result of our adjustment for confounders. Moreover, the data in Ayubi and Safiri's Table 1 were not the same as ours. The numbers for non–asthma–chronic obstructive pulmonary disease overlap syndrome (unaffected) cases were 174 and 218 instead of 8 and 10. These numbers can be estimated from Table E1 in the online supplement of our article.

We encourage other authors with similar data to consider applying Firth logistic regression or penalized logistic regression with data augmentation to reduce sparse data bias. ■

Author disclosures are available with the text of this letter at www.atsjournals.org.

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Preventing Respiratory Syncytial Virus Infection to Prevent Asthma: The Missing Link

To the Editor:

The association between early-life respiratory syncytial virus (RSV)-related lower respiratory tract infection and later asthma development is consistent across most studies with large effect sizes, a dose–response relationship, and observational evidence that preventing RSV in select populations decreases recurrent wheezing or asthma risk (1). A definitive clinical trial of prevention of RSV on childhood asthma, with an intervention such as palivizumab, has not been performed (2). The study by Mochizuki and colleagues [this issue, pp. 29–38] provides additional important observational data that support the finding that prevention of severe RSV during infancy decreases later wheezing in children, and provides us estimates of the effect size on both wheezing and asthma, which is essential information in designing a clinical trial with optimal power (3). Although this study is not a randomized clinical trial, and despite the small number of infants studied, infants who received palivizumab were significantly less likely to have recurrent wheezing throughout childhood. There was a nonsignificant effect on decreasing asthma at 6 years. We cannot infer much about the effect of palivizumab on asthma outcomes, as this study is too small and underpowered for the primary outcome of asthma. This study had 349 subjects receiving palivizumab and a comparison group of 95 infants who did not receive palivizumab. The effect size reported for asthma outcome with relative risk (0.82; 95% confidence interval, 0.39–1.70) lacks precision. Power calculations project a sample size of more than 5,000 subjects, using 18% relative reduction in asthma risk and the conservative scenario of only 21% children who did not receive palivizumab (4).

These types of observational studies are also very challenging to design and interpret, because the infants who receive palivizumab and those who do not receive palivizumab are significantly different (5). As a consequence, infants who received palivizumab differ fundamentally from infants who did not receive palivizumab, making confounding by indication a major concern in these studies. The best solution to this problem is to conduct a properly designed randomized controlled trial (2, 5). A randomized controlled trial will ultimately answer the question of whether prevention of infant RSV lower respiratory tract infection prevents later development of recurrent wheezing and asthma outcomes. In the absence of data from such a trial, we lack sufficient information to inform change in use of an expensive drug requiring intramuscular injections in infants. Thus, it is the right time for us in science and healthcare to review the evidence, to define its preventive and clinical implications, and to design and conduct a definitive trial. ■

Author disclosures are available with the text of this letter at www.atsjournals.org.

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Originally Published in Press as DOI: 10.1164/rccm.201702-0380LE on April 5, 2017

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Reply

From the Authors:

We agree with Gebretsadik and colleagues that a large randomized controlled trial (RCT) of the effect of preventing respiratory syncytial virus (RSV) on asthma is needed, partly based on the results of our study (1) [this issue, pp. 29–38]. However, two issues need be considered. The first is that we used a very narrow definition of atopy, given that there were 52 centers in the trial. Had we used a broader definition (6–13 skin prick tests instead of 1, and a clinical diagnosis of asthma, for example), it is possible that the proportion of children with asthma could have been higher: up to 31.6% in the control group (the prevalence of recurrent wheezing in our trial) (1). We did show an effect on recurrent wheezing with this proportion in the control group. The second is the practicality of performing an RCT for the asthma outcome. MedImmune, Inc. (Gaithersburg, MD), the sponsor of the original palivizumab trial (2), did explore the possibility of following up on children in the original trial, but it was difficult to find the original trial participants even a few years *post hoc*. Current RCTs of RSV using anti-RSV monoclonal antibodies in preterm infants (MEDI8897 [NCT02878330] and REGN2222 [NCT02325791]) have sample sizes of 1,500 and 1,515, respectively, which is far short of the 3,000–5,000 needed for a 3- to 6-year follow-up asthma endpoint. Given the costs of such trials, the length of follow-up, and the consideration that once licensed for prevention of RSV-related lower respiratory tract infection in these populations, it would be ethically difficult to conduct a second, much larger RCT in the same population, it is highly unlikely that an RCT for this indication would be pursued in these studies. However, a phase 3 maternal RSV vaccine study (NCT02624947) with a potential sample size of 8,618 could be one in which long-term follow up of the infants might prove fruitful.

Hence, there have been different approaches to trying to answer this question. Our first follow-up of subjects in an RCT of RSV immunoglobulin suggested that preventing RSV could have a long-term effect on lung function (3). Subsequently, our nonrandomized prospective double-cohort trials of palivizumab in late preterm infants in Europe, Canada (4), and Japan (1), and a prospective RCT of palivizumab in 434 preterm Dutch infants (5), suggested that preventing RSV could prevent recurrent wheezing till at least 6 years of age (1). A retrospective database analysis of two databases from California and Tennessee found no effect of palivizumab on asthma at 6 years of age (6), which is not dissimilar to the results of our much smaller prospective trial (1). Gebretsadik and colleagues suggest our results were biased because of confounding by indication. Confounding by indication was not an issue in either of the two RCTs (3, 5), but certainly was in our European/Canadian trial (4) and the retrospective database analysis from California/Tennessee (6). However, confounding by indication was less of an issue in our Japanese trial (1). In Japan, with free public health insurance and an indication for use, physicians could use palivizumab for late preterm infants, if they so chose. Of the 52 centers, 27 used palivizumab for all their subjects (n = 232), 9 used it for none (n = 36), and 16 had subjects in both groups (n = 176). Thus, confounding by indication was not an issue in 85% of our sites and 60% of our subjects, supported by our finding that there were very few differences in background demographic risk factors in our study. We await the results of the ongoing 6-year follow-up of the Dutch RCT, and our planned 9-year follow-up of this cohort, with a broader definition of asthma and lung function testing, to throw further light on the issue. ■

Originally Published in Press as DOI: 10.1164/rccm.201703-0533LE on April 5, 2017

Author disclosures are available with the text of this letter at www.atsjournals.org.

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