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***Shigella flexneri* serotype 3a: the rise of a superbug**

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Shigellosis is a highly contagious acute gastro intestinal infection conferred by faeco-oral transmission of the pathogen *Shigella* spp.¹ In low-income countries and high-risk regions, poor sanitation is responsible for about 165 million cases of shigellosis annually, with at least 1 million of these resulting in death.² In high-income countries and low-risk regions, shigellosis is typically associated with travel to high-risk regions (Africa, Asia, and Latin America).³ Since 2000, shigellosis has also been reported as a sexually transmitted infection (STI) among men who have sex with men (MSM).⁴ In most cases of shigellosis, treatment relies on replacement of fluids and salts lost due to severe diarrhoea, which usually lasts for less than a week.⁵ However, severe infections in young children and old adults, or immunocompromised people, might require antibiotic treatment.⁶ The emergence of *Shigella* spp strains with decreased antibiotic susceptibility is a growing public health concern.⁷

In *The Lancet Infectious Diseases*, Kate Baker and colleagues present a large-scale, cross-sectional genomic epidemiological study⁸ of shigellosis cases from 29 countries collected between 1995 and 2014. The authors whole-genome sequenced more than 300 clinical isolates of *Shigella flexneri* serotype 3a from high-risk and low-risk regions, including travel-associated and MSM-associated cases. The analysis of the data led to the identification of three main phylogenetic lineages. Two of these lineages were related to high-risk regions, with isolates collected from patients in high-risk regions clustering with isolates collected from patients living in low-risk regions who had suspect travel histories to those high-risk regions (Asia and Africa).

The third lineage was almost exclusively comprised of isolates from MSM living in low-risk regions with non-suspect travel histories to high-risk regions. Within this MSM-outbreak associated lineage, dated phylogeny construction showed that evolutionary relationships were not primarily determined by geographical origin, uncovering instead that a recently emerged monophyletic lineage of *S flexneri* serotype 3a is circulating in the MSM population intercontinentally, across regions traditionally considered low-risk for shigellosis.

Importantly, the analysis of the sequencing data also revealed the presence of antibiotic resistance genes (ARGs) in the MSM-outbreak associated lineage. All isolates in the lineage carried a common mobile genetic element that encoded resistance to four antimicrobial classes, suggesting that the ancestral strain of the lineage was already multidrug resistant

before its introduction into the MSM population. However, the distribution of other mobile genetic elements in the MSM-outbreak associated lineage showed that the lineage acquired additional elements that encoded resistance to further antimicrobial classes over the time-course of the emergence. In particular, prevalent sublineages contained plasmid pKSR100 that carried the ARGs *mphA* and *ermB*, and conferred high-level resistance to azithromycin. Azithromycin is a first-line or second-line treatment for several sexually transmitted diseases that were reported during interview with patients, including gonococcal and chlamydial infections.^{9, 10} Although determination of the exact circumstances of pKSR100 acquisition is difficult, presence of the plasmid probably conferred a selective advantage to the prevalent *S flexneri* serotype 3a sublineages circulating within the MSM population subject to antibiotic treatment(s) for unrelated sexually transmitted infections.

The notion that antibiotic resistance is selected as a consequence of antibiotic treatment is not new.¹¹ A well established concept in the field is the existence of a pool of antibiotic resistance genes, the so-called resistome, hosted by various microbes in the environment.¹² The transfer of this genetic information to human pathogens contributes to the emergence of multidrug resistant superbugs that thrive in patients, in spite of antibiotic therapy. The study by Baker and colleagues⁸ is important (and worrisome) because it provides the very clear demonstration that, in addition to the selection of antibiotic resistance among targeted pathogens, antibiotic treatment supports the selection of multidrug resistance in comorbid, non-targeted microbes, as evidenced by the ongoing rise of *S flexneri* serotype 3a to superbug status. Genomic studies and phylogeny construction have proven to be extremely powerful approaches to trace the evolution and dissemination of human pathogens.¹³ The conclusions drawn by these studies are difficult to ignore. The rapid dissemination of antibiotic resistance among human pathogens represents a major threat to public health.

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