95% CI) comparing the prevalence of miliary tuberculosis among BCG vaccinated individuals with that in unvaccinated individuals, in cross-sectional studies, stratified by latitude of study location (20° bands), ordered by year of study start. D + L, DerSimonian and Laird method; I – V, inverse variance method.

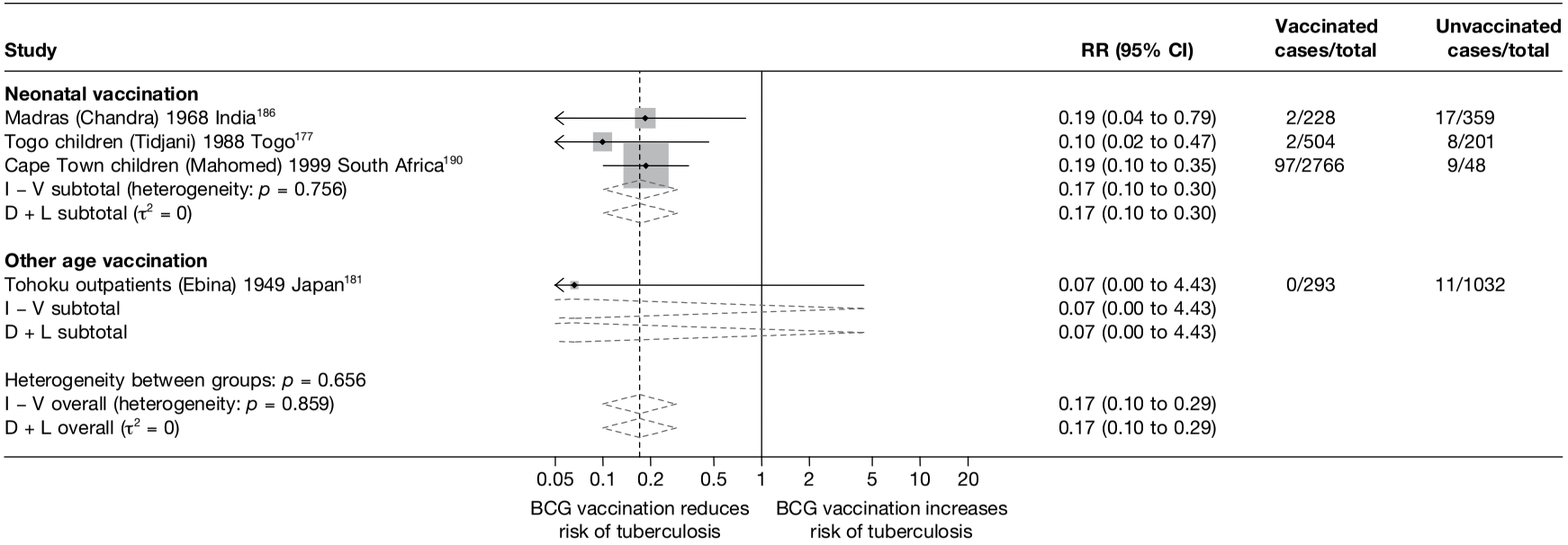

FIGURE 173 Risk ratios (with 95% CI) comparing the prevalence of meningeal tuberculosis among BCG vaccinated individuals with that in unvaccinated individuals, in cross-sectional studies, stratified by latitude age at vaccination, ordered by year of study start. D+L, DerSimonian and Laird method; I–V, inverse variance method.

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Extrapulmonary tuberculosis

Stratified analysis by 20° latitude, ordered by year study started

Case–control studies

See *Figure 174*.

Stratified analysis by age at vaccination, ordered by year study started

See *Figure 175*.

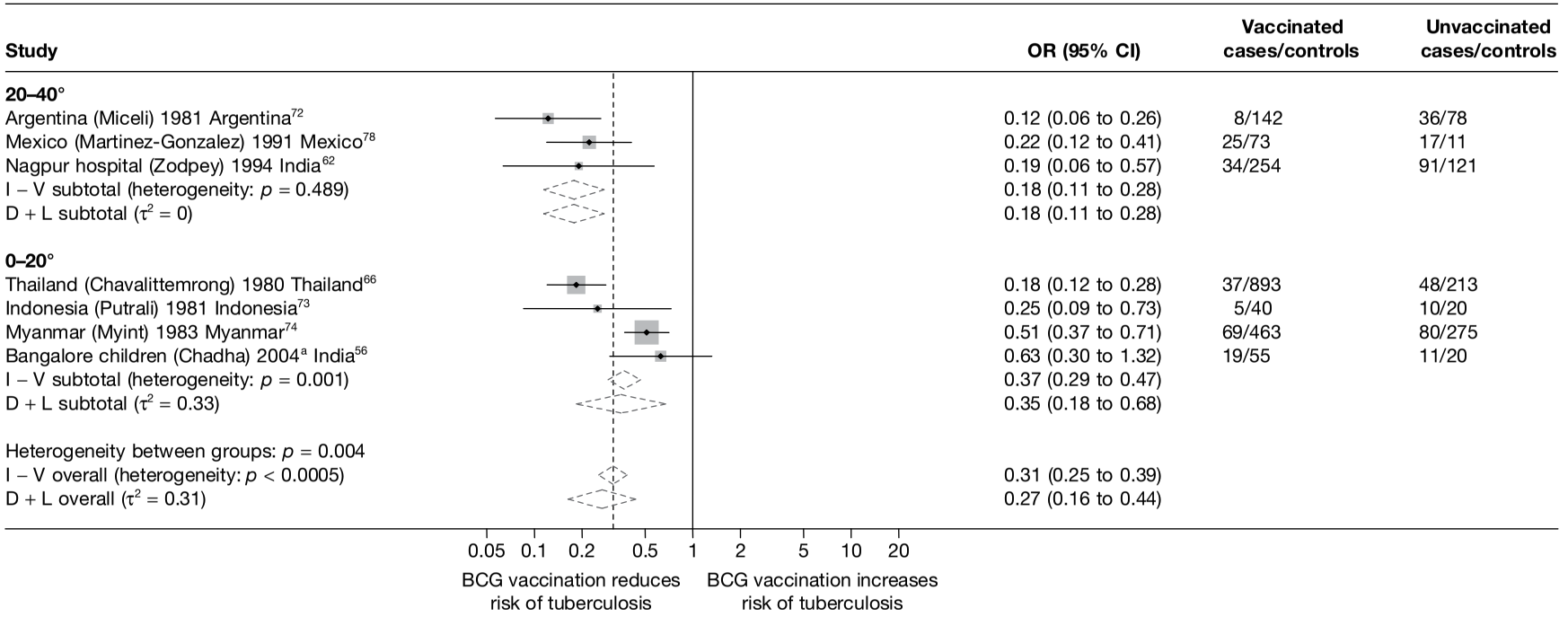

FIGURE 174 Odds ratios (with 95% CI) comparing the BCG vaccination status of extrapulmonary tuberculosis cases and control subjects in case–control studies, stratified by latitude of study location (20° bands), ordered by year of study start. a, Date of study publication was used if study start date was not available. D+L, DerSimonian and Laird method; I–V, inverse variance method.

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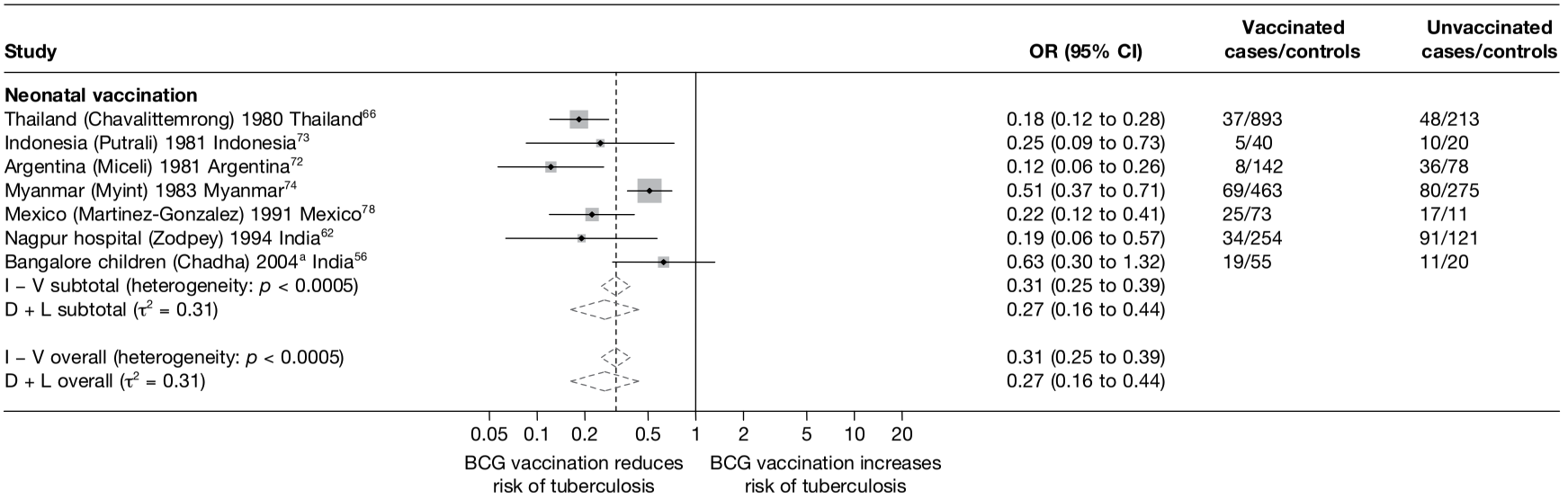

FIGURE 175 Odds ratios (with 95% CI) comparing the BCG vaccination status of extrapulmonary tuberculosis cases and control subjects in case–control studies, stratified by age at vaccination, ordered by year of study start. a, Date of study publication was used if study start date was not available. D+L, DerSimonian and Laird method; I–V, inverse variance method.

Stratified analysis by 20° latitude, ordered by year study started

Cohort studies

See *Figure 176*.

Case population studies

See *Figure 177*.

Cross-sectional studies

See *Figure 178*.

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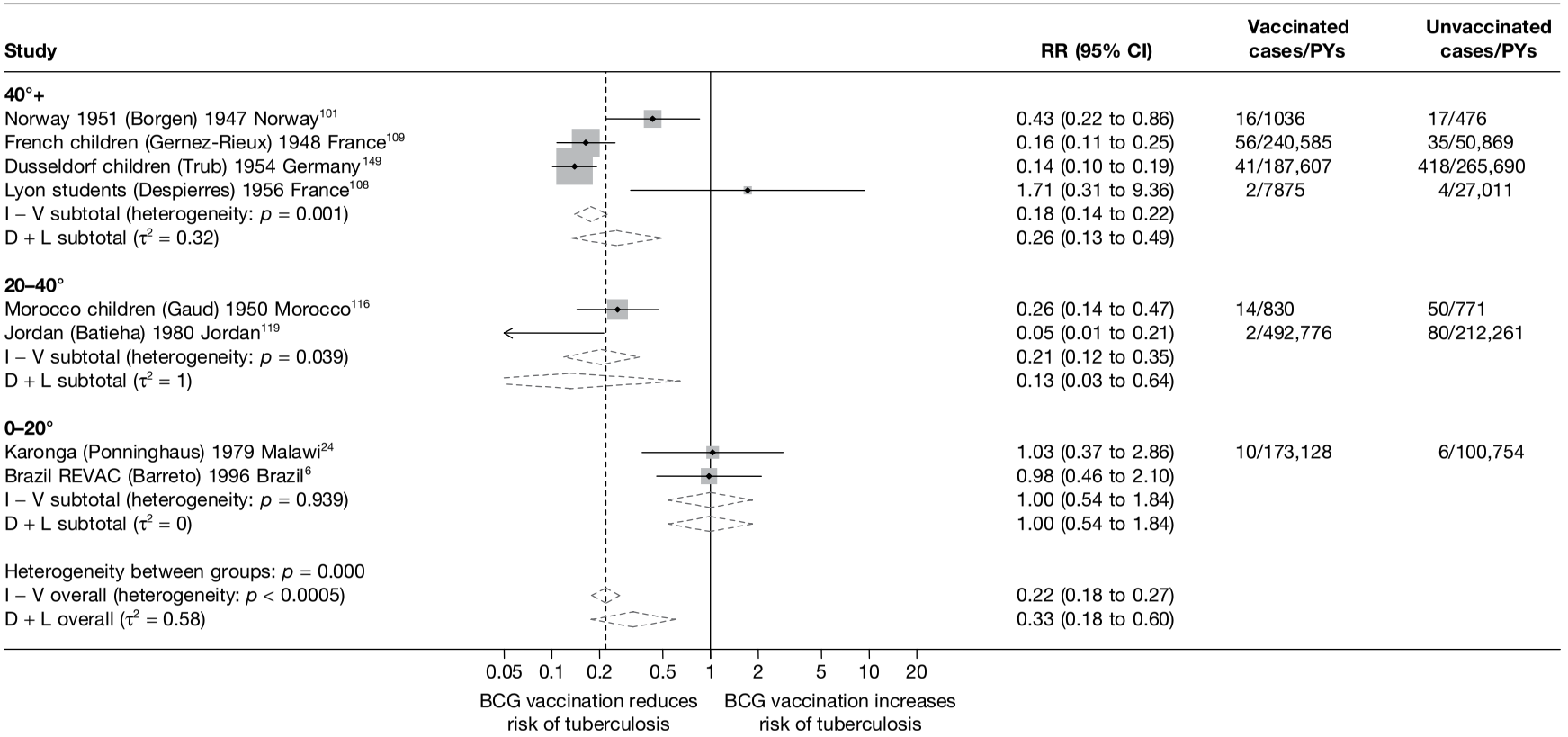

FIGURE 176 Rate ratios (with 95% CI) comparing the incidence of extrapulmonary tuberculosis among BCG vaccinated individuals with that in unvaccinated individuals for the longest duration of follow-up (see *Table 4*) in cohort studies, stratified by latitude of study location (20° bands), ordered by year of study start. D+L, DerSimonian and Laird method; I–V, inverse variance method.

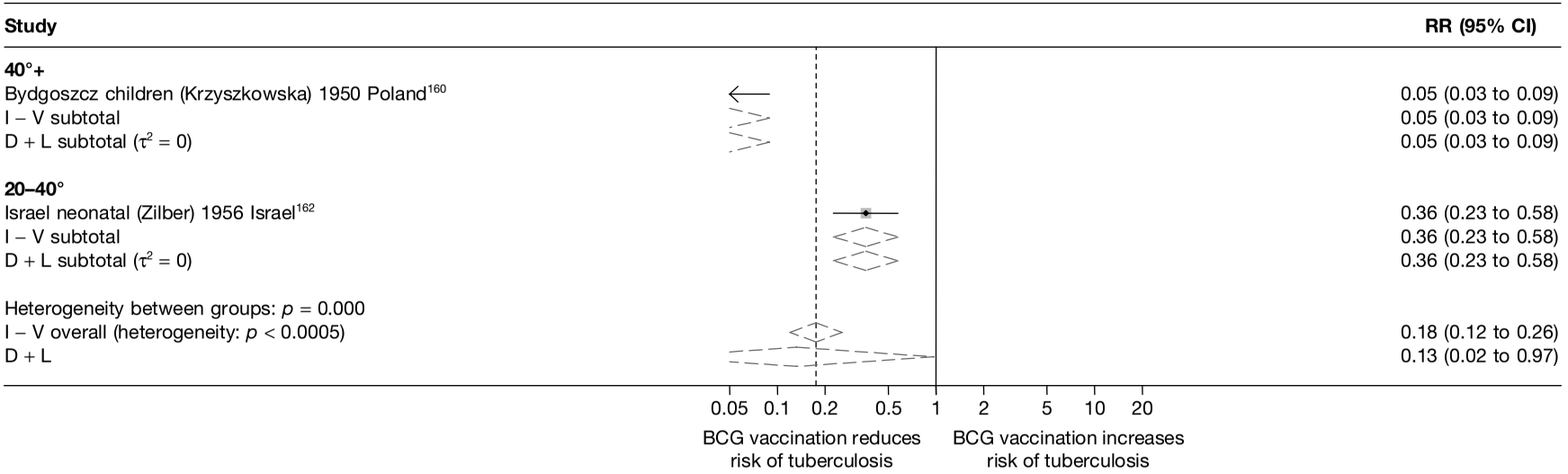

FIGURE 177 Rate ratios (with 95% CI) comparing the incidence of extrapulmonary tuberculosis among BCG vaccinated individuals with that in unvaccinated individuals for the longest duration of follow-up (see *Table 5*) in case population studies, stratified by latitude of study location (20° bands), ordered by year of study start. D + L, DerSimonian and Laird method; I – V, inverse variance method.

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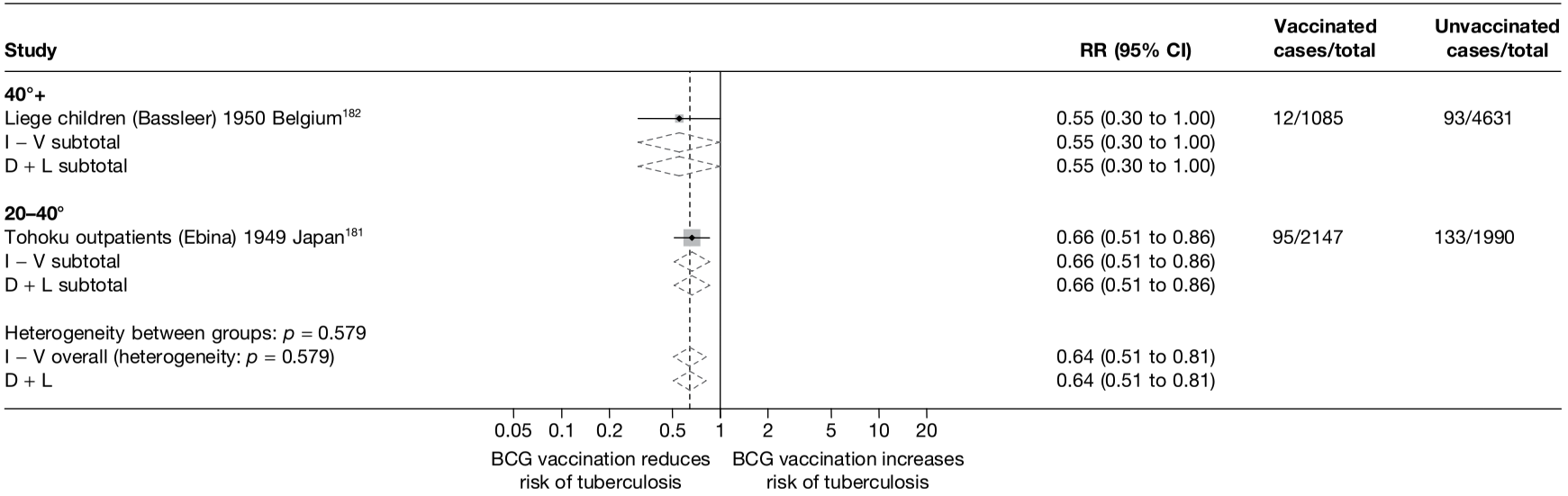

FIGURE 178 Risk ratios (with 95% CI) comparing the prevalence of extrapulmonary tuberculosis among BCG vaccinated individuals with that in unvaccinated in cross-sectional studies, stratified by latitude of study location (20° bands), ordered by year of study start. D + L, DerSimonian and Laird method; I – V, inverse variance method.

Stratified analysis by age at vaccination, ordered by year study started

See *Figure 179.*

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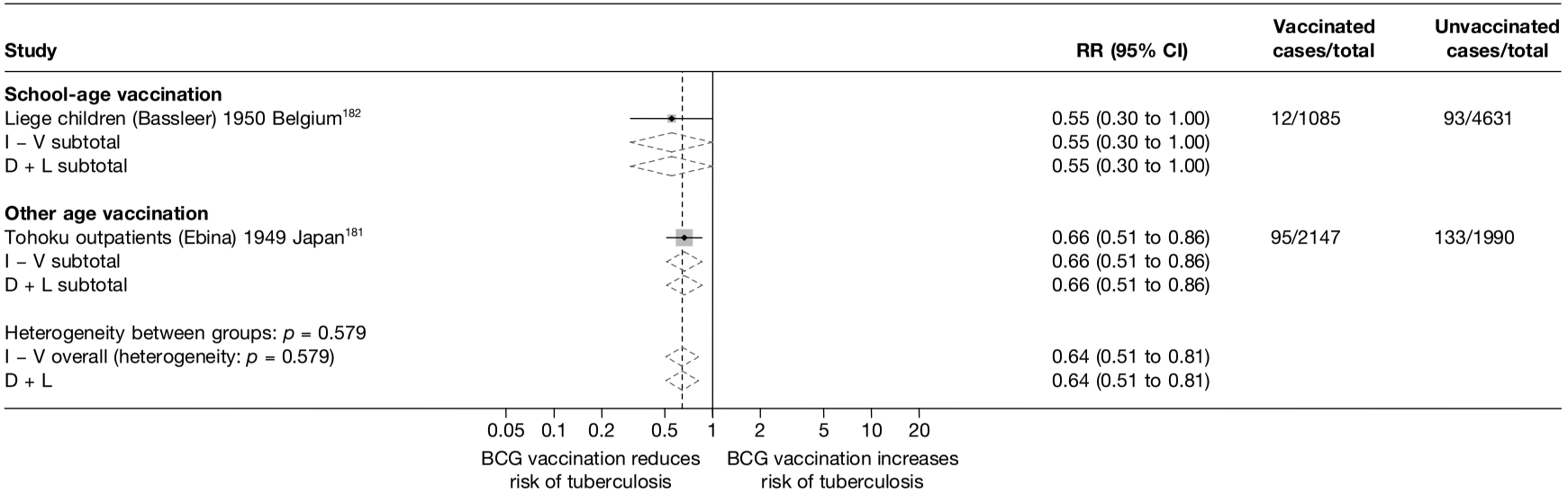

FIGURE 179 Risk ratios (with 95% CI) comparing the prevalence of extrapulmonary tuberculosis among BCG vaccinated individuals with that in unvaccinated in cross-sectional studies, stratified by age at vaccination, ordered by year of study start. D+L, DerSimonian and Laird method; I–V, inverse variance method.

Tuberculosis mortality

Stratified analysis by 20° latitude, ordered by year study started

Cohort studies

See *Figure 180.*

Cross-sectional studies

See *Figure 181.*

Results by gender and age for all outcomes

See *Table 33.*

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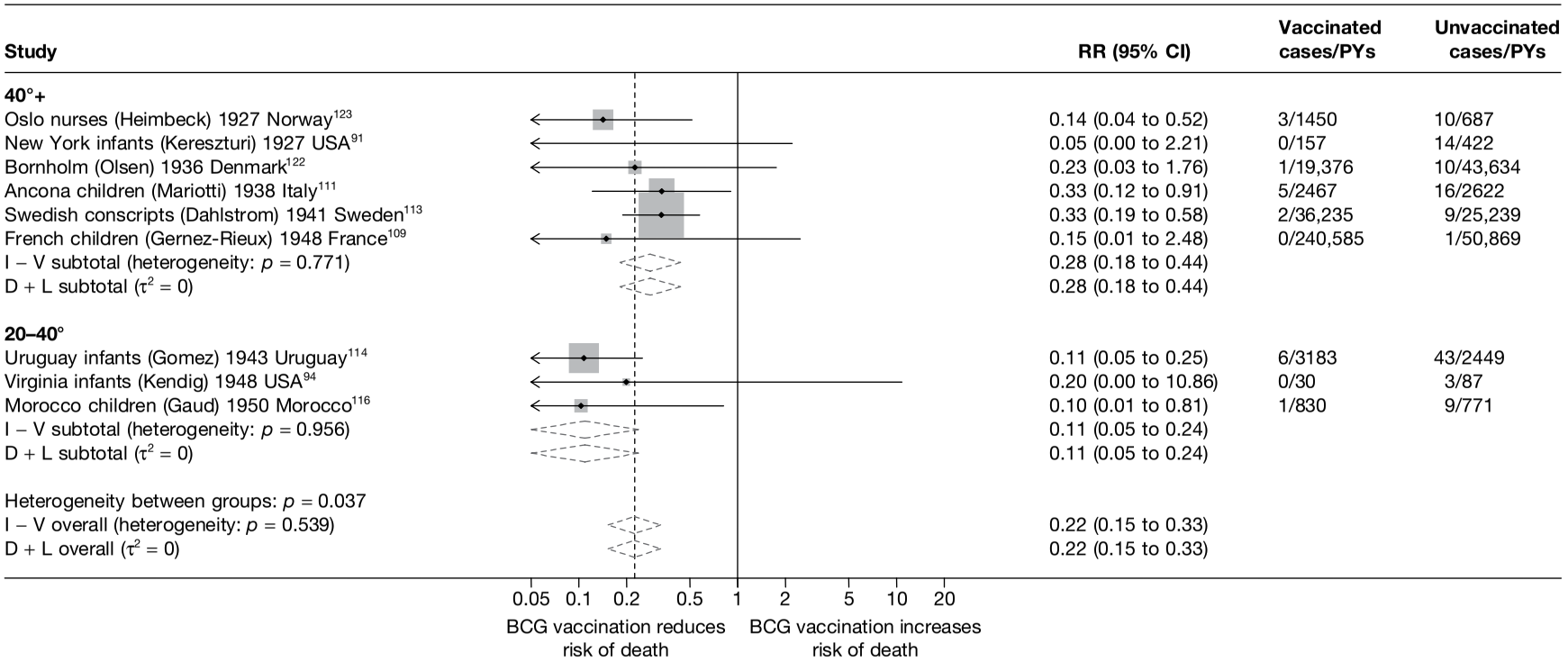

FIGURE 180 Rate ratios (with 95% CI) comparing the incidence of tuberculosis mortality among BCG vaccinated individuals to that in unvaccinated individuals for the longest duration of follow-up (see *Table 4*) in cohort studies, stratified by latitude of study location (20° bands), ordered by year of study start. D+L, DerSimonian and Laird method; I–V, inverse variance method.

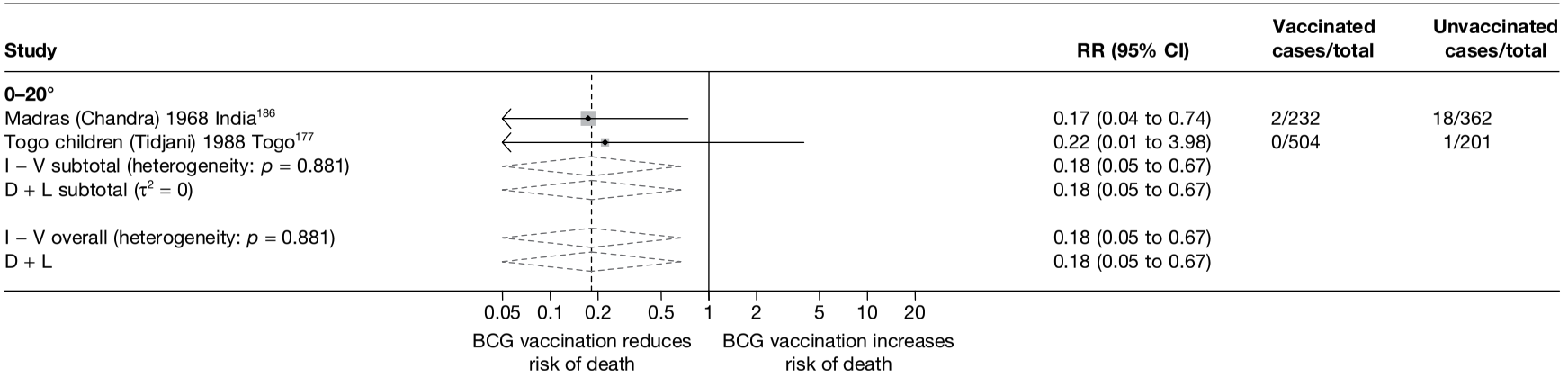

FIGURE 181 Risk ratios (with 95% CI) comparing the prevalence of tuberculosis mortality among BCG vaccinated individuals with that in unvaccinated individuals, in cross-sectional studies ordered by year of study start, by latitude of study location (20° bands). D+L, DerSimonian and Laird method; I–V, inverse variance method.

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TABLE 33 Incidence rates for BCG and unvaccinated groups, rate ratios and ratio of rate ratios (RRR) of vaccinated compared with unvaccinated by gender for RCTs

Study	Tuberculosis outcome	Gender	Vaccinated cases/ unvaccinated cases	BCG vaccinated PYs/unvaccinated PYs	Follow-up period	BCG vaccination incidence rate (95% CI) (per 100,000)	Unvaccinated incidence rate (95% CI) (per 100,000)	Rate ratio (95% CI)	RRRs for females vs. males (95% CI)
Chingleput[28]	Pulmonary tuberculosis	Male			15	74	70	1.06	0.92
		Female				37	38	0.97	
Madanapalle[53]		Male	2/8	11,324/12,700	13	17.7 (4.4 to 70.6)	63.0 (31.5 to 126.0)	0.28 (0.06 to 1.32)	0.43 (0.03 to 5.69)
		Female	1/9	11,924/12,946		8.4 (1.2 to 59.5)	69.5 (36.2 to 133.6)	0.12 (0.02 to 0.95)	
Native American[5]	All tuberculosis outcomes	Male	23/31	24,731/23,664	50	93.0 (61.8 to 140.0)	131.0 (92.1 to 186.3)	0.71 (0.41 to 1.22)	0.43 (0.19 to 0.98)
		Female	13/35	29,545/24,138		44.0 (25.5 to 75.8)	145.0 (104.1 to 202.0)	0.30 (0.16 to 0.57)	
Puerto Rico[15]		Male	80/78	453,678/243,250	20	17.6 (14.2 to 22.0)	32.1 (25.7 to 40.0)	0.55 (0.40 to 0.75)	1.67 (1.07 to 2.59)
		Female	106/63	490,881/267,458		21.6 (17.9 to 26.1)	23.6 (18.4 to 30.2)	0.92 (0.67 to 1.25)	

Case–control studies

TABLE 34 Odds ratios comparing the BCG vaccination status in cases and control subjects and ratios of ORs by gender, in case–control studies

Study	Tuberculosis outcome	Duration (years)	Gender	OR (95% CI)	Ratio of ORs for females vs. males 95% (CI)
Indonesia[73]	All tuberculosis morbidity outcomes	0–5	Female	0.60 (0.34 to 1.11)	
		0–5	Male	0.64 (0.39 to 1.11)	0.93 (0.42 to 2.05)
Myanmar[74]		0–1	Female	0.71 (0.30 to 1.83)	
		0–1	Male	0.30 (0.13 to 0.79)	
		1–2	Female	0.33 (0.18 to 0.64)	
		1–2	Male	1.00 (0.55 to 1.89)	
		2–3	Female	0.39 (0.20 to 0.79)	
		2–3	Male	0.65 (0.35 to 1.25)	
		3–4	Female	0.67 (0.30 to 1.64)	
		3–4	Male	1.24 (0.59 to 2.76)	
		4–5	Female	0.82 (0.41 to 1.71)	
		4–5	Male	0.63 (0.34 to 1.24)	0.70 (0.45 to 1.10)
Argentina[72]		0–0.5	Female	0.24 (0.03 to 2.47)	
		0–0.5	Male	1.92 (0.12 to 52.84)	
		0.5–1	Female	0.62 (0.18 to 2.63)	
		0.5–1	Male	0.56 (0.20 to 1.76)	
		1–2	Female	0.29 (0.11 to 0.85)	
		1–2	Male	0.37 (0.17 to 0.90)	
		2–3	Female	0.14 (0.03 to 0.70)	
		2–3	Male	0.37 (0.15 to 0.98)	
		3–4	Female	0.03 (0.00 to 0.61)	
		3–4	Male	0.28 (0.10 to 0.91)	
		4–5	Female	0.21 (0.06 to 0.85)	
		4–5	Male	0.11 (0.03 to 0.50)	
		5–6	Female	0.36 (0.12 to 1.25)	
		5–6	Male	0.13 (0.03 to 0.63)	0.84 (0.42 to 1.67)
Asian Children in UK[32]		0–12	Female	0.58 (0.25 to 10.99)	
		0–12	Male	0.41 (0.20 to 0.86)	1.41 (0.19 to 10.74)
Canada[63]		0–18	Female	0.19 (0.10 to 0.41)	
		0–18	Male	0.43 (0.24 to 0.85)	0.44 (0.17 to 1.13)
Nagpur Hospital[62]	Pulmonary tuberculosis	0–12	Female	0.42 (0.21 to 0.82)	
		0–12	Male	0.34 (0.12 to 0.92)	
		0–37	Female	0.56 (0.37 to 0.85)	
		0–37	Male	0.39 (0.25 to 0.61)	1.36 (0.79 to 2.33)
Nagpur Hospital[62]	Tuberculosis meningitis	0–12	Female	0.17 (0.06 to 0.50)	
		0–12	Male	0.10 (0.03 to 0.33)	1.70 (0.34 to 8.42)
Nagpur Hospital[62]	Extrapulmonary tuberculosis	0–30	Female	0.21 (0.13 to 0.33)	
		0–30	Male	0.16 (0.09 to 0.29)	1.31 (0.62 to 2.77)

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Cohort studies

TABLE 35 Risk ratios comparing the incidence of tuberculosis in BCG vaccinated individuals compared with that in unvaccinated and RRRs by gender, in cohort studies

Study	Potential follow-up period (years)	Gender	Cases in vaccinated/ unvaccinated group	Estimated PYs BCG vaccinated group/ estimated PYs unvaccinated group	RR (95% CI)	RRRs for females vs. males 95% (CI)
Seoul contacts[120] (all tuberculosis outcomes)	0–1	Female	12/9	124/28	0.30 (0.13 to 0.71)	0.80 (0.40 to 1.82)
	0–1	Male	7/17	97/36	0.15 (0.06 to 0.36)	
	1–2	Female	5/7	86/24	0.20 (0.06 to 0.63)	
	1–2	Male	4/5	84/31	0.30 (0.08 to 1.12)	
	2–3	Female	3/10	77/48	0.19 (0.05 to 0.69)	
	2–3	Male	5/5	78/47	0.60 (0.17 to 2.07)	
	3–4	Female	3/5	70/56	0.48 (0.11 to 2.01)	
	3–4	Male	2/14	75/48	0.09 (0.02 to 0.40)	
	4–5	Female	2/4	61/41	0.34 (0.06 to 1.86)	
	4–5	Male	3/4	54/58	0.81 (0.18 to 3.62)	

Cross-sectional studies

TABLE 36 Risk ratios comparing the prevalence of tuberculosis in BCG vaccinated individuals compared with that in unvaccinated and ratios of RRs by gender, in cross-sectional studies

Study	Tuberculosis outcome	Age at outcome (years)	Gender	Cases in vaccinated group/cases in unvaccinated group	Total BCG vaccinated/ total unvaccinated	RR (95% CI)	RRRs for females vs. males 95% (CI)
Bangkok Contacts[188]	All tuberculosis disease	0–1	Male	16/5	190/30	0.51 (0.20 to 1.28)	1.54 (0.87 to 2.74)
		0–1	Female	13/2	158/24	0.99 (0.24 to 4.11)	
		1–2	Male	19/13	145/33	0.33 (0.18 to 0.60)	
		1–2	Female	32/5	148/20	0.86 (0.38 to 1.96)	
		2–3	Male	22/6	143/24	0.62 (0.28 to 1.36)	
		2–3	Female	22/4	134/30	1.23 (0.46 to 3.31)	
		3–4	Male	14/6	113/35	0.72 (0.30 to 1.74)	
		2–4	Female	10/9	104/25	0.27 (0.12 to 0.59)	
		4–5	Male	3/8	68/20	0.11 (0.03 to 0.38)	
		4–5	Female	7/2	50/12	0.84 (0.20 to 3.54)	
Togo Contacts[177]	Pulmonary	0–1	Male	4/5	52/31	0.48 (0.14 to 1.64)	1.25 (0.69 to 2.28)
		0–1	Female	3/4	50/27	0.41 (0.10 to 1.68)	
		1–2	Male	4/5	52/31	0.48 (0.14 to 1.64)	
		1–2	Female	4/6	51/49	0.64 (0.19 to 2.13)	
		2–3	Male	1/11	75/37	0.04 (0.01 to 0.33)	
		2–3	Female	7/10	68/45	0.46 (0.19 to 1.13)	
		3–4	Male	1/9	84/38	0.05 (0.01 to 0.38)	
		2–4	Female	1/7	71/40	0.08 (0.01 to 0.63)	
		4–5	Male	5/10	75/42	0.28 (0.10 to 0.76)	
		4–5	Female	5/11	87/56	0.29 (0.11 to 0.80)	
		>5	Male	12/17	90/68	0.53 (0.27 to 1.04)	
		>5	Female	15/18	120/83	0.58 (0.31 to 1.08)	

Randomised controlled trials

TABLE 37 Risk ratios comparing the incidence of tuberculosis in BCG vaccinated individuals compared with that in unvaccinated and ratios of RRs by age at vaccination, in RCTs

Study	Age group (years)	Vaccinated cases	Unvaccinated cases	BCG vaccinated PYs	Unvaccinated PYs	BCG vaccination incidence rate (95% CI) (per 100,000)	Unvaccinated incidence rate (95% CI) (per 100,000)	Rate ratio (95% CI)
Chingleput (Madras)[28]	0–4	33	22	220,268	110,280	15.0 (10.7 to 21.1)	19.9 (13.1 to 30.3)	0.75 (0.44 to 1.29)
	5–9	58	38	217,637	108,973	26.6 (20.6 to 34.5)	34.9 (25.4 to 47.9)	0.76 (0.51 to 1.15)
	10–14	80	42	123,820	61,560	64.6 (51.9 to 80.4)	68.2 (50.4 to 92.3)	0.95 (0.65 to 1.38)
	15–24	94	34	81,798	38,960	114.9 (93.9 to 140.7)	87.3 (62.4 to 122.1)	1.32 (0.89 to 1.95)
	25–34	52	20	54,140	26,115	96.0 (73.2 to 126)	76.6 (49.4 to 118.7)	1.25 (0.75 to 2.10)
	>35	63	24	57,055	28,090	110.4 (86.3 to 141.3)	85.4 (57.3 to 127.5)	1.29 (0.81 to 2.07)
Madanapalle[53]	0–4	7	4	22,743	26,449	30.8 (14.7 to 64.6)	15.1 (5.7 to 40.3)	2.04 (0.60 to 6.95)
	5–14	10	13	20,249	21,830	49.4 (26.6 to 91.8)	59.6 (34.6 to 102.6)	0.83 (0.36 to 1.89)
	15–24	5	7	7566	8078	66.1 (27.5 to 158.8)	86.7 (41.3 to 181.8)	0.76 (0.24 to 2.40)
	25–34	6	11	5424	7075	110.6 (49.7 to 246.2)	155.5 (86.1 to 280.7)	0.71 (0.26 to 1.92)
	≥35	5	12	5183	6776	96.5 (40.2 to 231.8)	177.0 (100.6 to 311.8)	0.54 (0.19 to 1.55)

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Appendix 7

Final research protocol

Objectives

This review and meta-analysis will examine the changes in bacillus Calmette–Guérin (BCG) efficacy over time by a) age at vaccination, b) gender, c) site of disease, and d) country tuberculosis (TB) epidemiology (high, medium, low prevalence) with a focused discussion on how this information relates to use of BCG in the UK.

Research methods

The review will include a broad and comprehensive search for, and a critical assessment of, studies on the duration of protection of BCG. It will include all the studies in the previous review (Sterne and Rodrigues, *Int J Tuberculosis Lung Dis* 1998;**2**:200–7) and other relevant studies, including newer studies and observational studies.

Outcome measures

For trials and cohort studies we will extract rate ratios comparing unvaccinated with vaccinated individuals, with appropriate measures of precision, for successive time periods since vaccination.

For case–control and cross-sectional studies we will extract odds ratios, with appropriate measures of precision, where these can be related to time since vaccination. For example, in a population vaccinated in the first year of life, odds ratios in different age groups correspond to time since vaccination.

The precise time periods presented will depend on the detail with which the primary studies were reported.

When results are reported in sufficient detail, we will stratify by site of disease (e.g., miliary, meningitis, pulmonary, all TB), gender, and age at vaccination.

We will extract study characteristics that may relate to the extent or duration of protection, including geographic region and latitude, vaccine strain, and risk of bias in the results.

Search strategy

Search terms:

We will combine search terms of the disease (TB, tuberculosis, tubercle bacill*, *Mycobacterium tuberculosis*, *M. bovis*, *M. africanum*, *M. canetti*, *M. microti* and 'M.TB') with terms for the vaccination (BCG Vaccine, BCG, BCG Vacc*, BCG Imm*, bacillus calmette) to extract all possible studies on BCG efficacy from 1920 until present. For the time period of 1920 to 1965 we will also search on the term BCG to identify studies that are indexed differently from more modern studies, as such searches have revealed additional papers on the efficacy of BCG for protecting against TB.

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Databases:

The following search databases/engines will be used to find relevant papers: 1) MEDLINE (PreMEDLINE, Old MEDLINE), 2) Google scholar, 3) Embase, 4) Web of Science, 5) BIOSIS, 6) CINHAL, 7) Dissertation abstracts online database, 8) DARE, 9) SIGLE, 10) Scopus, 11) CAB Abstracts 12) British National Bibliography for Report Literature, 13) LILACS, 14) Global Health and Global Health Archives, 15) Index to Theses, 16) African healthline, and 17) ELDIS. Current trials/data will be searched using the: Cochran library, National Research Register, Health technologies assessment database and National guideline clearing house, clinicaltrials.gov, and control-trials.com. Search engines may be added, or redundant engines removed, following our consolation with a reference librarian and literature search specialist.

Additionally, all relevant manuscripts referenced in each reviewed manuscript will be searched for further articles. All BCG Reviews will be used to further gather references (from their reference lists).

Nominated experts in the area of TB and BCG will be contacted to determine if we are missing key references after our primary list is constructed.

We will include articles in all languages and studies carried out in humans.

Review strategy

Study eligibility and application of inclusion and exclusion criteria:

The titles and abstracts of papers identified will be screened by two reviewers. Given the unexpectedly large number of references on this topic, approximately 22,000, the initial title and abstract review will be split between the two reviewers by author surname alphabetically. The first 5% of titles and abstracts in each reviewer's section, total 10%, will be reviewed in duplicate and checked for agreement to ensure consistency in nominating papers for full review by both reviewers. All articles that are considered to potentially meet the eligibility criteria outlined below by either of the reviewers will be selected. The assessment of study eligibility of this initial selection will not be blinded to publication details such as journal or author names.

Once the title an abstract screening is complete, all papers that were identified as potentially meeting eligibility will be obtained and reviewed completely. Pertinent data for the review and meta-analysis will be extracted in duplicate by both reviewers and reviewer consistency will be monitored periodically to ensure consistency in data extraction. Any necessary adjustments to ensure consistency will be made as a result of this monitoring. Any inconsistencies will be reviewed and resolved by one of the study investigators. Consistency on key items will be evaluated and reported at completion of data extraction.

The criteria for inclusion and exclusion of studies in the review are:

A. Inclusion

Case–control, cohort (longitudinal), cross-sectional, research letters that present new data and controlled trial studies (regardless of randomization) on the efficacy of BCG on TB disease/mortality will be included regardless of follow-up time, population, or level or type of bias (this information will be collected and assessed as part of the review/meta-analysis)

Studies examining re-vaccination with BCG for protection against TB.

Full, peer-reviewed articles, non-peer reviewed articles (e.g., PNAS), conference abstracts, and dissertations should be included if focusing on the efficacy of BCG protection.

Studies examining vaccinated people in any age group (infants, school aged children, adults including occupational), gender, or region.

All languages.

All studies previously included in Sterne & Rodrigues. 1998. Does the efficacy of BCG decline with time since vaccination? *International Journal of Tuberculosis and Lung Disease*. 2(3): 200-207.

Studies without efficacy measures, but containing information sufficient to calculate these.

All human studies.

B. Exclusion

Studies that do not present new data, recent trials of modified or boosted BCG, studies on animals, and ecological studies will not be included in the review.

Data extraction

Two reviewers will independently use standard forms to extract data from all identified papers. Key data items will include study characteristics (authors, date, location, journal, sources of funding, study design), participant characteristics, inclusion criteria, organism (s), test used, BCG vaccine (strain, location, reported outcome measures).

Assessment of methodological quality

For RCTs, we will assess the risk of bias in results according to the methods described in Chapter 8 of the recently-published 5th edition of the Cochrane Handbook (Higgins JPT *et al.* 2008 see www.cochrane-handbook.org). For each domain, trial results will be assessed at high, unclear or low risk of bias.

Standardised tools for assessing the risk of bias in results from observational studies are not available.

For cohort studies, we will record whether assessments of vaccination status were made prospectively and whether outcomes were ascertained blind to vaccination status.

For case-control studies, we will record whether cases and control subjects were recruited blind to vaccination status, and whether the control subjects were sampled from the population that gave rise to the cases.

Statistical analysis

We will derive summary estimates of rate ratios (odds ratios for case-control studies), separately according to time period since vaccination, using both fixed and random-effects meta-analysis.

Because substantial between-study heterogeneity is a well-known feature of studies of BCG vaccination, we will report analyses stratified by geographic region and latitude, and report any potential biases identified when interpreting the results.

Due to the high frequency of adverse effects in HIV infected individuals, we will conduct separate analysis for studies involving HIV infected populations.

We will use fixed- and random-effects Poisson regression models to quantify rates of change in the duration of protection with time, allowing for between-study heterogeneity.

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We will conduct separate analyses for each type of study (trials, cohort studies, case–control studies, and cross-sectional), for different geographical areas, age at vaccination, site of TB disease, and gender. However, due to heterogeneity between studies, we may not be able to combine results from all studies of the same type, nor stratify on all variables of interest.

We will use random-effects Poisson regression models, and random-effects meta-regression models, to examine associations of study characteristics (including summary assessments of risk of bias) with the extent and duration of protection.

Ethics

This study will not require a review by a research ethics committee as it does not involve any patient or health care staff contact.

Output of the research

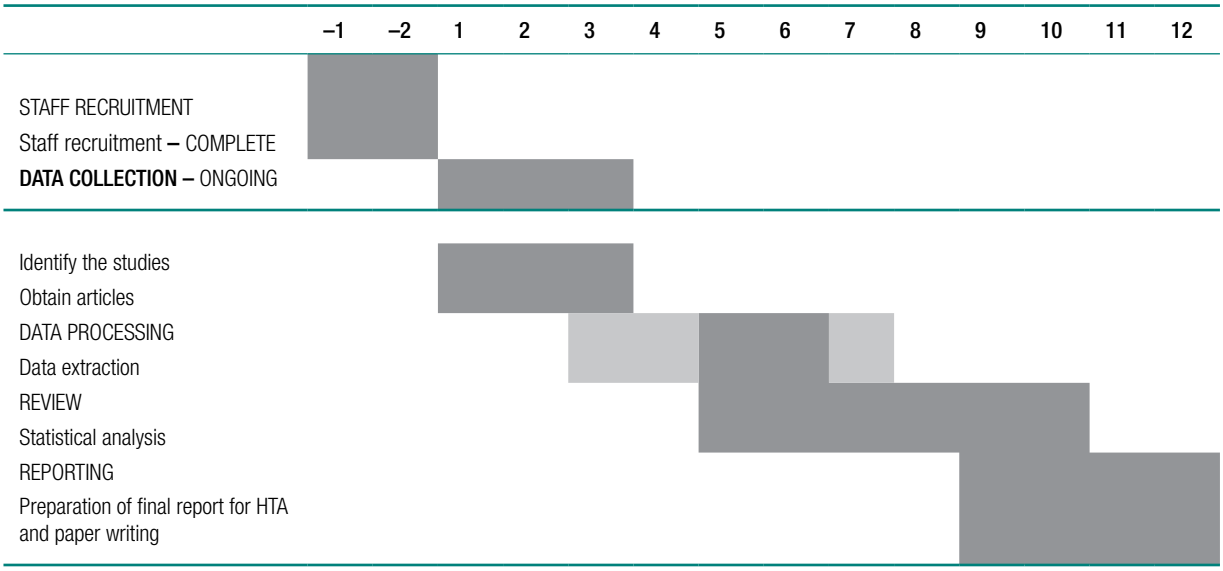
A comprehensive report of the findings with recommendations to the NIHR HTA including evidence for the duration of BCG protection by age at vaccination, gender, site of disease, and geographical area will be prepared.

This report will summarise findings particularly relevant to UK vaccination policy.

We will also identify the need for further research and the best way to answer questions arising from the review using primary research.

In addition to a formal report to the HTA, the research will be disseminated through peer reviewed publications, conference presentations and engagement with policy makers (Joint Vaccination and Immunisation Committee, Department of Health and the Health Protection Agency).

Project timetable



Milestones (1–5 linked to study objectives).

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