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Aquaculture, Exaptation, and the Origin of *mcr*-Positive Colistin Resistance

Felipe C. Cabello,[a] Henry P. Godfrey[b]

[a]Department of Microbiology and Immunology, New York Medical College, Valhalla, New York, USA
[b]Department of Pathology, New York Medical College, Valhalla, New York, USA

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The interesting work by Shen et al. (1) discusses the pathogenicity of *Aeromonas* for freshwater fish in passing but does not mention that *Aeromonas* are not only pathogenic for freshwater fish but also survive and cause furunculosis in aquacultured salmonids and other fish in the marine environment (1, 2).

Antimicrobials are heavily used both for metaphylaxis and for the treatment of *Aeromonas salmonicida*, strongly suggesting the generation and selection of *mcr*-positive *Aeromonas* spp. in this marine environment (1–3). These freshwater and saltwater environments are heavily contaminated with animal and human pathogens in many countries from the disposal of untreated sewage and the employment of so-called integrated aquaculture, where fish are raised on manures from antimicrobial-treated animals (3–5). They thus constitute hotspots for genetic recombination and horizontal gene transfer and are probably responsible for the worldwide dissemination of the *mcr* gene variants repeatedly found in bacterial genera containing human, terrestrial animal, and piscine pathogens (3, 4). Consistent with this, *mcr*-positive colistin resistance was first reported from China where intensive aquaculture and heavy antimicrobial use are common (6).

The relationship between excessive antimicrobial use, aquaculture, and the potential emergence of the *mcr* genes not only illustrates the accelerated dynamics of evolutionary events triggered by the use of large amounts of antimicrobials in aquaculture but may also exemplify "exaptation," defined by Gould and Vrba as a change in the function of a gene in the course of evolutionary succession (7, 8). The *mcr* genes may be an example of exaptation, since they are variants of phosphoethanolamine transferases originally found in aquatic *Shewanella* spp. (9). A modification of the lipopolysaccharide (LPS) core produced by these enzymes may provide protection for the cell wall in hypertonic marine environments but also against vertebrate antimicrobial peptides and lysozyme (9, 10). When transferred to *Aeromonas* and *Enterobacteriaceae* in environments rich in colistin residues, *mcr* genes may then endow the cells with resistance to this antimicrobial (1, 11, 12). In this regard, *mcr* genes appear to be similar to several plasmid-mediated quinolone resistance genes [*qnrA*, *qnrB*, *qnrS*, and *aac*(*6′*)-*Ib-cr*], which evolved long before the synthesis of quinolones and are widely distributed among aquatic bacteria; their original function is unknown, but they now provide resistance to quinolones following recent transfer to animal and human pathogens (13–15).

The findings of Shen et al. and others strongly suggest the aquatic environment is the new frontier in the accelerated evolution of antimicrobial resistance through its facilitation of recruitment and the exaptation of aquatic bacterial genes to the resistomes of animal and human pathogens (1, 6, 11–13, 15). Aquacultural activities are thus additional reactors, alongside terrestrial agriculture and hospitals, for the generation

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Address correspondence to Felipe C. Cabello, cabello@nymc.edu.

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and worldwide dissemination of antimicrobial resistance. The One Health paradigm (3, 14) linking environmental, piscine, and human health makes interventions to prevent detrimental connections ever more urgent. This is particularly important in the face of the rapid growth of intensive aquaculture accompanied by the passage of massive amounts of antimicrobials into the freshwater and marine environments and the global marketing of aquacultured products containing bacteria with newly captured genes from the aquatic resistome (3, 6, 14).

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