Clinical Infectious Diseases Advance Access published May 20, 2014



# Reply to Mills and Linkin.

**James R. Price[1], Tanya Golubchik[2], Daniel J. Wilson[3,4], Derrick W. Crook[3,5], A. Sarah Walker[3,5], Timothy E.A. Peto[3,5], John Paul[1,6], Martin J. Llewelyn[1,7]**

[1]Department of Microbiology and Infection, Royal Sussex County Hospital, Eastern Road, Brighton, UK

[2]Department of Statistics, University of Oxford, 1 South Parks Road, Oxford, UK

[3]Nuffield Department of Clinical Medicine, Experimental Medicine Division, John Radcliffe Hospital, Oxford, UK

[4]Wellcome Trust Centre for Human Genetics, Roosevelt Drive, Oxford

[5]NIHR Oxford Biomedical Research Centre, John Radcliffe Hospital, Oxford, UK

[6]Public Health England, Royal Sussex County Hospital, Eastern Road, Brighton, UK

[7]Division of Medicine, Brighton and Sussex Medical School, Falmer, UK

Corresponding Author: Dr Martin Llewelyn, Reader and Honorary Consultant in Infectious Diseases, Division of Medicine, Brighton and Sussex Medical School, University of Sussex, Falmer, East Sussex, BN1 9PS, UK. Email: m.j.llewelyn@bsms.ac.uk ; Tel: 01273 876671; Fax: 01273 877884

Alternative contact author: Dr John Paul, Regional Microbiologist South East Region, Department of Microbiology and Infection, Royal Sussex County Hospital, Eastern Road, Brighton, UK, Email: john.paul@phe.gov.uk; Tel: 01273 696955 Ext 4615

Dear Editor: In their letter [1] Mills and Linkin question the conclusion of our recent study that patient-to-patient transmission of *S. aureus* rarely occurs on an intensive care unit (ICU) [2]. Over 14 months, we detected only 7 patient-to-patient transmissions using whole-genome sequencing, a finding that strongly supports our conclusions. Furthermore, patient-to-patient transmission accounted for only a minority of the observed acquisitions. It is important to emphasize that we conducted our study in the context of enhanced infection prevention measures including scrupulous hand-hygiene, environmental decontamination and washing of patients with chlorhexidine. Our results suggest that these measures are highly effective in preventing transmission.

Mills and Linkin base their criticism on calculation of confidence intervals around proportions; in fact our observed 18.9% (7/37) *S. aureus* acquisitions that could plausibly represent patient-to-patient transmissions, based on whole-genome sequencing, has an exact binomial 95% confidence interval (CI) [3] of 8.0-35.1% (this method better allows for the small number of acquisitions than the Wald/normal approximation used in [1]).

Mills and Linkin pay particular attention to methicillin-resistant *S. aureus* (MRSA) acquisitions (actually 5/15 (33%, 95% CI 11.8-61.6%) patient-to-patient transmissions from Figure 2 in our paper; patient 35 acquired 2 MRSA strains of differing *spa*-types). Approaches that focus on effects within small subgroups that have not been pre-defined are widely recognized as flawed [4, 5]. We did not pre-define subgroups as we knew the number of *S. aureus* acquisitions to be limited before we performed sequencing to identify transmissions. The 95% CI within any subgroup will widen substantially because of the even smaller size, making inference on the basis of 95% CI alone problematic. If, as recommended [4,5], we consider heterogeneity across subgroups (albeit in exploratory/post-hoc analyses), comparing the 33% of MRSA acquisitions that are plausible transmissions with the corresponding 9% (2/22; 95% CI 1.1-29.2%) of methicillin-sensitive *S. aureus* (MSSA) acquisitions, we find weak evidence for such an effect (two-sided p=0.10 by Fisher's exact test). In our study context of enhanced infection prevention practice, larger numbers would be needed to

confirm whether or not MRSA could be responsible for greater patient-to-patient transmission than MSSA, and to estimate the proportion of acquisitions that could be due to patient-to-patient transmission more precisely.

Conflict of Interests
JP, TP, ASW, ML, and TG have received institutional grant support from UK Medical Research Council and Wellcome Trust joint grant.

**References**

1. Mills JP and Linkin DR Data on Whole-Genome-Sequencing is Insufficient to Rule Out Patient-to-Patient Transmission as a Significant Source of Staphylococcus aureus Acquisition in an ICU. Clin Infect Dis. **2014**;

2. Price JR, Golubchik T, Cole K, et al. Whole-genome sequencing shows that patient-to-patient transmission rarely accounts for acquisition of Staphylococcus aureus in an intensive care unit. Clin Infect Dis. **2014**;58:609-18.

3. Clopper CJ, Pearson ES.. The use of confidence of fiducial limits illustrated in the case of the binomial. Biometrika **1934**;26;404-413.

4. Altman DG, Bland JM Interaction revisited: the difference between two estimates. **BMJ**; 2003;326:219

5. Matthews JNS, Altman DG. Interaction 2: compare effect sizes not P values. **BMJ**;1996;313: 808.