

are linear (4), and require that the timing of the intervention being studied be prespecified. Applying these linear models to nonlinear data may therefore produce a spurious inflection point at the time of the prespecified intervention (4). By varying the intervention time of interest in successive segmental regression analyses of the authors' own data, we were able to produce statistically significant inflection points at the start of each year between 2005 and 2008, emphasizing that it is artefactual in origin. Similar concerns have been raised about the recently published analysis of IE hospitalizations in England (5). Small, noisy datasets such as this one are particularly susceptible to error (the number of cases of IE per unit time is a single data point, so the effective sample size is 12 [number of years for which data are available] not 457,052 [number of IE-related hospitalizations in the data]).

The association between the revised guidelines and increased streptococcal IE reported by the authors is a statistical artefact, and their own data prove that restricted use of antibiotics for IE prophylaxis seems to have had no measurable adverse impact on the health of the American public.

\*Dhruv S. Kazi, MD, MSc, MS  
Ann F. Bolger, MD

\*Department of Medicine (Cardiology)  
University of California, San Francisco  
1001 Potrero Avenue, Room 5G1  
San Francisco, California 94110  
E-mail: [kazi@ucsf.edu](mailto:kazi@ucsf.edu)

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Please note: Dr. Bolger has reported that she has been an author of the American Heart Association Guidelines on the Prevention of Endocarditis, and currently chairs the American Heart Association Committee on Rheumatic Fever, Endocarditis and Kawasaki Disease. Her role there, as in this written piece, is to critically assess the evidence underlying the ongoing work by this committee. She does not see this as a role that biases her work, but mentions it in the spirit of full disclosure. Dr. Kazi has reported that he has no relationships relevant to the contents of this paper to disclose.

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## REPLY: Caveat Emptor

Antibiotics, Endocarditis, and Statistical Artifacts



We read with great interest the letter by Drs. Kazi and Bolger on our study “Trends in Infective Endocarditis Incidence, Microbiology, and Valve Replacement in the United States From 2000 to 2011” (1). We agree with Drs. Kazi and Bolger that any intervention in the field of medicine gets adopted in practice gradually after the publication of a “practice changing guideline” or late-breaking clinical trial. However, in this era of information technology, most physicians (at least in the United States) have ready access to journals and tend to update themselves swiftly. Moreover, publications often make it to journals in e-format ahead of print (for instance, the American College of Cardiology/American Heart Association guideline was e-published in April 2007, but appeared in print in October 2007). Hence, we believe it is reasonable to use this year as a start of practice change as opposed to hypothetical cut off (beginning of 2008) proposed by Drs. Kazi and Bolger. However, as we mentioned in our limitation section, we did not study the antibiotic prescription data to precisely answer the concerns by Drs. Kazi and Bolger.

Further, we compared the annual rates of hospitalizations for infective endocarditis (IE) before and after the introduction of the 2007 IE antibiotic prophylaxis guidelines using segmented regression analysis of the interrupted time series. The linear model is a good fit based on adjusted  $R^2$  value for the model (adjusted  $R^2 = 0.87$  for IE hospitalization trend). This method has been used in IE trends study in the past as well (2). Furthermore, as evident in Table 1 in our paper (1), the rate of *Streptococcus* IE-related hospitalization increased significantly over the study period (2000 to 2011). As we discussed in our study, change in antibiotic prophylaxis is a speculation. Other possibilities include increase in enterococcus IE subset, and increasing survival of IE risk-prone populations, such as adults with congenital heart disease and device implants. In the absence of prospective randomized data, the differing results from alternative breakpoint in segmented regression as done by Drs. Kazi and Bolger does not refute our hypothesis, but further echoes the need for ongoing monitoring of the impact of new guidelines. Finally, observations made from administrative database should be considered

“hypothesis generating” and not decisive. Rigorous prospective data is needed before drawing conclusions by Drs. Kazi and Bolger that “restricted use of antibiotic for IE prophylaxis appears to have had no measurable adverse impact on the health of the American public.”

\*Sadip Pant, MD  
Samir Patel, MD  
Nileshkumar Patel, MD  
Abhishek Deshmukh, MD  
Jawahar L. Mehta, MD, PhD  
\*Cardiovascular Medicine  
University of Louisville

Department of Cardiovascular Medicine  
526 S Jackson Street  
Louisville, Kentucky 40202  
E-mail: [sadipant@gmail.com](mailto:sadipant@gmail.com)  
<http://dx.doi.org/10.1016/j.jacc.2016.01.075>

Please note: The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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