Salmonella monophasic harboring plasmid-mediated resistance genes to enrofloxacin and ceftiofur is expanding in swine in the Midwest

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Key Points:

- A genetically distinct clade of *Salmonella* 4,[5],12:i:- (also referred to as *S.* monophasic), harboring multiple antimicrobial resistance genes (including to ampicillin, streptomycin, sulfonamides, and tetracyclines) became the predominant *S.* monophasic type in swine in the U.S. during 2014-2016
- Phenotypic resistance to enrofloxacin (fluoroquinolone) and ceftiofur (3rd generation cephalosporin) was present in a proportion these isolates, and whole genome sequencing revealed the presence of the plasmid-mediated genes
- These plasmid-mediated resistance genes could potentially transfer horizontally to other microorganisms and augment the problem of antimicrobial resistance to these critically important antibiotics

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Non-typhoidal *Salmonella enterica* causes an estimated one million cases of foodborne salmonellosis in the U.S. annually. Although The National Antimicrobial Resistance Monitoring System (NARMS) data indicate that the proportion of human clinical isolates of *Salmonella* that are multiple drug resistant has decreased by around 50% since 1995, antimicrobial resistance in *Salmonella* was rated as a serious concern by the Center for Disease Control and Prevention (CDC), in particular to fluoroquinolones and cephalosporins. The *S.* monophasic emerged globally in the recent years and pig products have been identified as a source in some foodborne outbreaks. The prevalence of *S.* monophasic, and phenotypic resistance (minimum inhibitory concentration (MIC) above the cut-off value for this bacteria) to enrofloxacin increased in swine clinical samples in the Midwest during 2006 and 2016. During this period, injectable enrofloxacin was approved by the Food and Drug Administration (FDA) for treatment of swine respiratory disease and colibacillosis in piglets (in 2008 and 2014, respectively); therefore, the objective of the study was to characterize the *S.* monophasic in swine in the U.S Midwest.

We used whole genome sequencing to compare *S.* monophasic isolates collected from livestock in the Midwest with isolates collected from different sources in the U.S. and Europe. We then determined the antimicrobial resistance genotypes and presence of other virulence factors that could help to explain the emergence of this variant.

Salmonella monophasic formed two main genetic clades regardless of source and geographical origin (**Figure 1**). Most (84%) isolates recovered in the U.S. during 2014-2016, including 50 isolates (out of 51) originating mainly from swine in the Midwest, were part of an emerging clade genotypically resistant to ampicillin, streptomycin, sulphonamides and tetracyclines. In the Midwest samples, phenotypic resistance to enrofloxacin (11 out of 50; 22%) and ceftiofur (9 out of 50; 18%) was found in conjunction with plasmid-mediated resistance genes. This is of particular concern because fluoroquinolones and 3rd generation cephalosporins are often used to treat invasive *Salmonella* infections in people. Furthermore, because the genes were plasmid borne there is greater likelihood for horizontal transfer of these genes to other bacterial strains.

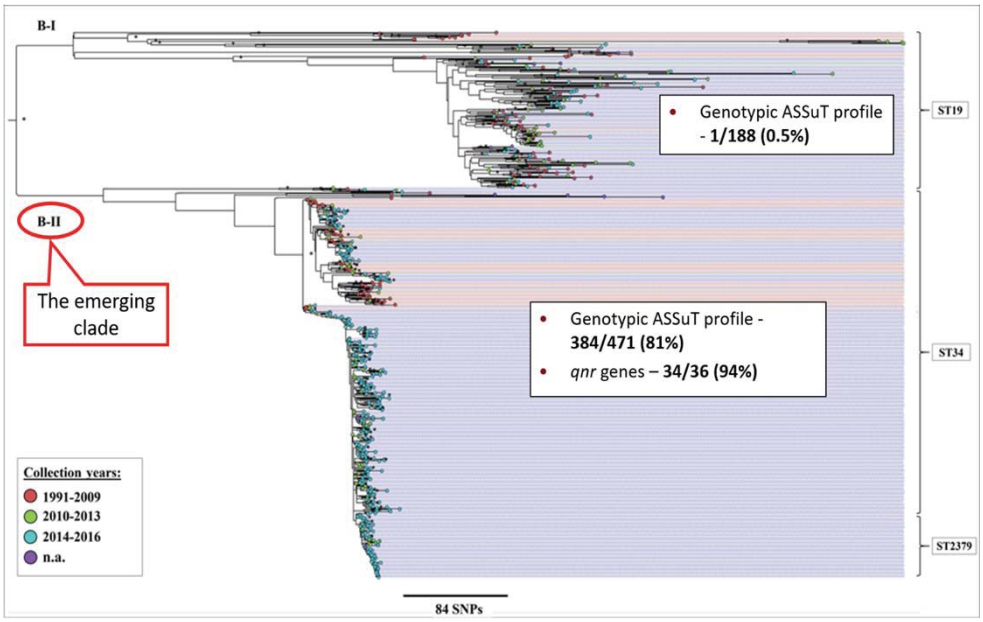

Figure 1. Maximum likelihood tree of *S.* monophasic collected in the U.S. and Europe during 1991-2016. The two major clades are indicated as B-I and B-II. Tip colors indicate of the period of sample collection: 1991-2009 (red), 2010-2013 (green), 2014-2016 (turquoise) and not available (n.a.; purple). The location of samples collection is indicated by the background color: Europe (red), U.S. (blue) and not available (green). ASSUT= presence of resistance genes against ampicillin, streptomycin, sulfonamides, and tetracyclines. qnr genes – conferring resistance to quinolones.

Further details may be found at the manuscript summarizing this work: Elnekave E, Hong S, Mather AE, et al. **Salmonella enterica Serotype 4,[5],12:i:- in Swine in the United States Midwest: An Emerging Multidrug-Resistant Clade**. Clin Infect Dis **2018**; 66(6): 877-85.

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