ERRATUM

The September 2018 Practice Alert, "CDC recommendations for the 2018-2019 influenza season" contained an error (*J Fam Pract*. 2018. 67:550-553). On page 552, under "Available vaccine products," the article listed "one standard dose IIV4 intradermal option." This was incorrect. Sanofi Pasteur, the manufacturer of standard dose Intradermal IIV4, discontinued the production and supply of Fluzone Intradermal Quadrivalent vaccine at the conclusion of the 2017-2018 influenza season.

Did this COPD Clinical Inquiry miss the mark—or not?

It would be more accurate to say that there may be a diminished efficacy of azithromycin for patients with GOLD IV COPD and age ≤65 years.

In the Clinical Inquiry, "Does prophylactic azithromycin reduce the number of COPD exacerbations or hospitalizations?" (*J Fam Pract.* 2018;67:384-385), Lyon et al state that azithromycin "doesn't benefit patients ≤65 years, patients with GOLD [Global Initiative for Obstructive Lung Disease] stage IV COPD [chronic obstructive pulmonary disease], current smokers, or patients not using oxygen (strength of recommendation [SOR]: **B**, randomized controlled trials [RCTs])." These categorical statements are misleading, and clinicians should ignore most of them when considering azithromycin for their patients with severe COPD.

The authors cited groups that were identified in a posthoc analysis[1] of the only large trial involving azithromycin for the treatment of COPD to date.[2] *P* values for the interaction of azithromycin with GOLD stage (*P*=.04), smoking (*P*=.03), and age (*P*=.02) were significant, but the mean effects (hazard ratios [HRs]) for GOLD stage IV, smoking, and age ≤65 were .84, .99, and .84, respectively. It would be more accurate to say that there may be a diminished efficacy of azithromycin for patients with GOLD IV COPD and age ≤65 years. Only smokers appear to show no response, although the lower end of the 95% confidence interval was 0.71. The *P* value for the interaction of azithromycin with no long-term oxygen use (*P*=.23) was not significant, and it is incorrect to infer that oxygen use or nonuse predicts response.

The authors correctly state that the "significance of the results is limited because the study was not originally powered for this level of subgroup analysis," but this statement is buried later in the article.

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References

1. Han MK, Tayob N, Murray S, et al. Predictors of chronic obstructive pulmonary disease exacerbation reduction in response to daily azithromycin therapy. *Am J Respir Crit Care Med.* 2014; 189:1503-1508.
2. Albert RK, Connett J, Bailey WC, et al. Azithromycin for prevention of exacerbations of COPD. *N Engl J Med.* 2011;365:689-698.

Author's response

Your statement that the evidence-based answer regarding the lack of benefit of azithromycin in patients ≤65 years of age, with stage IV COPD, current smokers, and patients not using oxygen is "misleading" is a bit of an overstatement.

It is fair to say, however, that our statement regarding lack of efficacy among these subgroups of patients should be softened a bit since the data are from subgroup analyses, which should never be the source of definitive conclusions. And you point out that the 95% confidence intervals [CIs] of the HRs for these subgroups of patients do not include a potentially significant effect (0.68, 0.71, 0.61, and 0.65, respectively), so it is possible there is a Type II error, which would lead one to conclude there is no effect for these subgroups when there is one.

Regarding oxygen therapy, in this Clinical Inquiry, we presented data from the direct subgroup analysis, which revealed no difference in COPD exacerbations between the azithromycin and placebo groups for patients not receiving long-term supplemental oxygen (HR=0.80; 95% CI, 0.62-1.03); however, you are correct to point out that the oxygen use subgroup interaction (patients on oxygen vs patients not on oxygen), which we did not include in this Clinical Inquiry, did not reach significance (*P*=.23), casting some doubt on the authors' conclusion of no effect for patients not on oxygen.

On the whole, I feel this Clinical Inquiry accurately summarized the existing evidence and that additional research is needed to better define the utility of azithromycin in these subgroups of patients.

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