Ability of blaNDM to disseminate worldwide into extensively drug-resistant bacterial hosts poses a major challenge to infection control and treatment: a global multi-centred whole-genome sequencing analysis

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Background: New Delhi metallo-β-lactamase genes (\(bla_{\text{NDM}}\)) are found in diverse Gram-negative bacterial strains. While tracking spread of bacterial clones has revolutionised infection control of many drug-resistant bacteria (e.g., MRSA, VRE, Mtb), deciphering spread of \(bla_{\text{NDM}}\) is complicated by two additional tiers of gene spread: inter-plasmid gene module transposition and inter-bacterial plasmid conjugation.

Material/methods: To discern \(bla_{\text{NDM}}\) transmission pathways to inform infection control, \(bla_{\text{NDM}}\)-positive isolates were collected worldwide (19 study sites in China, Czech Republic, India, United Kingdom, Malaysia, Oman, Pakistan, Qatar, Saudi Arabia, United Arab Emirates, United States, Vietnam and Singapore) over 5.3 years (December 2009 to April 2015). Whole genome sequences of the \(bla_{\text{NDM}}\) isolates (N=473) were analyzed for genomic species, plasmid groupings and resistomes. Genomic transmission clusters were defined with a single nucleotide polymorphism (SNP) threshold based on pairwise Hamming distances (E. coli: 78 SNPs, K. pneumoniae: 118 SNPs).

Results: The majority of isolates were collected from Singapore (N=368, 78%) while the remaining were isolates from 12 other countries in Asia (N=56, 11.8%), Europe (N=35, 7.4%), the Middle East (N=13, 2.8%) and North America (1, 0.2%). Out of the 473 \(bla_{\text{NDM}}\)-positive isolates, 467 (98.7%) had a human origin, while 6 (1.3%) had an environmental origin. The main Enterobacteriaceae were K. pneumoniae (N=178, 37.6%), E. coli (N=147, 31.1%) and E. cloacae (N=62, 13.1%). One hundred and twenty-eight unique sequence types (STs) were identified amongst the Enterobacteriaceae. Bacterial strain type (STs) were diverse, though international ‘high-risk’ clones E. coli ST131 (N=17, 3.4%), K. pneumoniae ST147 (N=16, 3.4%) and K. pneumoniae ST11 (N=12, 2.5%) were the commonest STs. Of all plasmid incompatibility groups detected, IncFI (N=332, 70.2%) was most predominant. The colistin-resistance conferring gene, mcr-1, was detected in 7 isolates (6 from Singapore and 1 from China). Resistome analysis showed that 452 isolates (95.6%) carried at least one non-NDM β-lactamase gene. Additionally, most isolates carried at least one gene conferring resistance to aminoglycosides (N=426, 90.1%), fluoroquinolones (N=300, 63.4%), trimethoprim (N=329, 70%), sulfonamides (N=368, 77.8%), macrolides (N=236, 49.9%), phenicol (N=294, 62.2%), fosfomycin (N=237, 50.1%), and tetracyclines (N=266, 56.2%). In total, 17 genetic clusters involving 68 isolates were identified. All 17 genetic clusters were limited to Singapore and no international transmission cluster was detected.

Conclusions: Globally, \(bla_{\text{NDM}}\) genes disseminate in diverse bacterial species with no predominant bacterial clones, suggesting that \(bla_{\text{NDM}}\) can exploit multiple gene dissemination pathways. The complex genetic pathways of \(bla_{\text{NDM}}\) spread poses a major challenge to infection control and therapeutic efforts worldwide.