Title:
Does Salmonella want to coexist with phages?

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Abstract:
Salmonella enteritidis (SE) is a pathogen commonly associated with foodborne illnesses, especially originating from poultry. Since December 2018, antimicrobial growth promoters are banned in Canada, and control within broiler production is challenging. Bacteriophages (phages), viruses that infect bacteria, are the closest silver bullet to target pathogens given their degree of host specificity. In a series of experiments, a SE phage resistant (PR) strain was analysed to better understand the resistance mechanism. The resistance was reverted soon as phages were removed, but not lost. It was maintained at a constant level after 3 subcultures, being completely reverted after 8 subcultures. PR strains had a lower relative Efficiency of Plating (EOP, $P<0.05$) than the wild type (WT) strain. Visible lysis indicated that an intermediary resistance state maintained by the host. The resistance mechanism, changes in the lipopolysaccharide (LPS) receptor to avoid phage adsorption, confirmed that susceptible cells were produced by PR cells, as phage adsorption and propagation observed in the PR strain was lower than in the WT strain ($P<0.05$). The PR strain displayed "fitness trade-off," represented by slower growth, albeit bearing the phage resistance as advantage, whilst the WT had faster growth but suffered from the phage attack. However, the intermediary resistant population possessed the best of the two worlds: Fast growth and resistance to phages, with a virtually unaffected growth curve when phages were added, in comparison to the WT and PR strains. In summary, the intermediary population was at an advantage. Although the frequency of bacteriophage insensitive mutants (BIM) of previously existent PR mutants in the population was defined as 1 cell in every 1.7x105 CFU/mL for the entire population, a reverse mathematical relationship of loss of resistance proved difficult to define and has is yet to be studied. Since only the PR cells can be producing new susceptible cells, it seems that, yes, SE "wants" to coexist with its phages, although the anthropomorphic "want" may have a molecular explanation, yet to be proven

in the future. Loss of resistance to phage is a relatively new subject in phage ecology, but the mechanisms proposed so far, such as loss of CRISPR immunity, does not fit the LPS changes and reduced phage adsorption reported here. We suspect that WT cells produced by PR strains may function as scout cells, and cellular communication via warning molecules may be released by these cells. Meanwhile, scout cells may greatly boost genetic variety in a population, which could be interesting to the species.