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Reply to "Susceptibility of *Streptococcus pyogenes* to Trimethoprim-Sulfamethoxazole"

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We thank Gelfand et al. (1) for their interest in our article on the *in vitro* susceptibility of *Streptococcus pyogenes* to trimethoprim-sulfamethoxazole (SXT) (2). We agree that the two cases outlined by Gelfand et al. act as cautionary points for clinical practice, as there are currently no good clinical trial data to support the use of SXT for the treatment of *S. pyogenes* skin and soft tissue infections (SSTI). Our aim in publishing the *in vitro* data is to challenge the misconception that all *S. pyogenes* isolates are inherently resistant to SXT and hence open the way for clinical trials to more precisely determine the role for SXT in the treatment of *S. pyogenes* infections.

In the two clinical scenarios presented by Gelfand et al., the absence of SXT susceptibility data for the *S. pyogenes* isolates is concerning. Other reasons for treatment failure that are not elucidated include incomplete adherence, poor absorption, and the reality that the conditions of both of these patients might have deteriorated regardless of the antibacterial used. One wonders why the authors prescribed SXT for these SSTI despite their understanding of the traditional teaching that *S. pyogenes* is largely resistant to SXT. Perhaps it was due to the need for a simple, palatable, oral antibacterial regimen that would treat undifferentiated SSTI, in the era of highly methicillin-resistant *Staphylococcus aureus* (MRSA) prevalence. We are in agreement with Gelfand et al. that human clinical studies are urgently needed to respond to this challenge.

The results of our clinical trial comparing oral SXT with intramuscular benzathine penicillin for impetigo treatment will inform treatment decisions and generate confidence in the use of SXT for impetigo treatment in our region and possibly beyond. To date, with recruitment of 660 participants completed, despite two-thirds of the participants presenting with severe impetigo, none have been hospitalized with invasive *S. pyogenes* infection due to presumed treatment failure. Although the numbers in our study are not large enough to detect a trend for bacteremia or other complications of inadequate treatment, we might have seen clinical outcomes similar to those Gelfand et al. have experienced if SXT really has no role in the treatment of impetigo. Spontaneous resolution of mild impetigo may occur; however, the natural history of impetigo, particularly when severe, is neither completely understood nor benign (3).

We agree that the role of thymidine and its availability in the context of damaged host tissues (4) are unknown with respect to the treatment of SSTI with SXT. There are now numerous trials under way that involve the use of SXT for SSTI (http://clinicaltrials.gov/), and the results are eagerly awaited to better define the clinical utility of SXT in such settings.

Rather than claiming *in vitro* data being less relevant than clinical efficacy, we would argue that *in vitro* data should be used to inform the design of appropriate clinical trials to determine the clinical role for SXT, particularly in an era with a truncated antimicrobial pipeline and high rates of mixed SSTI due to MRSA and *S. pyogenes*.

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