

Correspondence

Reply

To the Editor:

We thank McCallum and her colleagues¹ for their interest in our study.² They raise the concern that based on the previously published negative studies of azithromycin in the setting of bronchiolitis, our finding of a decreased likelihood of post-respiratory syncytial virus (RSV) recurrent wheezing (RW)² does not warrant further follow-up studies. As indicated by McCallum et al,¹ 3 trials have evaluated “long-term” outcomes of macrolide therapy, including a small ($n = 21$) trial from Turkey³ using clarithromycin² and 2 from McCallum et al,^{4,5} which found that 1⁴ or 3⁵ doses of azithromycin did not improve acute bronchiolitis severity and did not prevent respiratory readmission during the following 6 months.

Potential reasons for the disparate findings between these reports are multifactorial, including differences in outcome measures, durations of follow-up, dosing regimens, the baseline risk for future respiratory morbidity of study participants, and different causative viruses.

We suspect that major explanations for the differences between our findings² and those of others^{4,5} relate to the duration of follow-up and the indicator of long-term efficacy. In our study,² we found (Fig 1) that the azithromycin and placebo groups did not differ in risk of recurrent wheezing after 6 months of follow-up ($P = .07$), but after 12 months of follow-up, there was a significant reduction in risk among azithromycin-treated children ($P = .048$), indicating that the major effect of azithromycin therapy is not related to wheezing illnesses shortly after bronchiolitis but rather illnesses more than 6 months after the initial bronchiolitis.

In addition, the outcome of readmission was not a sensitive marker for azithromycin efficacy in our study because readmission was very uncommon, with only 3 of 39 infants readmitted over 12 months. In contrast, nearly 30% of the population in the studies by McCallum et al^{4,5} required readmission over 6 months, which suggests differing susceptibility to respiratory morbidity between the study populations, which likely contributes to differences in the overall findings. Although our study participants were otherwise healthy infants hospitalized for acute RSV bronchiolitis, almost 90% of the population in studies by McCallum et al^{4,5} included indigenous infants from Australia and New Zealand. Indigenous infants have greater lung morbidity than do nonindigenous infants,⁵ with higher rates of airway bacterial colonization resulting in recurrent pneumonia and bronchiectasis. Finally, although all patients in our study experienced bronchiolitis due to RSV infection,² only 44% of the patients in the studies by McCallum et al^{4,5} had confirmed RSV infection. If our findings are specific to RSV bronchiolitis, Dr McCallum's trials demonstrating no long-term effects of azithromycin may reflect lack of efficacy in the setting of non-RSV bronchiolitis.

In summary, although it is clear that macrolides do not improve acute bronchiolitis severity, our pilot study strongly suggested that azithromycin during RSV bronchiolitis may be an effective intervention to attenuate the outcome of post-RSV RW and potentially asthma. Because asthma carries a significant burden on affected individuals and society, and because up to 13% of childhood asthma cases are attributable to severe RSV

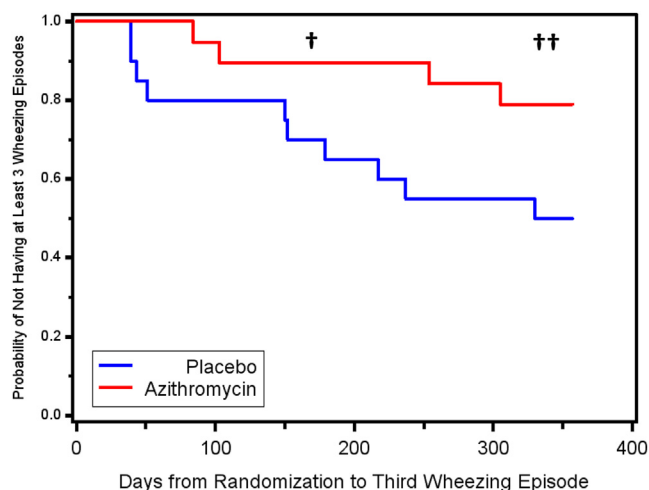


FIG 1. Probability of not having at least 3 episodes of wheezing. A significant reduction in the likelihood of recurrent wheeze is noted after 12 months of follow-up ($P = .048$ ††), but not after 6 months ($P = 0.07$ †). Adapted from Beigelman et al.²

bronchiolitis,⁶ azithromycin as a potential disease-modifying approach to attenuate, and even prevent, post-RSV RW should be further investigated in a more definitive trial.

Avraham Beigelman, MD, MSCI

Leonard B. Bacharier, MD

From the Division of Allergy, Immunology and Pulmonary Medicine, Department of Pediatrics, Washington University School of Medicine and St Louis Children's Hospital, St Louis, Mo E-mail: beigelman_a@kids.wustl.edu.

This study was supported by the Washington University Institute of Clinical and Translational Sciences grant (grant no. UL1 TR000448) from the National Center for Advancing Translational Sciences subaward KL2 TR000450, and the Children's Discovery Institute of Washington University and St Louis Children's Hospital. This study was also supported in part (REDCap data base) by the Clinical and Translational Science Award (grant no. UL1 TR000448) and Siteman Comprehensive Cancer Center and National Cancer Institute Cancer Center (support grant no. P30 CA091842).

Disclosure of potential conflict of interest: A. Beigelman has received research support from the National Center for Advancing Translational Sciences (grant no. UL1 TR000448, subaward KL2 TR000450), the Children's Discovery Institute of Washington University and St Louis Children's Hospital, and the National Heart, Lung, and Blood Institute (NHLBI)/the National Institute of Allergy and Infectious Diseases (NIAID)/the National Institutes of Health (NIH) AsthmaNet/Inner City Asthma Consortium (ICAC). L. B. Bacharier has received consultancy fees from Aerocrine, GlaxoSmithKline, Genentech/Novartis, Merck, Schering, Cephalon, DBV Technologies, Teva, and Meda; has received research support from the NHLBI/NIAID/NIH AsthmaNet/ICAC; and has received lecture fees from Aerocrine, AstraZeneca, Genentech/Novartis, GlaxoSmithKline, Merck, Schering, and Teva.

REFERENCES

- McCallum GB, Chang AB, Grimwood K. Further clinical trials on macrolides for bronchiolitis in infants are unnecessary. *J Allergy Clin Immunol* 2015;136:XXX-XXX.
- Beigelman A, Isaacson-Schmid M, Sajol G, Baty J, Rodriguez OM, Leege E, et al. Randomized trial to evaluate azithromycin's effects on serum and upper airway IL-8 levels and recurrent wheezing in infants with respiratory syncytial virus bronchiolitis. *J Allergy Clin Immunol* 2015;135:1171-8.e1.
- Tahan F, Ozcan A, Koc N. Clarithromycin in the treatment of RSV bronchiolitis: a double-blind, randomised, placebo-controlled trial. *Eur Respir J* 2007; 29:91-7.
- McCallum GB, Morris PS, Chatfield MD, MacLennan C, White AV, Sloots TP, et al. A single dose of azithromycin does not improve clinical outcomes of children

- hospitalised with bronchiolitis: a randomised, placebo-controlled trial. *PLoS One* 2013;8:e74316.
5. McCallum GB, Morris PS, Grimwood K, Maclellann C, White AV, Chatfield MD, et al. Three-weekly doses of azithromycin for indigenous infants hospitalized with bronchiolitis: a multicentre, randomized, placebo-controlled trial. *Front Pediatr* 2015;3:32.
 6. James KM, Gebretsadik T, Escobar GJ, Wu P, Carroll KN, Li SX, et al. Risk of childhood asthma following infant bronchiolitis during the respiratory syncytial virus season. *J Allergy Clin Immunol* 2013;132:227-9.

<http://dx.doi.org/10.1016/j.jaci.2015.07.013>