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BCG vaccination to prevent childhood asthma – a revised meta-analysis

To the Editor

We read with great interest the systematic review by Navaratna *et al*, in particular the section on BCG vaccination to prevent childhood asthma. The authors conclude there is an absence of effect based on two meta-analyses, the first of four cohort studies and the second of two randomised control trials (RCTs).[1] For the cohort studies, the combined risk ratio is reported as 0.92 (95% confidence interval (CI) 0.59 to 1.46), but the results of two of these studies appear to have been misinterpreted by the authors, leading to an erroneous conclusion to the meta-analysis.[2,3]

In the first cohort study, Bager *et al* report a beneficial effect of BCG vaccination with an adjusted odds ratio for asthma of 0.53 (95% CI 0.03 to 0.95) compared with unvaccinated subjects.[2] The 1.63 risk ratio reported in Navaratna *et al*'s figure 3 appears to be the impact of age at vaccination (0 vs 7 years) from Bager *et al*'s table 2.

In the second cohort study, Marks *et al* report in their table 2 the effect of BCG on childhood asthma in two separate lines, according to parental history of asthma. In children born to non-asthmatic parents, the relative risk is 1.26 (95% CI 0.92 to 1.73), whereas in children who have one or two asthmatic parents the relative risk is 0.61 (95% CI 0.32 to 1.13).[3] Navaratna *et al*'s figure 3 includes only the former group with a 1.26 risk ratio, with no justification for excluding the latter group in the meta-analysis.

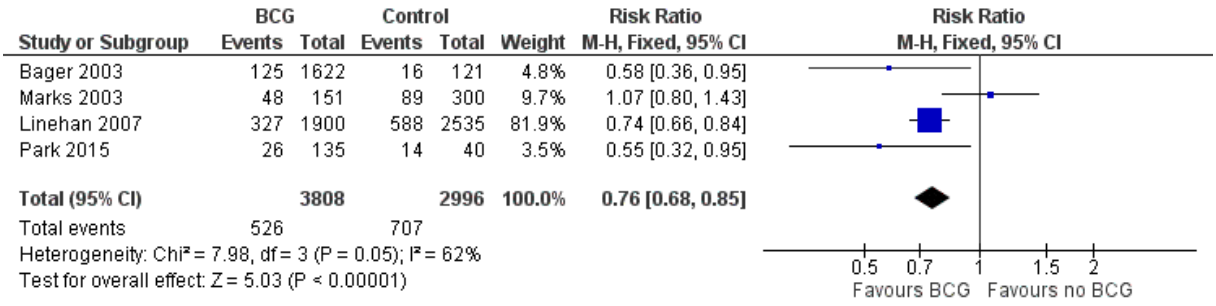
When combining the correct results from the same four cohort studies, we find a strong beneficial effect of BCG on childhood asthma with a risk ratio of 0.76 (95% CI 0.68 to 0.85, P<0.0001) (Figure). Importantly, this means the conclusion by Navaratna *et al* is incorrect and should state that studies in fact show BCG vaccination prevents childhood asthma.

Navaratna *et al*'s systematic review did not identify any RCT reporting BCG's effect on childhood asthma. Instead, the authors included two RCTs in their meta-analysis reporting on infant wheeze, assessed between 13 and 18 months of age, and concluded an absence of effect with a combined risk ratio of 0.93 (95% CI 0.65 to 1.34).[1] As asthma cannot be reliably diagnosed before 5 years of age (as the majority of wheezing pre-schoolers do not develop asthma),[4] we question the relevance of including these two RCTs in the meta-analysis.

In conclusion, we respectfully disagree with Navaratna *et al*'s conclusion and, based on our updated meta-analysis of the same four cohort studies, believe that observational studies to date suggest BCG has a beneficial effect on asthma prevention, in line with previous meta-analyses.[5,6]

Given the limitations and bias inherent to observational studies, RCTs assessing the impact of BCG on childhood asthma are needed. The results of the *Melbourne Infant Study: BCG for allergy and infection reduction* (MIS BAIR) RCT, in which participants are followed up for at least 5 years, should be available soon, and will more reliably determine the impact of neonatal BCG vaccination on the incidence of asthma.[7]

Figure: Revised forest plot for the association between BCG vaccination and childhood asthma in the four cohort studies included in the meta-analysis by Navaratna *et al.*



BCG, bacille Calmette-Guérin; CI, confidence interval; M-H, Mantel-Haenszel.

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