Appendix
Letter to the editor: Clinical impact of antimicrobial resistance: Design matters

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Marie-Laurence Lambert and colleagues1 carried out a large retrospective study in ICUs from ten European countries. They concluded that ICU-acquired pneumonia and BSI substantially increased mortality and prolonged ICU stay, while the additional effect of antimicrobial resistance in this group of patients was relatively modest. We believe that this study design is unlikely to fully capture the public health effect of antimicrobial resistance for two reasons: first, patients with bacterial infection in ICUs often receive early empirical treatment that typically covers the resistance phenotypes that the authors chose as exposures; and second, the median follow-up was limited to 5 days, and this short follow-up might have concealed the long-term effects of treatment failure. The authors included a summary estimate for the effect of resistance in their discussion, thereby neglecting the pathogen specific effect of antimicrobial resistance on mortality. We have reported data for more than 2,000 patients with S. aureus or E. coli BSI with follow-up beyond hospital discharge, and pathogen-specific estimates showed that resistance increased mortality 30-days after infection by 80–150%.2,3 In a study with 90-day follow-up, the hazard of death in those with MRSA bacteraemia was twice that of MSSA.4 We conclude that to address the burden of disease attributable to antimicrobial resistance, comprehensive enrolment of patients is needed, including those in non-ICU settings, with follow-up beyond hospital discharge and a pathogen-specific approach to inform health-care providers and the public about the importance of this health threat.


Authors’ reply
We thank Hajo Grundmann and colleagues, our associated partners of the BURDEN project, for their comments; however, we would like to correct two factual inaccuracies. First, our study was not “neglecting the pathogen-specific effect of antimicrobial resistance on mortality” because it provided two tables with pathogen-specific data for outcome. Second, the statement about short follow-up could be misunderstood. Although the median follow-up was 5 days (IQR, 3–10 days), patients were followed up throughout their stay in the ICU. For patients who were discharged from the ICU alive, the median follow-up after BSI, for example, ranged from 9 days to 20 days depending on the micro-organism and its resistance pattern. Another comment was that “patients with bacterial infection in ICUs often receive early empirical treatment that typically covers the resistance phenotypes that the authors chose as exposures”. Although this comment is true, we clearly stated that our results only applied to the most common patterns of resistance and that our study aimed to measure the real-life effect of these resistance patterns. Whether this effect was due to differences in appropriateness of treatment was beyond the scope of our study. We agree that the public health effects of antimicrobial resistance and disease should be studied at different levels of health care and not only in ICUs. The study by Marlieke de Kraker and colleagues adds important information about this effect at the hospital level. We compared the outcomes of *S. aureus* BSIs between our study and de Kraker and colleagues’ study. Both studies allowed for an exploration of the burden of BSIs and for the additional burden of resistance and showed remarkably similar results (Table). Therefore, the main difference between the two studies is not in their results, but in the interpretation of these results. Although de Kraker and colleagues emphasize resistance, we emphasized the high effect of the infections for two reasons: because a large proportion of these infections are preventable and because with no infection, there is no infection with resistant micro-organisms. In our study, the effect of resistance was even smaller, and the effect of the infection was larger for other micro-organisms—e.g., *Pseudomonas aeruginosa* and *E. coli*—than for

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Table. Mortality related to S. aureus BSIs in two studies with different designs

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Adjusted estimates for the burden of BSI and resistance*</th>
<th>Burden of resistance: ratio of ORs and SHRs for MRSA vs MSSA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time-matched sub-cohort of patients in hospitals in Europe</td>
<td>Mortality 30-days after infection or enrolment</td>
<td>OR 4.4 (2.8-7.0)</td>
</tr>
<tr>
<td>Cohort of patients in ICU in Europe</td>
<td>Mortality in ICU</td>
<td>SHR 3.3 (2.5-5.2)</td>
</tr>
</tbody>
</table>

*Factors of adjustment differed between the studies. SHR=subdistribution hazard ratio.