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Pan-aminoglycoside resistance: the emergence of 16S rRNA methyltransferases in the UK

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Background: 16S rRNA methyltransferases (16S RMTases) are an emerging resistance mechanism, and cause high-level resistance (MICs ≥256 mg/L) to all clinically-relevant aminoglycosides in Gram-negative bacteria. The aim of this study was to identify the prevalence of 16S RMTase genes (*armA*, *rmtA-H* and *npmA*) in isolates from the Antimicrobial Resistance and Healthcare Associated Infections (AMRHAI) Reference Unit's collection at Public Health England (PHE). These isolates were sent to AMRHAI as they displayed unusual resistance profiles, especially carbapenem resistance.

Material/methods: *Acinetobacter baumannii* (n=550) and Enterobacteriaceae (n=817) isolates from 2004-2015 displaying pan-aminoglycoside resistance (amikacin, gentamicin and tobramycin MICs of ≥64, ≥32 and ≥32 mg/L, respectively) were screened for *armA*, *rmtA-H* and *npmA* by PCR. Whole-genome sequencing (WGS) data, available for 449 Enterobacteriaceae, were analysed to identify 16S RMTase genes and sequence types (STs).

Results: Five hundred and twenty-seven (95.8%) *A. baumannii* and 755 (92.4%) Enterobacteriaceae were positive for 16S RMTase genes (Figure). *armA*, *rmtB*, *rmtC*, *rmtE*, *rmtF* and various two gene combinations were identified; no *rmtA*, *rmtD*, *rmtG*, *rmtH* or *npmA* genes were detected. The vast majority (94.5%, 1211/1282) of 16S RMTase-positive isolates also produced a carbapenemase where bla_{OXA-23} + bla_{OXA-51} (n=490), $bla_{OXA-23-like}$ (n=5), bla_{OXA-40} + bla_{OXA-51} (n = 4), bla_{NDM} + bla_{OXA-23} + bla_{OXA-51} (n=3) and $bla_{OXA-51-like}$ (n=2) were found in *A. baumannii* and bla_{NDM} (n=527), $bla_{OXA-48-like}$ (n=112),

bla$_{NDM}$ + *bla*$_{OXA-48-like}$ (n=59), *bla*$_{KPC}$ (n=5), *bla*$_{VIM}$ (n=2), *bla*$_{GES}$ (n=1), and *bla*$_{NDM}$ + *bla*$_{VIM}$ (n = 1) were found in Enterobacteriaceae. Four hundred and ninety (93.2%) *A. baumannii* isolates positive for *armA* belonged to international clone II. In Enterobacteriaceae, WGS data demonstrated that *armA*, *rmtB*, *rmtC* and *rmtF* were found in diverse sequence types (STs); 25 *E. coli* STs and 30 *K. pneumoniae* STs were identified. *E. coli* ST410 (19/87, 19.5% total *E. coli* isolates; from eight laboratories) and *K. pneumoniae* ST14 (111/312, 35.6% total *K. pneumoniae* isolates; from 25 laboratories) were most common. Travel history was available for only 9.8% (125/1282) patients with 16S RMTase-positive isolates; India was the most frequently visited country between 2009-2015 (40/125, 32.0% patients); 32 (80.0%) of these isolates had NDM carbapenemases.

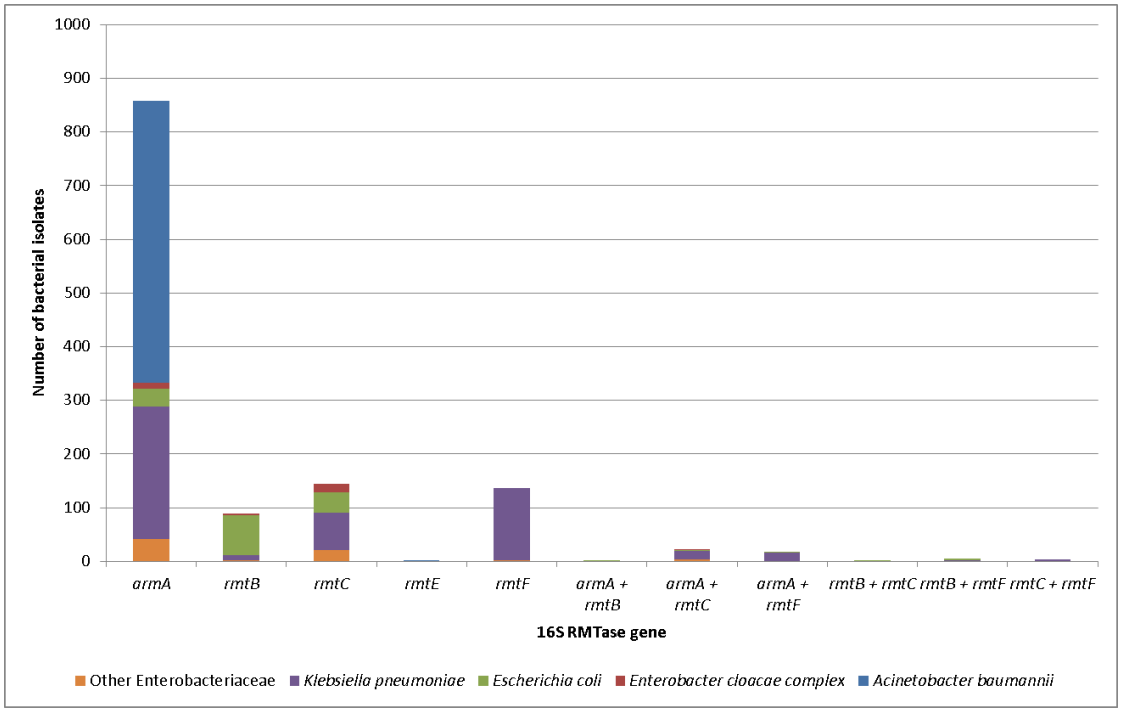

Figure: 16S RMTase-positive isolates broken down by genus/species

Conclusions: 16S RMTase activity has been identified as the major mechanism conferring pan-aminoglycoside resistance in this group of Gram-negative organisms displaying unusual resistance phenotypes, predominantly carbapenem resistance. This combination of carbapenemase and 16S RMTase genes poses a serious threat to the treatment of multidrug-resistant Gram-negative isolates with already limited treatment options should this combination become more widespread. 16S RMTase genes appear to be spreading through co-selection with carbapenemase genes, which is supported by their carriage in high-risk clones known to be carbapenemase producers such as *A. baumannii* international clone II, *E. coli* ST410 and *K. pneumoniae* ST14.