Interventions against multidrug-resistant, metal tolerant *Salmonella enterica* serovar I 4,[5],12:i:-

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Of the >2600 *Salmonella* serovars, *Salmonella enterica* serovar I 4,[5],12:i:- (serovar I 4,[5],12:i:-) is a monophasic variant of serovar Typhimurium whose prevalence has increased globally over the last 2 decades. In the U.S., serovar I 4,[5],12,i:- has emerged as the fourth most frequent cause of human salmonellosis and the most prevalent multidrug-resistant (MDR; resistant to ≥3 antimicrobial classes) serovar. Genome sequence analysis of an isolate linked to a 2015 pork outbreak involving 188 infections and the recall of 523,380 pounds of pork (USDA15WA-1) revealed two genetic insertions: a MDR module encoding mercury tolerance and antimicrobial resistance genes (ampicillin, streptomycin, sulfisoxazole, tetracycline), and a mobile genetic element referred to as *Salmonella* Genomic Island 4 (SGI-4) encoding metal tolerance genes (copper, arsenic, silver). Serovar I 4,[5],12,i:- isolates associated with swine are significantly more likely to contain the MDR module and the SGI-4 metal-tolerance island compared to strains associated with other food animal sources. Phenotypic analyses revealed that: 1) SGI-4 from serovar I 4,[5],12,i:- can be transferred to other *Salmonella* strains by conjugation, 2) SGI-4 in serovar I 4,[5],12,i:- confers elevated tolerance to copper, arsenic and antimony compounds, and 3) exposure to copper increased the gene expression of 38 metal tolerance genes (copper, arsenic, silver, and mercury). Potentially, the presence of metal tolerance genes in serovar I 4,[5],12:i:- benefits environmental survival and/or swine colonization in metal-containing settings, thereby promoting the increased prevalence of this serovar globally. The emergence and expansion of this clinically relevant MDR *Salmonella* necessitates mitigation on the farm and in the processing plant environment. Evaluation of the Enterisol Salmonella T/C® vaccine as a pre-harvest intervention tool revealed a significant 1-2 log reduction of serovar I 4,[5],12:i:- fecal shedding and intestinal tissue colonization (ileocecal lymph nodes, Peyer's patch region of the ileum, and cecum) in vaccinated pigs compared to mock-vaccinated pigs. Furthermore, we have investigated an antimicrobial peptide (AMP) as a potential surface disinfectant against serovar I 4,[5],12:i:- biofilms. Biofilms are a major contributor in the persistence of *Salmonella* in food-processing facilities because the complex bacterial community of the biofilm adheres firmly to inert surfaces and are recalcitrant to disinfectants and antibiotics. In our biofilm assays, the AMP not only prevented serovar I 4,[5],12:i:- from forming a biofilm, it also disturbed an already formed biofilm. Altogether, our data support current concerns that acquisition of SGI-4 may facilitate bacterial survival in various metal environments, and interventions such as vaccination and AMPs may be used as mitigation tools to reduce metal-tolerant, MDR serovar I 4,[5],12:i:- in the pig environment to enhance food safety and public health.

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