Antibiotic-resistant infections, particularly those caused by multidrug-resistant (MDR) organisms (MDROs), pose a major threat to global public health. Critically ill patients with prior antibiotic exposure [1, 2] or comorbidities [2] are particularly vulnerable to infection with MDR pathogens, which can increase mortality, hospitalization costs, and length of hospital stays [3–5]. Though antibiotic resistance negatively impacts patients globally [6], analyses of the burden of resistance have been understudied in low- and middle-income countries (LMICs) [4, 7–9], even though rising incomes, lower drug costs, and unrestricted sales have led to increasing antibiotic use and higher rates of resistance [10–12].

While MDROs are a significant global concern, they pose an increased risk in LMICs, where a large proportion of health-care facilities have inadequate hospital environmental conditions and insufficient availability of standard infection prevention and control items [13, 14]. Improved awareness of the burden of antibiotic resistance can help lower resistance-related morbidity and mortality and is necessary for developing prevention and control items [13, 14]. Widespread use of broad-spectrum agents has driven the spread of MDROs in both community and hospital settings [8, 9, 12, 13, 15]. Despite rapid increases in resistance...
and widespread acknowledgement of the issue, the mortality burden of antibiotic resistance remains largely understudied in India. We used multi-institutional hospital data from a large Indian hospital system to examine factors associated with mortality among patients tested for those MDROs that have been prioritized by the World Health Organization (WHO). The resulting data on the mortality burden of antibiotic resistance can aid in the development of policy efforts to prioritize antibiotic resistance as a public health threat in LMICs, as well as provide a baseline for future efforts to quantify the burden of resistance across LMICs.

**METHODS**

**Study Design and Data Collection**

We conducted a retrospective, multi-institutional, observational study across India using data from Fortis Healthcare Limited, an integrated health-care service provider. Antimicrobial susceptibility test (AST) results from January 2015 to December 2015 were collected from 10 tertiary and quaternary referral hospitals’ microbiology databases. The hospitals ranged in size from 120 to 350 beds and were geographically dispersed: 5 were in Northern India (4 in New Delhi district and 1 in Jaipur, Rajasthan), 2 in Western India (Mumbai, Maharashtra), 2 in Southern India (Bengaluru, Karnataka), and 1 in Eastern India (Kolkata, West Bengal). All hospitals were equipped with their own microbiology laboratories. There were 7 hospitals that used the VITEK 2 system (bioMérieux, Marcy l’Etoile, France) to conduct organism identification and AST; 3 hospitals used biochemical tests for organism identification and the Kirby-Bauer disk diffusion method for AST. All hospitals categorized AST results based on the Clinical and Laboratory Standards Institute criteria at the time of testing, except for colistin resistance to vancomycin or teicoplanin. For Gram-negative organisms, only isolates tested against at least 1 agent in 3 or more antimicrobial classes were included in analyses. *E. coli* and *K. pneumoniae* were categorized by the following MDR categories: (1) non-susceptible to 3 or more antimicrobial classes; (2) non-susceptibility to beta lactam/beta-lactamase inhibitors; and (3) non-susceptibility to all 5 antimicrobial classes, which we defined as XDR. *Enterococcus* spp. were considered MDR if they were non-susceptible to vancomycin or teicoplanin. For Gram-negative organisms, any isolates tested against at least 1 agent in 3 or more antimicrobial classes were included in analyses. *E. coli* and *K. pneumoniae* were categorized by the following MDR categories: (1) non-susceptible to 3 or more antimicrobial classes; (2) non-susceptibility to beta lactam/beta-lactamase inhibitors; and (3) non-susceptibility to all 5 antimicrobial classes, which we defined as XDR. Finally, for *P. aeruginosa* and *A. baumannii*, we defined MDR as non-susceptibility to 3 or more antimicrobial classes and XDR as non-susceptibility to all 5 antimicrobial classes.

**Statistical Analysis**

To evaluate patient mortality in relation to MDR, we conducted multivariate logit regression analyses, adjusting for age, sex, hospital location, and specimen source. For overall analyses, patients with multiple organisms were collapsed to a single row and the highest resistance level was used. Sub-analyses were conducted for each pathogen, as well as groups of pathogens (ie, Gram-negative and Gram-positive), and were restricted based on the clinical significance of specific specimen sources and the availability of mortality data. *Enterococcus* infections were restricted to bloodstream, CSF, and urinary infections, based upon previous studies demonstrating significant clinical outcomes among patients with bacteriuria of *Enterococcus* spp. [18]. Because the 2 most common *Enterococcus* spp.—*E. faecalis* and *E. faecium*—can have distinct antimicrobial susceptibility profiles, we analyzed each species separately. Regression models were clustered at the hospital level to account for differences between hospitals in management and treatment of infections. All analyses were performed using Stata 14 (StataCorp, College Station, TX).
RESULTS

A total of 19,811 AST results from 13,086 patients were obtained from 10 hospitals between January and December 2015. Of these, 5,103 records met all inclusion criteria (Figure 1). The overall mortality rate was 13.1% (n = 581) (Table 1); however, the mortality rate was higher in patients infected with *A. baumannii* (29.0%) and lower in patients infected with *E. coli* (8.8%) and *Staphylococcus aureus* (11.0%; Supplementary Table 2).

Patients that died were older, on average, and were more likely to have obtained their isolate in the ICU (Table 1). They were also more likely to have a *K. pneumoniae* or *A. baumannii* infection, compared to discharged patients. Overall, mortality rates among patients with MDR infections were highest among those caused by Gram-negative bacteria (17.7%), as opposed to those caused by Gram-positive bacteria (10.8%), particularly in the ICU, where 26.9% of patients with Gram-negative MDR infections died, compared to 16.0% of patients with Gram-positive MDR infections.

Controlling for age, sex, site of infection, and the number of coinfections, we found increased odds of mortality among patients with MDR infections (odds ratio [OR] 1.57, 95% confidence interval [CI] 1.14–2.16) and XDR infections (OR 2.65, 95% CI 1.81–3.88; Table 2). Restricting the analysis to non-ICU inpatients only, patients with MDR infections had significantly higher odds of mortality (OR 1.74, 95% CI 1.06–2.87), as did patients with XDR infections (OR 2.87, 95% CI 1.80–4.57). Similarly, ICU patients had a higher likelihood of mortality if they had an XDR infection (OR 2.07, 95% CI 1.24–3.26).

However, we found these associations were largely driven by patients with Gram-negative MDR infections, where the odds of mortality for XDR infections were 3.15 (95% CI 2.01–4.94) in the non-ICU and 2.01 (95% CI 1.12–3.59) in the ICU (Supplementary Table 3). In contrast, XDR Gram-positive infections were only significantly associated with mortality among non-ICU inpatients (OR 2.93, 95% CI 1.03–8.37). The infection-onset location (community vs hospital) was not a significant factor for any organism (data not shown).

**Gram-negative Infections: Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, and Acinetobacter baumannii**

Patients with *E. coli* infections resistant to multiple drug classes, including beta-lactam/beta-lactamase inhibitors, had higher odds of mortality after controlling for other factors, though for *K. pneumoniae*, only XDR infections were significantly associated with higher mortality (Table 3). Compared to non-MDR *E. coli*, the odds of mortality were 2.63 (95% CI 1.29–5.35) times higher for MDR *E. coli*; 2.23 (95% CI 1.65–3.01) times higher for beta-lactam/beta-lactamase inhibitor resistant *E. coli*; and 2.34 (95% CI 1.40–3.90) times higher for XDR *E. coli*. Compared to non-MDR *K. pneumoniae*, the odds of mortality were 2.29 (95% CI 1.45–3.62) times higher for XDR *K. pneumoniae*. Among patients tested for colistin-resistance, 9 (0.8%) *E. coli* cases and 38 (4.6%) *K. pneumoniae* cases were non-susceptible, with 2 and 10 deaths reported among them, respectively.

Among patients with *P. aeruginosa* infections, mortality was not significantly associated with MDR infections (OR 1.15, 95% CI 0.65–2.04) or XDR infections (OR 1.76, 95% CI 0.84–3.72). However, among patients with *A. baumannii* infections, MDR was associated with 2.81 (95% CI 1.50–5.27) times higher odds of mortality than similar susceptible infections (Table 3). Notably, patients with *A. baumannii* infections also had higher likelihoods of dying if they were located in the ICU (OR 1.66, 95% CI 1.28–2.16). *A. baumannii* and *P. aeruginosa* infections of the lower-respiratory system were also strongly associated with a greater likelihood of mortality.

**Gram-positive Infections: Staphylococcus aureus and Enterococcus spp.**

Infections with more than 1 pathogen (ie, coinfections) comprised a small proportion of all Gram-positive infections and were not found to be significantly associated with either *S. aureus* or *Enterococcus spp.* infections. Therefore, we restricted

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**Figure 1.** Study inclusion/exclusion flowchart of AST results. Abbreviations: AST, antimicrobial susceptibility testing; ICU, intensive care unit.
Our results indicate that patients who acquire MDR bacterial infections, as opposed to similar drug-susceptible infections, have greater odds of mortality. Interestingly, we observed higher odds of mortality among patients with MDR and XDR infections whose isolates were obtained outside the ICU. These results may be due to differences in severity of illnesses, which we were unable to control for. Additionally, we only examined the first isolate from an individual, and thus the future course of current knowledge of the burden of antibiotic resistance in LMICs, particularly related to MDR infections, is severely lacking. In this study, we used multi-institutional antimicrobial-susceptibility data to assess the burden of MDR among the WHO’s priority list of antimicrobial resistance (AMR) bacteria on patient mortality in India. While India is the largest global antibiotic consumer, on a per-capita basis it has antibiotic consumption levels similar to other LMICs [12].

Table 1. Demographic and Clinical Characteristics of Patients With Culture-confirmed Bacterial Infections

| Organism | All Cases (N = 4437) | Inpatients (n = 3282) | Non-ICU (n = 1155) |
|----------|----------------------|-----------------------|--------------------|
| **Total N** | 4437 (100.0) | 3856 (86.9) | 581 (13.1) |
| **Median age (IQR)** | 58 (40–69) | 57 (38–69) | 61 (48–70) |
| **Age in years** | | | |
| 0–11 | 253 (5.7) | 229 (5.9) | 24 (4.1) |
| 12–44 | 1070 (24.1) | 970 (25.2) | 100 (17.2) |
| 45–64 | 1560 (35.2) | 1334 (34.6) | 226 (38.9) |
| >64 | 1554 (35.0) | 1323 (34.3) | 231 (39.8) |
| **Female** | 1767 (39.8) | 1561 (40.5) | 206 (35.5) |
| **ICU** | 1154 (26.0) | 891 (23.1) | 263 (45.3) |

Abbreviations: ICU, intensive care unit; IQR, interquartile range.

For species-level analyses, the pathogen counts (N = 5103) include all isolates meeting multidrug-resistant testing criteria, including isolates obtained from the same patient for different organisms (ie, co-infecting pathogens).

Enterococcus spp. include E. faecalis (47.3%), E. faecium (42.3%), E. gallinarum (0.7%), and unknown Enterococcus spp. (9.3%).
Enterobacter spp. include E. cloacae (67.7%), E. dissolvens (27.8%).

Table 2. Mortality Odds Among Patients With Culture-confirmed Bacterial Infections

| Resistance pattern | All Cases (N = 4437) | Inpatient (n = 3282) | Non-ICU (n = 1155) |
|--------------------|----------------------|-----------------------|--------------------|
| **OR (95% CI)** | | | |
| Non-MDR | Referent | Referent | Referent |
| MDRa | 1.57 (1.14–2.16)** | 1.74 (1.06–2.87)** | 1.24 (0.81–1.88) |
| XDRb | 2.65 (1.81–3.88)*** | 2.87 (1.80–4.57)*** | 2.01 (1.24–3.26)*** |
| **Age (years)** | | | |
| 0–11 | Referent | Referent | Referent |
| 12–44 | 1.09 (0.68–1.75) | 1.14 (0.65–1.99) | 1.05 (0.46–2.41) |
| >64 | 1.60 (1.08–2.40) | 1.52 (0.84–2.75) | 1.82 (0.70–4.71) |
| **Female** | 1.62 (0.81–3.28) | 1.59 (0.81–3.13) | 1.74 (0.58–5.24) |
| **Site of infection** | | | |
| Other | 2.39 (1.52–3.74)*** | 2.34 (1.61–3.38)*** | 2.67 (1.20–5.95)** |
| Urine | Referent | Referent | Referent |
| Wound | 1.26 (0.96–1.65) | 1.20 (0.74–1.94) | 1.38 (0.82–2.21) |
| Lower respiratory | 3.45 (2.19–5.42)*** | 2.45 (1.28–4.69)*** | 3.75 (2.49–5.64)*** |
| Blood/CSF | 5.34 (2.58–11.08)*** | 5.29 (2.30–12.17)*** | 4.27 (3.00–6.09)*** |
| **Co-infection** | | | |
| None | Referent | Referent | Referent |
| Single | 1.34 (1.02–1.78)* | 1.18 (0.82–1.69) | 1.51 (0.82–2.78) |
| Multiple | 1.64 (0.96–2.47) | 1.69 (1.22–2.35)** | 1.48 (0.50–4.36) |

Logit regression is with clustered standard errors at the hospital level.

Abbreviations: CI, confidence interval; CSF, cerebrospinal fluid; ICU, intensive care unit; MDR, multidrug-resistant; OR, odds ratio; XDR, extensively drug-resistant.

aMDR is defined as nonsusceptibility to 1 or more agents in 3 or more antimicrobial classes (ie, aminoglycosides, third-/fourth-generation cephalosporins, fluoroquinolones, beta-lactam/β-lactamase inhibitors, and carbapenems) for Gram-negative organisms; nonsusceptibility to oxacillin and/or cefoxitin (anti-staphylococcal beta-lactams) for Gram-positive Staphylococcus aureus; and non-susceptibility to vancomycin and/or teicoplanin (glycopeptides) for Gram-positive Enterococcus spp.

bXDR is defined as nonsusceptibility to 1 or more agents in all 5 antimicrobial classes for Gram-negative organisms; and nonsusceptibility to oxacillin and/or cefoxitin and to 1 or more agents in the antimicrobial class aminoglycosides for Gram-positive S. aureus.

Isolation of 2 or more pathogens (ie, S. aureus, Enterococcus spp., Escherichia coli, Klebsiella pneumoniae, Enterobacter spp., Pseudomonas aeruginosa, and Acinetobacter baumannii) from a single patient.

As rates of antibiotic use in LMICs converge with those of HICs [12], there has been increasing acknowledgment of and concern over the problem of antibiotic resistance in LMICs. However, results of all patients with Gram-positive infections to those without coinfections. Controlling for the higher mortality rates associated with S. aureus bacteremia or CSF infections, no significant difference in mortality rates was observed between patients with MRSA infections compared to those with methicillin-susceptible S. aureus (MSSA) infections (Table 4). However, patients with MRSA infections that were also non-susceptible to aminoglycosides had a greater likelihood of mortality, compared to MSSA-infected patients (OR 2.75, 95% CI 1.16–6.52). Among patients who acquired MRSA infections with an additional resistance to linezolid (n = 1) or a reduced susceptibility (ie, intermediate resistance) to vancomycin (n = 1) or teicoplanin (n = 1), all survived.

Glycopeptide resistance in Enterococcus spp. was not associated with any increased likelihood of mortality, regardless of species, after controlling for patient demographics (Table 4). Non-susceptibility to linezolid was detected in 2 (4.8%) patients with a glycopeptide-resistant Enterococcus infection, 1 of whom died.

**DISCUSSION**

As rates of antibiotic use in LMICs converge with those of HICs [12], there has been increasing acknowledgment of and concern over the problem of antibiotic resistance in LMICs. However,
of hospitalization (which may have included the ICU) was not taken into account.

Given the high rates of hospital infections caused by MDR Gram-negative organisms in LMICs [19, 20], we examined their relative mortality impact, compared to Gram-positive infections. We found that Gram-negative MDRO infections were associated with higher mortality rates, especially among patients in the ICU. However, the high odds of mortality associated with Gram-negative XDR infections among all patients suggests that more rapid identification of Gram-negative infections in both ICU and non-ICU patients, particularly those with bacteremia or lower-respiratory infections, may help reduce the clinical burden of MDR and improve mortality outcomes overall.

In India, infections with MDR and XDR Gram-negative bacteria are frequent [8, 13, 21, 22] and pose a significant challenge to clinicians due to severely limited therapeutic options. Once a pillar for empiric antibiotic therapy, third-generation cephalosporins are largely ineffective against infections of extended spectrum beta-lactamase–producing Enterobacteriaceae [13], and rates of carbapenem resistance are as high as 57% in some Indian health-care settings [21]. High rates of resistance are strongly related to patient outcomes, as indicated by our study; patients infected with MDR E. coli, XDR K. pneumoniae, and MDR A. baumannii were 2 to 3 times more likely to die than patients with non-MDR infections. These associated clinical outcomes appear consistent with existing research in smaller studies, showing MDR and XDR to be predictors of worse clinical outcomes, particularly among patients with XDR K. pneumoniae bacteremia, which in LMICs have been attributed to mortality rates up to 32–50% [4, 9].

Our findings also highlight the clinical importance of MDR and XDR strains of A. baumannii infections. The increased odds of mortality associated with MDR A. baumannii infections were consistent with previous studies linking carbapenem resistance to higher mortality rates and longer hospitalizations [3]. Able to survive in the hospital environment for extended periods of time [23], A. baumannii and P. aeruginosa are commonly implicated in device-associated infections. In particular, A. baumannii has a remarkable propensity for acquiring genetic material from other organisms, allowing it to develop extensive resistance over the last few decades [23].

### Table 3. Mortality Odds Among Patients With Gram-negative Infections

| Resistance pattern | Escherichia coli (n = 1907) | Klebsiella pneumoniae (n = 1370) | Pseudomonas aeruginosa (n = 591) | Acinetobacter baumannii (n = 520) |
|--------------------|-----------------------------|---------------------------------|---------------------------------|---------------------------------|
|                    | OR (95% CI)                  | OR (95% CI)                     | OR (95% CI)                     | OR (95% CI)                     |
| Non-MDR            | Referent                     | Referent                        | Referent                        | Referent                        |
| MDRa               | 2.63 (1.29–5.35)**           | 1.47 (0.92–2.24)**              | 1.15 (0.65–2.04)                | 2.81 (1.50–5.27)**              |
| MDR + beta-lactamase inhibitorsb | 2.23 (1.65–3.01)***** | 1.20 (0.61–2.37)                | NA                              | NA                              |
| XDRc               | 2.34 (1.40–3.90)**           | 2.29 (1.45–3.62)*****           | 1.76 (0.84–3.72)                | 2.26 (0.77–6.61)                |
| Age (years)        |                             |                                 |                                 |                                 |
| 0–11               | 1.62 (1.02–2.57)*            | 2.47 (1.01–6.07)*               | 1.86 (0.91–3.83)                | 2.69 (0.62–11.63)               |
| 12–44              | 1.09 (0.65–1.36)             | 1.80 (0.90–3.62)                | 0.64 (0.17–2.38)                | 0.83 (0.30–2.27)                |
| 45–64              | 1.50 (0.65–3.46)             | 3.05 (1.38–6.74)**              | 0.83 (0.21–3.22)                | 1.09 (0.45–2.68)                |
| >64                | 1.19 (0.42–3.39)             | 3.20 (1.23–8.31)*               | 0.74 (0.24–2.22)                | 1.97 (0.63–6.14)                |
| Female             | 0.83 (0.54–1.27)             | 0.84 (0.60–1.17)                | 1.05 (0.73–1.50)                | 1.40 (0.99–1.97)                |
| ICU                | 1.57 (0.89–2.79)             | 2.10 (1.36–3.25)**              | 2.09 (1.25–3.49)**              | 1.66 (1.28–2.16)*****           |
| Site of infection  |                             |                                 |                                 |                                 |
| Other              | 1.62 (1.02–2.57)*            | 2.47 (1.01–6.07)*               | 1.86 (0.91–3.83)                | 2.69 (0.62–11.63)               |
| Urine              | Referent                     | Referent                        | Referent                        | Referent                        |
| Wound              | 0.61 (0.32–1.14)             | 1.45 (0.82–2.55)                | 1.33 (0.68–2.59)                | 2.09 (0.30–14.54)               |
| Lower respiratory  | 1.61 (1.05–2.47)*            | 2.70 (1.52–4.79)**              | 2.67 (1.77–4.03)*****           | 3.77 (1.58–9.99)**              |
| Blood/CSF          | 3.28 (2.21–4.85)*****        | 6.67 (2.32–19.15)*****          | 2.76 (1.24–6.13)*               | 4.52 (1.41–14.46)***            |
| Coinfectiond       |                             |                                 |                                 |                                 |
| None               | Referent                     | Referent                        | Referent                        | Referent                        |
| Single             | 2.41 (1.65–3.52)*****        | 1.55 (1.28–1.88)*****           | 2.16 (1.38–3.38)**              | 1.35 (0.70–2.60)                |
| Multiple           | 3.92 (2.15–7.13)*****        | 2.31 (1.37–3.89)**              | 2.96 (1.62–5.41)*****           | 2.20 (1.38–3.50)*****           |

Logit regression is with clustered standard errors at the hospital level.

Abbreviations: CI, confidence interval; CSF, cerebrospinal fluid; ICU, intensive care unit; MDR, multidrug-resistant; NA, not applicable; OR, odds ratio; XDR, extensively drug resistant.

aNon-susceptibility to 1 or more agents in 3 or more antimicrobial classes (ie, aminoglycosides, third/fourth-generation cephalosporins, fluoroquinolones, beta-lactamase inhibitors, and carbapenems), excluding non-susceptibility to beta-lactamase inhibitors.

bNon-susceptibility to 1 or more agents in the antimicrobial class of beta-lactamase inhibitors.

cNon-susceptibility to 1 or more agents in all 5 aforementioned antimicrobial classes.

dIsolation of 2 or more pathogens (ie, Staphylococcus aureus, Enterococcus spp., E. coli, K. pneumoniae, Enterobacter spp., P. aeruginosa, and A. baumannii) from a single patient.

*P < .05. **P < .01. ***P < .001.
of glycopeptide resistance in enterococci infections, our study found no significant impact on unadjusted mortality risk associated with vancomycin-resistant enterococci infections [27]. However, contrary to findings from a previous study [28], which reported an increased unadjusted mortality risk associated with vancomycin-resistant enterococci infections, our study found no significant impact of glycopeptide resistance in Enterococcus infections. This result held true after restricting the analysis to blood cultures only (data not shown), which may be explained by the relatively few deaths associated with Enterococcus spp. in our study (35, 12.1%), as well as the limited number of isolates of clinical significance.

There are several limitations to the study. The lack of complete clinical data precluded us from capturing potentially important variables, including severity of illness, comorbid conditions, and time to effective therapy, all of which are associated with mortality among MDR-infected patients [29, 30]. However, previous studies controlling for comorbidities and severities of illnesses have shown independent associations between increased mortality and inappropriate antimicrobial therapy for those infections most commonly caused by MDROs [30, 31]. In addition, though we classified infections as hospital- or community-associated, based on the time of isolate collection, we lacked more detailed information on the timing of collection, as well as information on prior hospitalizations, which prevented us from a more accurate classification of infection-acquisition location. This may explain why we found no difference in mortality rates related to community vs hospital onset, even though prior studies have shown varied rates of resistance and attributable mortality rates based on infection-onset locations [9]. Alternatively, the high rates of MDRO in the community [8, 9] may mean that there is little difference between the pathogens transmitted in the hospital and the community. Further study is needed to understand the burden of high community rates of MDROs in resource-limited settings. Finally, while our study was based on multi-institutional data across India, our findings were not able to capture the heterogeneity of India's health-care landscape and may not be generalizable to specific communities or clinical settings.

For *S. aureus* infections, we found a significant difference in mortality between MRSA infections, with additional resistance to aminoglycosides and MSSA infections. These findings support existing evidence that MRSA infections are more likely to be resistant to other antibiotics than MSSA infections [24, 25] and suggest that MDR may, in part, be driving higher inpatient mortality rates among *S. aureus* infections, as demonstrated in previous studies [26].

Since the late 1970s, *Enterococcus* spp. have been recognized as a leading cause of health-care–associated urinary and bloodstream infections [27]. However, contrary to findings from a 2016 systematic review [28], which reported an increased adjusted mortality risk associated with vancomycin-resistant enterococci infections, our study found no significant impact of glycopeptide resistance in *Enterococcus* infections. This result held true after restricting the analysis to blood cultures only (data not shown), which may be explained by the relatively few deaths associated with *Enterococcus* spp. in our study (35, 12.1%), as well as the limited number of isolates of clinical significance.

### Table 4. Mortality Odds Among Patients With Gram-positive Infections

| Resistance pattern | Staphylococcus aureus (n = 237) | Enterococcus spp. (n = 192) | Enterococcus faecalis (n = 99) | Enterococcus faecium (n = 40) |
|-------------------|---------------------------------|------------------------------|-------------------------------|-------------------------------|
| OR (95% CI)       | OR (95% CI)                     | OR (95% CI)                  | OR (95% CI)                   | OR (95% CI)                   |

**Logit regression is with clustered standard errors at the hospital level. – denotes observations excluded from analysis due to clinical insignificance or no observed mortalities. Patients with corrections were excluded from analysis due to small sample sizes and statistical insignificance in relation to mortality. Enterococcus spp. includes the species *E. avium*, *E. faecalis*, *E. faecium*, and unknown Enterococcus spp.**

**Abbreviations: CI, confidence interval; CSF, cerebrospinal fluid; ICU, intensive care unit; MSSA, methicillin-susceptible *S. aureus*; MRSA, methicillin-resistant *S. aureus*; NA, not applicable; OR, odds ratio.**

*Non-susceptibility to oxacillin and/or cefoxitin (anti-staphylococcal beta-lactams), excluding non-susceptibility to aminoglycosides; no deaths occurred among MRSA infections with additional resistance to linezolid.*

**Non-susceptibility to oxacillin and/or cefoxitin and to 1 or more agents in the antimicrobial class of aminoglycosides.**

**Non-susceptibility to vancomycin and/or teicoplanin (glycopeptides).**

*P < .05. **P < .01. ***P < .001.
While data were observational, preventing establishment of causality, our results provide strong quantification of the association between mortality and MDR patterns in a representative LMIC, and highlight the significant threat MDR and XDR pathogens pose to human health in developing countries. The high mortality odds underscore the urgent need to improve understanding of the burden of mortality and morbidity attributable to MDR and XDR Gram-negative pathogens in LMICs. In fact, our results are likely an underestimate of the overall burden of MDR infections; we only examined mortality, but resistant infections are also associated with increases in morbidity and hospital costs [5]. Future research should prospectively enroll patients with MDR pathogen and adequate controls to improve understanding of the burden of resistance and to provide greater insight into the attributable risks of morbidity and mortality.

Research aimed at understanding the genetic and biochemical mechanisms of antimicrobial resistance in XDR Gram-negative pathogens is critically needed, as available therapeutic options, including those in the pipeline, are ineffective against existing molecular mechanisms, such as New Delhi metallobeta-lactamase, which are highly prevalent among XDR Gram-negative pathogens. Furthermore, increased surveillance is necessary to understand the extent of resistance in the community and the hospital, and to better quantify the impact that community transmission has on hospital infection patterns. As resistance can spread worldwide rapidly, investment by both LMICs and HICs into these research areas should be of utmost priority to combat the emergence and spread of MDR pathogens and conserve the global efficacy of antibiotics.

Supplementary Data
Supplementary materials are available at Clinical Infectious Diseases online. Consisting of data provided by the authors to benefit the reader, these materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes
Disclaimer. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

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