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Letter to the Editor

MCR-1: rethinking the origin

Sir,

The recent description of the *mcr-1* gene [1], which confers a transferable mechanism of colistin resistance, has changed the current scenario of resistance to this antibiotic. This has become one of the most prolific topics, with 130 papers published since the first electronically available version of the original paper.

The *mcr-1* gene encodes a phosphoethanolamine transferase that leads to modification of lipid A by addition of phosphoethanolamine. This mechanism was already known to emerge by selection under antibiotic pressure but was only supposed to be obtained by mutation in regulatory pathways that include this (and other) lipopolysaccharide decoration [2].

Following preliminary analysis of the protein sequence, the authors stated that 'The evolutionary relationship between MCR-1 and the phosphoethanolamine transferase of polymyxin-producing bacteria, *Paenibacillus* spp, indicated a potential intergeneric transfer of the gene from the chromosome of unknown polymyxin-producing bacteria to *E. coli*' [1].

More recently, Baron et al. not only highlighted that MCR-1 is 'closely related' to phosphoethanolamine transferase (EptA) described in *Paenibacillus sophorae* but also suggested that the coding gene could have been recruited from this species, arguing that 'it is known that bacteria which can synthesise an antibiotic are able to simultaneously resist it' [3]. However, we consider that assuming these two facts may carry an implicit mistake because paenibacilli are Gram-positive bacteria that lack lipopolysaccharide (and therefore lipid A) and consequently are naturally resistant to polymyxins. Moreover, the GenBank sequence for the lipid A phosphoethanolamine transferase of *P. sophorae* (NCBI reference sequence **WP_036596266.1**) shows that the protein record was suppressed because it is no longer annotated on any genome. Even if speculative, it might have occurred that a sequence from a Gram-negative bacterium was erroneously annotated as belonging to this species.

In the 1960s, it was assumed that any bacterium able to synthesise an antimicrobial compound should have a 'detoxifying' method that could be the origin of clinically relevant resistance mechanisms. However, this postulate faded away with the availability of sequencing methods [4,5]. In fact, still very few clinically resistance mechanisms can be traced down to their original source, in general corresponding to chromosomal markers whose genes are in many cases almost silent and not clinically relevant in their producers. Among them, some SHV enzymes and OqxAB efflux pumps (originally located in the chromosome of *Klebsiella pneumoniae*), plasmid CTX-M enzymes (not as ancestors but recruited as they were, originally located in the chromosome of different *Kluyvera*), or other plasmid-mediated quinolone resistance determinants such as QnrA (originally from *Shewanella*) are good examples [5–7]. The emergence of plasmid-mediated colistin resistance genes resembles that of some plasmid-mediated AmpC β-lactamases, where recognition of derepressed mutants and, before that, the presence of finely tuned systems heralded recruitment in suitable platforms. Time and further work will show the most probable ancestors, or precisely define their pre-existence in a Gram-negative bacterium as found today after recruitment.

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