Convergence of carbapenem-resistance and hypervirulence in *Klebsiella pneumoniae*

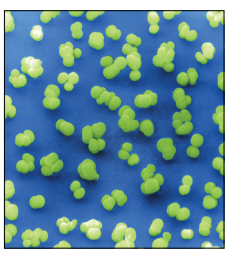
Klebsiella pneumoniae, first described in 1882, remains a common cause of community-acquired and hospital-acquired infections; but strikingly, the past three decades have witnessed the emergence of two largely non-overlapping *K pneumoniae* populations: one multidrug resistant (MDR) and one hypervirulent. These strains belong primarily to a few major clonal groups (CGs), such as the *K pneumoniae* carbapenemase (KPC)-producing CG258 strains, which cause about 50% mortality in high-risk patients admitted to hospitals; and CG23 strains, which are associated with community-acquired pyogenic liver abscess. A worrisome concern is that the virulence and resistance could converge, producing strains that are able to cause severe and untreatable invasive infections.[1,2]

In *The Lancet Infectious Diseases*, Danxia Gu[3] and colleagues describe a fatal outbreak caused by bla_{KPC-2}-harbouring carbapenem-resistant-hypervirulent *K pneumoniae* ST11 strains in a hospital in eastern China in 2016. The hypervirulence was caused by the acquisition of a roughly 170 kb pLVPK-like virulence plasmid into a classic ST11 carbapenem-resistant *K pneumoniae* strain. The investigators[3] further identified 11 (3%) additional carbapenem-resistant-hypervirulent *K pneumoniae* isolates from among 387 ST11 strains from 25 provinces in China. Their study describes an alarming evolutionary event: plasmid-mediated convergence of multidrug-resistance and hypervirulence in an epidemic carbapenem-resistant *K pneumoniae* clone. Indeed, a similar hospital outbreak between 2013 and 2015, which was caused by carbapenem-resistant-hypervirulent *K pneumoniae* ST11 strains, was reported previously;[4] however, the virulence and resistance plasmids were not characterised in that outbreak. The transfer of virulence plasmids into successful carbapenem-resistant *K pneumoniae* ST11 strains raises concerns that these organisms might not only cause severe untreatable infections in hospitals, but could result in serious life-threating infections in the community.

There have now been several reports, mostly from China,[5,6] of sporadic cases or small outbreaks due to carbapenemase-producing (mainly KPC) K1 or K2 hypervirulent *K pneumoniae* strains. Notably, these carbapenem-resistant-hypervirulent *K pneumoniae* strains are the result of horizontal transfer of resistance plasmids into hypervirulent *K pneumoniae* strains (eg, K1 serotype ST23). These examples of plasmid-mediated convergence of resistance and virulence, seen in the repeated creation of MDR hypervirulent *K pneumoniae* strains, present a major infection control challenge.

It is clear that mobile element and plasmid-mediated gene spread, mostly in Gram-negative pathogens, are driving a global crisis. A report from China[7] describing plasmid-mediated colistin resistance (MCR-1) is a dramatic example. Historically, the pLVPK virulence plasmids have been restricted to hypervirulent *K pneumoniae* backgrounds, especially ST23 K1 strains. Gu and colleagues' report[3] provides an example in which the host–plasmid relationship changed in a highly predominant *K pneumoniae* ST11 background. It is unclear whether this change is a result of the expansion of the plasmid's host range or the evolution of the bacterial host to acquire and maintain the virulence plasmid. Understanding the molecular mechanisms underlying the plasmid host expansion and adaptation with respect to antimicrobial resistance and virulence will be necessary to control both the spread of MDR hypervirulent *K pneumoniae* strains and the spread of the resistance and virulence plasmids. In place of the traditional view of molecular epidemiology focusing on the spread of pathogenic strains, it would be better to instead adopt the view of plasmid epidemiology, with surveillance strategies tracking the resistance and virulence plasmids (and genes) rather than just specific host strains.

It is likely that the high prevalences of hypervirulent *K pneumoniae* (about 20–40%)[8-10] and carbapenem-resistant *K pneumoniae* (average 7·6% in 2015 and >10% in most of eastern China) in Chinese hospitals has contributed to the emergence these carbapenem-resistant and hypervirulent organisms. Neighbouring regions of the Asia-Pacific Rim with high prevalences of hypervirulent *K pneumoniae* and carbapenem-resistant *K pneumoniae* should be on alert for the emergence and dissemination of carbapenem-resistant hypervirulent



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K pneumoniae. The emergence of these strains raises important questions about their prevalence and the correct treatment strategies and infection control measures. Moreover, the prevalence of carbapenem-resistant *K pneumoniae*, hypervirulent *K pneumoniae*, and carbapenem-resistant hypervirulent *K pneumoniae* in the community in China is largely unknown. We encourage our Chinese colleagues to take joint efforts to undertake surveillance to measure the prevalence and clinical impact of the carbapenem-resistant *K pneumoniae* and carbapenem-resistant hypervirulent *K pneumoniae* strains, both in the hospital and communities.

The carbapenem-resistant hypervirulent *K pneumoniae* strains[3,4] remain susceptible to a few antibiotics, such as tigecycline and colistin, and the need for effective antibiotics is paramount. The development of β-lactam inhibitors with a companion β-lactam, such as ceftazidime with avibactam and ceftolozane with tazobactam, provides some hopeful alternatives. Vaccines, phage therapy, strategies to inhibit plasmid transfer, and shutting down of virulence gene expression are all optimistic options; however, the reality is that we are now in a crisis. The keys to success in preventing the transmission of carbapenem-resistant hypervirulent *K pneumoniae* strains are early detection and containment of spread through comprehensive infection control measures. Active surveillance should not only focus on antimicrobial resistance, but also the virulence characteristics and even the strain backgrounds. Failure to control its early spread right now, will make a a global epidemic of carbapenem-resistant hypervirulent *K pneumoniae* hard to avoid.

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