

## Selected Summaries

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### Does BCG vaccination protect against childhood asthma?

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El-Zein M, Parent ME, Benedetti A, Rousseau MC. (INRS-Institut Armand-Frappier, Institut National de la Recherche Scientifique, Laval, Quebec, Canada.) Does BCG vaccination protect against the development of childhood asthma? A systematic review and meta-analysis of epidemiological studies. *Int J Epidemiol* 2010;**39**:469–86.

#### SUMMARY

A systematic review and meta-analysis was done to assess the association between BCG vaccination and childhood asthma. A systematic search using appropriate keywords was done for dissertations in PubMed, Embase, Cochrane central register for controlled trials, and the library and archives in Canada. All study designs were included liberally to explore the effects of methodological differences on the association. The meta-analysis aimed to include those studies which had reported on the association between exposure to BCG and the development of asthma and/or wheezing among children  $\leq 19$  years of age.

The indicators for BCG exposure used were BCG vaccination, tuberculin response and scar diameter. The indicators for childhood asthma used were asthma *per se*, ever wheezing and current wheezing. The data were extracted by one researcher using a data extraction form, and the information was cross-checked by a second researcher. The information collected included the first author's name, inclusion and exclusion criteria, sample size, indicators of exposure, age of subjects at exposure, asthma and/or wheezing outcomes, adjustment variables, odds ratios and 95% confidence intervals, and population characteristics such as age, etc.

The methodological quality of each study was reviewed independently and critically appraised by two researchers. Disagreements between the reviewers were identified and discussed, and a final score was determined for each paper by consensus. Each individual study was assigned an overall rating score using a validated 'epidemiological appraisal instrument'. From each study, the adjusted odds ratio was selected. The crude odds ratio was selected if no adjustments had been done. An overall pooled summary odds ratio for the association between indicators of BCG exposure and asthma was estimated using a random-effects model when heterogeneity was present. A fixed-effect model was used when heterogeneity was absent. Statistical heterogeneity was evaluated using the Cochran chi-square heterogeneity test Q and the extent of heterogeneity by the  $I^2$  test. Sensitivity and subgroup analyses were done to assess the robustness of the result. The Funnel plot and Egger test were done to assess publication bias.

Of the 23 studies included in the meta-analysis, 10 were cohort, 5 case-control and 8 cross-sectional studies. The studies were done in 15 countries. A meta-analysis of all 23 studies reporting on any of the 3 indicators of exposure to BCG revealed that these studies were statistically heterogeneous. Heterogeneity was mostly apparent when tuberculin response was the indicator of exposure to BCG. Analysis of the 16 studies in which the exposure indicator was BCG vaccination,

*per se*, found them to be homogeneous; the overall pooled odds ratio was 0.86 (0.79–0.93), indicating a protective effect of BCG vaccination with the occurrence of asthma in childhood using the fixed-effect model. Sensitivity analysis revealed that no single study was influencing the results. The Egger test suggested an absence of publication bias. A subgroup analysis of 13 studies having either the highest or intermediary quality scores showed a similar association; the odds ratio was 0.87 (0.80–0.94) with no evidence of heterogeneity.

The authors concluded that exposure to BCG vaccine in early life might influence immune maturation and prevent the development of asthma, and hence might have far-reaching public health implications. They recommended prospective clinical experiments with longer follow up.

#### COMMENT

About 300 million people suffer from asthma all over the world.<sup>1</sup> Globally, the 12-month prevalence of asthma in the age group of 13–14 years varies from 1.6% to 36.8%.<sup>2</sup> Asthma is the most common chronic illness among children. In India, the overall weighted mean prevalence of childhood asthma is 2.74%.<sup>3</sup> In 2001, the cost of treatment of chronic mild asthma and chronic moderate and severe asthma in India was Rs 436 and Rs 16 200 per patient per year, respectively. By 2016, the cost of chronic mild and chronic moderate and severe asthma would increase to Rs 835 and Rs 31 045 per patient per year, respectively.<sup>4</sup>

The results of this study support the view that exposure to BCG vaccine in early life prevents asthma, possibly through a modulation of the immune maturation process. This meta-analysis included a larger number of studies compared with a previous meta-analysis,<sup>5</sup> and the studies were from 15 different countries. There were 3 studies from non-English language journals and 1 unpublished study. The meta-analysis was reported in great detail, and provided information about each included and excluded study. By inclusion of different study designs, variability could be assessed. As mentioned by the authors, the limitations were inherent to observational studies, mainly bias and confounding.

A few methodological issues deserve attention. No information was provided on the number of observers who actually checked the eligibility of the studies, and the strategy to resolve the disagreements, if any. This meta-analysis included 2 studies in which the original authors had studied the association between the scar diameter and asthma.<sup>6,7</sup> In these 2 studies, almost all participants had received the BCG vaccine; hence, no comments can be made on the possible protective effect of the vaccine. These studies should not have been included if the protective effect of BCG vaccine was being assessed.

It is not clear if there was blinding of the researchers of the meta-analysis to the authors, institutions and journals, both during the quality assessment and data extraction. This could have led to information bias. The authors restricted the final analysis to the 16 studies, which showed 14% protection from childhood asthma.

The National Rural Health Mission was launched in India in the year 2005, to address the health needs of the rural population, especially the vulnerable sections of society. Under the overall umbrella of this Mission, the *Janani Suraksha Yojana* has integrated cash assistance with antenatal care during the pregnancy period, institutional care during delivery and the immediate post-

partum period in a health centre, by establishing a system of coordinated care by a field-level health worker.<sup>8</sup> A new group of community-based functionaries called Accredited Social Health Activist (ASHA) has been identified as change agents for health in villages.<sup>9</sup> With these concerted efforts, the proportion of institutional deliveries and immunization coverage is likely to increase. With this increase, the proportion of neonates who are administered BCG vaccine at birth would also increase. The existing 78% coverage of BCG vaccination<sup>10</sup> would improve further. Protection from the development of asthma would be an added possible benefit for these immunized children.

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## Chest radiographs in the ICU: Routine or on demand?

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### SUMMARY

This study aimed to determine whether obtaining chest radiographs (CXR) in patients admitted to intensive care units on a 'demand' basis was a more effective and efficient method compared with routine daily CXR (which is as per the present American Roentgen Association guidelines).

Twenty-one intensive care units (ICUs) from 18 hospitals in France participated in the study. Each ICU enrolled 20 patients, who at the time of enrolment were on mechanical ventilation. The period of study extended till the time of discharge of the patient or up to 30 days of ventilation. Patients undergoing ventilation for <72 hours were excluded from the analysis.

In the first treatment period, the 21 ICUs were randomly allocated to use either a 'routine' or 'demand' strategy to order CXR. After a washout period of 1 week, the second strategy was used. Since in most ICUs worldwide all medical staff in a given unit use the same strategy to decide when to do a CXR, randomization was done at the

level of the ICU (cluster-randomized design) rather than at the patient level.

In the 'routine' strategy, all mechanically ventilated patients had a daily CXR, regardless of their clinical status. In the 'on-demand' strategy, mechanically ventilated patients had a CXR done if warranted by the clinical findings on the morning rounds. In both strategies additional unscheduled CXRs were allowed, if necessary.

The primary outcome measure was the mean number of CXRs per patient-day of mechanical ventilation; the key secondary outcome measures were days of mechanical ventilation, length of stay in the ICU and mortality of patients during their stay in the ICU.

Acute respiratory failure with or without pulmonary oedema, septic shock and acute renal failure were among the most common causes of admission to the ICU. Overall, 425 patients were assigned to have CXR by a 'routine' and 424 by an 'on-demand' strategy. A total of 7755 CXRs were done during both treatment periods under both strategies.

The mean number of CXRs per patient-day of ventilation was 32% lower with the on-demand strategy than with the routine strategy (95% CI 25–38;  $p < 0.0001$ ). However, the difference in the total number of routine and on-demand CXRs was not significant when the analysis was restricted to CXRs with new findings that led to diagnostic/therapeutic interventions (728 routine CXRs contributed/led to 824 procedures in 264 patients, whereas 729 'on-demand' CXRs led to 834 interventions;  $p = 0.77$ ). The 'on-demand' strategy was associated with a large and significant decrease in CXRs during the morning hours and with a small and non-significant increase in unscheduled CXRs. There was no significant difference between the secondary outcomes in both strategies (days of mechanical ventilation, duration of ICU stay and mortality).

### COMMENT

The issue of whether CXRs in mechanically ventilated patients in the ICU should be done on a 'routine' basis or only 'on demand' has been intensely debated in the past 2 decades. Routine CXRs are done in the majority of ICUs worldwide. The ostensible reason has been the high prevalence of findings on CXRs of ICU patients.