

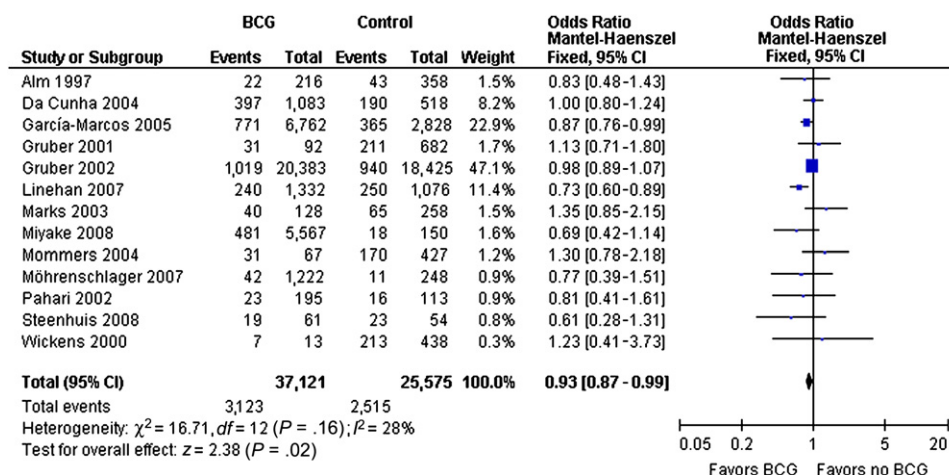


FIG 1. Updated fixed effects model forest plot showing the odds ratios and 95% CIs for the association between BCG vaccination and asthma.

searches earlier in 2008—hence its omission; we are confident that this would have been identified for inclusion in planned updates of our systematic review. The trial by Steenhuis et al⁵ included a number of relevant outcome measures (ie, specific IgE, eczema, rhinitis, and asthma-related outcomes); hence, it clearly satisfied our inclusion criteria. It is furthermore the only experimental study that has been undertaken to date. We do nonetheless acknowledge that asthma-related data in children of this age need to be interpreted carefully.

Our plan to investigate sources of heterogeneity were stipulated *a priori*, centering on the impact of family history and region of birth; where appropriate, sensitivity analyses were undertaken by removing studies judged to be at high risk of bias to assess the robustness of the pooled estimates.

We have redone the asthma meta-analysis now including unpublished data from the study by Mommers et al⁶ (Mommers M, personal communication, December 2010) and also including the data from the study by Wickens et al.³ This resulted in a revised pooled odds ratio of 0.93 (95% CI, 0.87-0.99) for the relationship between BCG vaccination and asthma (Fig 1).

Although we welcome the opportunity to correct the asthma analysis, overall, our conclusion remains unchanged: BCG vaccination is not associated with protection against allergic sensitization or disease; it may, however, have a possible modest protective role against the development of asthma, which warrants further investigation using more rigorous designs.

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The asthma predictive index remains a useful tool to predict asthma in young children with recurrent wheeze in clinical practice

To the Editor:

We thank Dr Brand¹ for his correspondence about the utility of the Asthma Predictive Index (API) to identify which preschoolers with recurrent wheeze will have asthma at school age. As was pointed out in our review,² we postulated that the simplicity and reasonably good likelihood ratio of the API allows its use in every health care setting worldwide. However, that sentence was not in agreement with Dr Brand, and he stated 3 reasons that we think are incorrect.

First, he made an important confusion about the entry criteria and outcomes used in the original API study done in the Tucson cohort.³ Dr Brand¹ stated that "Therefore the API was developed to predict which of these preschool ever wheezers would have persistent wheeze by the age of 6 years." However, it is important to clarify that in the Tucson cohort the entry criterion used for the stringent API was infants/preschoolers with recurrent wheezing (≥ 3 episodes per year), and the outcome was active asthma, which was defined as "if he or she had asthma diagnosed by a physician with at least one episode of asthma during the previous year or had more than three episodes of wheezing during the previous year regardless of a diagnosis of asthma."³

Second, he stated that a prediction rule developed can only be applied in clinical practice when it has been validated

prospectively and independently in a different cohort. He follows by saying the following: “to my knowledge, this has never been done with the API...Before concluding that the API can be used in different populations, formal validation studies must be performed.”¹ The arguments of Dr Brand are correct; however, it is important to clarify the following.

The development of a clinical prediction rule includes 3 steps: derivation, validation, and an impact analysis.⁴ Moreover, the validation step involves a narrow and a broad validation. Completing the different steps will move up the hierarchy of a prediction rule, allowing its confident application by clinicians. The API was developed in the original study by using a statistical method that yielded the factors with predictive power for asthma, thereby completing the derivation step. Then the authors applied this score to the same group of patients used for the identification of the predictive factors. This can be considered a narrow validation, reaching evidence level 3 and allowing the use of the prediction rule with caution and only if patients in their clinical settings are similar to those in the study. The next step, the broad validation, considers testing the rule in multiple clinical settings with different prevalences. In this respect Dr Brand is not aware of a prospective study recently done in a developing country in which 130 Colombian infants were recruited (mean age, 27.2 ± 5.9 months) and followed up to 5 to 6 years of age for active asthma by using the API score and the same outcome of the original API study.³ They found that the stringent API had a sensitivity of 43% and specificity of 79% (Rodríguez-Martínez C, personal communication). Recognizing that more studies need to be done in other populations before being able to recommend the API as a universal diagnostic test, it can be used with caution in patients similar to those in the original study.

Third, Dr Brand used a hypothetical example in which “the prevalence of asthma is 40% instead of the 20% value in the Tucson study” and showed a reduction in negative predicted value from 90% to 59% and an increase in positive predictive value up to 83%.¹ However, contrary to what was stated, we think that in settings with a higher prevalence of asthma, the positive predicted value is more useful than the negative predicted value to select patients in whom to establish early asthma management. Also, as we know, according to the more recent International Study of Asthma and Allergies in Childhood study,⁵ the highest prevalence of asthma among children aged 6 to 7 years is 37.6% in Costa Rica, and the following 5 countries with higher prevalences are Australia at 27.2%, New Zealand at 24%, Panama at 23.5%, Brazil at 21.3%, and the United Kingdom at 20.9%. Nevertheless, we remarked in the revision² that because positive and negative predicted values depend on the prevalence of the disease, “another approach to analyze the results of a diagnosis test is to determine the likelihood ratio (LR), which is relevant in clinical practice.” Indeed, the usefulness of a diagnostic test should be analyzed by calculating likelihood ratios rather than predictive values because they are independent of the prevalence.⁶ Given that the likelihood ratio for the positive value in the stringent API is 7.3 in the original study, the pretest probability of asthma moves from 30% to more about 80%. This posttest probability is high enough to be considered above the threshold for a confident diagnosis of the condition of asthma (treatment threshold), therefore strongly suggesting no more testing.⁷

Finally, Dr Brand stated¹ that “the index is not useful in predicting the long-term prognosis of preschool children with more severe or recurrent wheeze in clinical practice. Clinicians should

counsel parents who visit their practice with their preschool child for troublesome recurrent wheeze that it is impossible to reliably predict whether their child’s respiratory symptoms will disappear or persist beyond the sixth birthday.” We totally disagree with his statement, as was explained above and because many longitudinal studies found that most of the major and minor criteria used in the API were predictors of later asthma. For example, in another study done in Tucson,⁸ persistent eosinophilia throughout childhood until the age of 11 years was associated with the presence of chronic asthma independently of atopy (skin prick test). Inversely, in France⁹ an absence of eosinophilia alone predicted 91% of remissions of wheezing in infants. A German study¹⁰ found that allergic sensitization during the first 2 years of life was associated with asthma among subjects 7 to 22 years of age only if a positive parental history of asthma was present. Finally, in recent data from the Tasmanian Longitudinal Health Study, childhood eczema and rhinitis in combination predicted the persistence of childhood asthma to adult asthma until the age of 44 years (Martin PE, personal communication).

For all the reasons above explained, we still think that the simplicity and reasonably good likelihood ratios of the stringent API should encourage its use for early asthma diagnosis among young children with recurrent wheeze in clinical practice in many health care settings.

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