## Reply to Gelfand and Cleveland

To the Editor—We greatly appreciate the correspondence by Gelfand and Cleveland. The central problem emphasized by our work is the instability of resistance phenotypes. An implicit assumption in routine methods of clinical microbiology is that susceptibility and resistance are stable characteristics, at least over the time course relevant to treatment of an infection. While this is generally true, our work indicates that a modest but unknown fraction of strains may revert from highly susceptible to highly resistant during the course of treatment. Standard laboratory methods are not designed to recognize this phenomenon and do not distinguish between reversion to resistance and superinfection. Gelfand and Cleveland point out an important implication of this lack of precision that we did not discuss: a case like the one we described would likely be mistaken for a nosocomial methicillin-resistant *Staphylococcus aureus* (MRSA) superinfection and could result in litigation and/or the financial penalties associated with early readmission. In such circumstances, reversion to resistance could be distinguished from a nosocomial superinfection with a high level of confidence by a combination of DNA sequencing and in vitro reversion testing, but only if clinical isolates collected during the course of treatment were banked and available for analysis.

The problem of latent resistance raises other considerations. For example, one tenant of antibiotic stewardship posits that withdrawal of an antibiotic will result

in a decline in the frequency of resistance, allowing reintroduction of the antibiotic with renewed efficacy at a later date. However, in the absence of antibiotic, the reduced fitness associated with expression of the resistance gene may be circumvented not only by loss of the gene, but also by its inactivation, perhaps by a reversible mutation. Indeed, this on-again off-again selection is precisely thought to drive the evolution of the phase variation that controls many bacterial characteristics. Thus, while stewardship efforts may be effective in reducing the overall frequency of resistance, an unintended side effect may be an increase in the relative frequency of latent reversible resistance.

As Gelfand and Cleveland imply, latex agglutination assays would not reliably identify *mecA*-positive methicillin-susceptible *S. aureus* (MSSA). The truncated penicillin binding protein 2a (PBP2a) produced by strain B1 is unstable and rapidly degraded. In the second *mecA*-positive MSSA strain we describe, J522BDU, the susceptible parent produces a very small amount of PBP2a as a result of misreading at the ribosome level, which is unlikely to be detected by latex agglutination. After reversion, both strains produce abundant PBP2a and would be identified as MRSA by the latex agglutination method.

The suggestion by Gelfand and Cleveland that ceftaroline is a potential treatment option for *mecA*-positive MSSA infection seems reasonable. Clearly, clinical experience is needed to discover which of the potential therapeutic options are effective. Gaining this experience is complicated by the fact that a minority of clinical laboratories perform polymerase chain reaction (PCR) analysis for *mecA*, and those that routinely perform *mecA* PCR analysis report *mecA*-positive isolates as MRSA even if the isolates are susceptible in phenotypic tests. As a result, treating physicians are unaware that they may be dealing with latent resistance. Correcting this information deficit is the first necessary step to recognizing the most-effective treatment strategies.

## Note

***Potential conflicts of interest.*** All authors: No reported conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

**Megan K. Proulx,[1] Richard T. Ellison III,[1,2] and Jon D. Goguen[1]**

[1]Department of Microbiology and Physiological Systems, and [2]Division of Infectious Disease, University of Massachusetts Medical School, Worcester

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Correspondence: J. D. Goguen, University of Massachusetts Medical School, 368 Plantation St, ASC8-2047, Worcester, MA 01655 (jon.goguen@umassmed.edu).

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