ramR mutations affecting fluoroquinolone susceptibility in epidemic multidrug-resistant Salmonella enterica serovar Kentucky ST198
Sylvie Baucheron, Simon Le Hello, Benoît Doublet, Etienne Giraud, François-Xavier Weill, Axel Cloeckaert

To cite this version:
Sylvie Baucheron, Simon Le Hello, Benoît Doublet, Etienne Giraud, François-Xavier Weill, et al.. ramR mutations affecting fluoroquinolone susceptibility in epidemic multidrug-resistant Salmonella enterica serovar Kentucky ST198. Frontiers in Microbiology, 2013, 4, pp.1-6. 10.3389/fmicb.2013.00213. pasteur-01109819

HAL Id: pasteur-01109819
https://hal-pasteur.archives-ouvertes.fr/pasteur-01109819
Submitted on 27 Jan 2015

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L’archive ouverte pluridisciplinaire HAL, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d’enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.
**INTRODUCTION**

Fluoroquinolones, together with extended-spectrum cephalosporins, are the treatment of choice for nontyphoid salmonellosis, as stable resistance to the most common members of different families of antimicrobial agents (ampicillin, chloramphenicol, streptomycin, sulfonamides, and tetracycline) has developed during the 1990s with the epidemic *Salmonella enterica* serovar Typhimurium phage type DT104 (Cloeckaert and Schwarz, 2001). Emerging resistance to fluoroquinolones in *Salmonella* spp. has been reported for both human and animal cases and is thus threatening to become a serious public health problem (Cloeckaert and Chaslus-Dancla, 2001; Piddock, 2002; Velge et al., 2005; Giraud et al., 2006). Of particular concern is the international spread of ciprofloxacin-resistant serovar Kentucky ST198 (Le Hello et al., 2011). This clone is not only highly resistant to ciprofloxacin but also multidrug-resistant (MDR) due to the presence of the *Salmonella* genomic island 1 (SGI1) carrying a multiple antibiotic resistance gene cluster, mostly variant SGI1-K carrying another resistance gene cluster (Doublet et al., 2008; Le Hello et al., 2011). SGI1 was initially identified in MDR serovar Typhimurium DT104 (Boyd et al., 2001), but not the MDR serovar Typhimurium DT104 clone neither other MDR *S. enterica* serovars carrying SGI1 or variants of it, have to our knowledge been reported to display this high-level ciprofloxacin resistance.

In *Salmonella* spp., quinolone/fluoroquinolone resistance is mostly attributed to point mutations in the quinolone resistance-determining regions (QRDRs) of the target genes gyrA, gyrB, parC, and parE. For the gyrA gene, coding for the A subunit of DNA gyrase, mutations resulting in amino acid changes at Ser83 (to Phe, Tyr, or Ala) or at Asp87 (to Gly, Asn, or Tyr) are the most frequently observed in nalidixic acid-resistant strains (Cloeckaert and Chaslus-Dancla, 2001; Piddock, 2002; Velge et al., 2005; Giraud et al., 2006). High-level fluoroquinolone resistance has been reported in several *S. enterica* serovars (Choleraesuis, Schwarzengrund, Typhimurium) and is essentially due to the combination of several target gene mutations of which the most frequent are double mutations resulting in modifications of both residues 83 and 87 of GyrA together with one mutation leading to the amino acid change Ser80Ile in the ParC subunit of topoisomerase IV (Baucheron et al., 2002, 2004; Chu et al., 2005). In addition two main other mechanisms have been reported consisting of active afflux mediated by the chromosomally-encoded AcrAB-TolC efflux system and target protection by Qnr proteins which are mostly encoded by plasmids acquired by horizontal transfer (Giraud et al., 2006). However, according to the literature over 15 years, these mechanisms appear less frequently and thus from an epidemiologic point of view seem of lesser importance than multiple target gene mutations to reach high-level ciprofloxacin resistance and compromise treatment.

In the case of ciprofloxacin resistance in serovar Kentucky ST198, three combinations of multiple target modifications, acquired in a possible sequential way, have been reported consisting of a first GyrA Ser83Phe modification, followed by three different situations of a second GyrA modification at position 87, i.e., Asp87Asn, Asp87Gly, or Asp87Tyr, and finally the ParC modification Ser80Ile (Le Hello et al., 2011). Qnr proteins have not been reported yet as additional mechanism for this epidemic...
clone, and active efflux has been suspected in a previous study due to a moderate increase of production in some isolates of the AcrA protein belonging to the AcrAB-ToLC efflux system (Weill et al., 2006).

In the present study we assessed the frequency of enhanced efflux by AcrAB-ToLC in a subset of serovar Kentucky ST198 strains of the 2000–2005 period of the epidemic. In case of significant increased production of AcrAB-ToLC we investigated more deeply the regulatory mechanisms behind this overproduction, in particular the involvement of the ramR regulatory protein belonging to the AcrAB-ToLC efflux system (Weill et al., 2008; Kehrenberg et al., 2009; Hentschke et al., 2010; Akiyama and Khan, 2012).

**MATERIALS AND METHODS**

The 27 serovar Kentucky ST198 strains selected for this study are shown in Table 1. Bacterial isolates were selected for this study, based on their evolutionary history following the emergence of target gene mutations initially in gyrA at the commencement of the epidemic in 2000–2002, followed by isolates with additional mutations (in gyrA and parC) toward the end in 2002–2005 and which demonstrated a higher MIC toward ciprofloxacin. An additional criterion for selection consisted of the differences observed in ciprofloxacin MICs suggestive for another resistance mechanism than target gene mutation. MICs were determined as described previously (Baucheron et al., 2002, 2004). SGI1

---

**Table 1 | Salmonella enterica serovar Kentucky ST198 strains analyzed in this study.**

| Strain | Country | Year of isolation | Antimicrobial resistance profile | SGI1 | PFGE type | CIP MIC (µg/ml) | Substitution(s) in the QRDR of: | Mutation(s) in efflux pump regulatory regions | AcrA production ratio |
|--------|---------|------------------|---------------------------------|------|-----------|----------------|-------------------------------|---------------------------------------------|------------------|
| 00 1059 | Egypt   | 2000             | AMX NAL                          |      |           |                |                               |                               |                  |
| 01 2100 | Egypt   | 2001             | AMX STR SPT GEN SUL TET NAL      |      |           |                |                               |                               |                  |
| 02 2818 | Egypt   | 2002             | AMX STR SPT GEN SUL TET NAL      |      |           |                |                               |                               |                  |
| 02 2691 | Egypt   | 2002             | AMX STR SPT GEN SUL TET NAL      |      |           |                |                               |                               |                  |
| 02 8051 | Egypt   | 2002             | AMX STR SPT GEN SUL TET NAL      |      |           |                |                               |                               |                  |
| 02 8141 | Egypt   | 2002             | AMX STR SPT GEN SUL TET NAL      |      |           |                |                               |                               |                  |
| 02 9866 | Egypt   | 2002             | AMX STR SPT GEN SUL TET NAL CIP  |      |           |                |                               |                               |                  |
| 03 9270 | India   | 2003             | NAL                              |      |           |                |                               |                               |                  |
| 04 2049 | Egypt   | 2004             | NAL CIP                          |      |           |                |                               |                               |                  |
| 04 4567 | Egypt   | 2004             | AMX STR SPT GEN SUL TET NAL CIP  |      |           |                |                               |                               |                  |
| 04 6248 | Egypt   | 2004             | STR SPT GEN SUL TET NAL CIP      |      |           |                |                               |                               |                  |
| 04 7734 | Egypt   | 2004             | AMX STR SPT GEN SUL TET NAL      |      |           |                |                               |                               |                  |
| 04 8262 | Egypt   | 2004             | STR SPT GEN SUL TET NAL CIP      |      |           |                |                               |                               |                  |
| 04 9384 | Egypt   | 2004             | AMX STR SPT GEN SUL TET NAL CIP  |      |           |                |                               |                               |                  |
| 05 0490 | Egypt   | 2005             | STR SPT GEN SUL TET NAL CIP      |      |           |                |                               |                               |                  |
| 05 0520 | Egypt   | 2005             | AMX NAL CIP                      |      |           |                |                               |                               |                  |
| 05 1016 | Kenya/Tanzania | 2005 | NAL CIP                          |      |           |                |                               |                               |                  |
| 05 1199 | Egypt   | 2005             | STR SPT GEN SUL NAL CIP          |      |           |                |                               |                               |                  |
| 05 2131 | Egypt   | 2005             | AMX NAL CIP                      |      |           |                |                               |                               |                  |
| 05 2354 | Kenya/Tanzania | 2005 | AMX STR SPT GEN SUL TET NAL CIP  |      |           |                |                               |                               |                  |
| 05 3290 | Egypt   | 2005             | AMX STR SPT GEN SUL TET NAL CIP  |      |           |                |                               |                               |                  |
| 05 3883 | Kenya/Tanzania | 2005 | AMX STR SPT GEN SUL TET NAL CIP  |      |           |                |                               |                               |                  |
| 05 4680 | Sudan   | 2005             | STR SPT GEN SUL TET NAL CIP      |      |           |                |                               |                               |                  |
| 05 7714 | Unknown | 2005             | AMX NAL CIP                      |      |           |                |                               |                               |                  |
| 05 8560 | Tunisia | 2005             | AMX STR SPT GEN SUL TET NAL CIP  |      |           |                |                               |                               |                  |
| 05 236 | Egypt   | 2005             | AMX NAL CIP                      |      |           |                |                               |                               |                  |
| 05 5111 | Libya   | 2005             | AMX SUL TET NAL CIP              |      |           |                |                               |                               |                  |
Table 2 | Primers used for PCRs.

| Primer used and target region | Primer | Nucleotide position relative to the LT2 strain genome* | Oligonucleotide sequence(s) (5’ to 3’) | Size (bp) | Annealing temp (°C) | References |
|------------------------------|--------|------------------------------------------------------|---------------------------------------|-----------|---------------------|------------|
| detection of mutations       |        |                                                      |                                       |           |                     |            |
| ramR-ramA                    | ram5   | 638085                                               | TCGTGAAAGGCCGATTTCCAG                 | 958       | 60                  | This study |
|                              | ram6   | 639042                                               | GTGATAAAGCCGGCAAAGGAA                 |           |                     |            |
| acrR-acrA                    | acrR1  | 533463                                               | CAGTGGTCCGTTTTATG1                    | 992       | 58                  | Ollier et al., 2005 |
|                              | acrR2  | 534454                                               | ACAGAATAGCCGACACAGAAGA                |           |                     |            |
| marC-maro-marR-maroA         | marR1  | 159745                                            | CAGTGGTTGCGTTGGCAGT                  | 787       | 60                  | This study |
|                              | marR2  | 1598245                                            | GCTACGGGACGAGAGACAGA                  |           |                     |            |
| soxS-soxR                    | sox1   | 4503970                                            | CTACAGGGGTTACGCTAC                    | 915       | 60                  | This study |
|                              | sox2   | 4504884                                            | CGGCGCTTACAGGTTAC                    | 60        |                     |            |
| acrS-acrE                    | acrS1  | 3560054                                            | TTGGCCATTAATGCCTCCAC                  | 1094      | 62                  | This study |
|                              | acrS2  | 3561128                                            | ATGATGATAGAGGCAGGGAG                   |           |                     |            |
| qRT-PCR                      |        |                                                      |                                       |           |                     |            |
| gmk                          | gmk-f  | 3933294                                            | TTGGCAGGGGAGGCTT                     | 62        | 60                  | Baucheron et al., 2012 |
|                              | gmk-r  | 3933355                                            | GCAGCGAGTGCCGCTAGT                   |           |                     |            |
| gyrB                         | gyrB-f | 40040275                                            | TCTCCTCAGACGACAAAAGATAC              | 81        | 60                  | Baucheron et al., 2012 |
|                              | gyrB-r | 4004196                                            | CGCTCCAGCAGTTGCTATC                   |           |                     |            |
| rrs                          | rrs-f  | NA**                                                 | CAAACGGCGGCGGTAAT                     | 57        | 60                  | Baucheron et al., 2012 |
|                              | rrs-r  | NA**                                                 | TTACTGCAGCAATACGTTG                   |           |                     |            |
| ramA                         | ramA-f | 639180                                              | GCGTGAAGGAGGCTAAAC                   | 167       | 60                  | Baucheron et al., 2012 |
|                              | ramA-r | 639346                                              | GGCATGCTTTTGCATGCA                    |           |                     |            |
| acrA                         | acrA-f | 533120                                              | GAAACCGCGCAGTACACCT                   | 220       | 60                  | Baucheron et al., 2012 |
|                              | acrA-r | 532901                                              | CCTGTTGACGGAAACATTG                   |           |                     |            |
| tolC                         | tolC-f | 3349107                                             | GAGCGCAGGAGAATAGT                     | 67        | 60                  | Baucheron et al., 2012 |
|                              | tolC-r | 3349173                                             | CCGGTTATCCAGGGTGTG                    |           |                     |            |

*GenBank NC_003197.
**NA: Not Applicable due to the number of copies of this gene in Salmonella.

detection and characterization were performed as described previously (Boyd et al., 2001; Doublet et al., 2008). Efflux pump production was assessed by Dot blot using an anti-AcrA polyclonal antibody as described previously (Abouzeed et al., 2008). Occurrence of mutations affecting acrAB and tolC expression was determined by PCR and sequencing the regulatory regions ramR-ramA, acrR-acrA, marC-maro-marR-maroA, soxS-soxR, and acrS-acrE using primers listed in Table 2. Transcription levels of ramA, acrA, and tolC were determined by qRT-PCR as described previously (Giraud et al., 2013).

RESULTS AND DISCUSSION

As shown in the Table 1 most of the strains selected carried SGI1 or variants of it and were thus MDR. They were all from human cases in France who acquired their infection during travel to Africa or India. As assessed by Dot blot, most of the strains (n = 24) did not show significant increased production of AcrA relative to susceptible serovar Kentucky reference strain 98K (AcrA production ratios from 1 to 2; Table 1). Relative to strain 98K, three strains showed a 3-fold increased AcrA production, and more suggestive for increased active efflux three strains a 5- to 6-fold increased production of AcrA (Table 1). Among these regulatory regions, mutations were detected only in the ramR open reading frame and in only three strains of this study (Table 3). The mutations were distinct frame shift mutations and consisted of a GATC duplication for strain 02-2818, a G insertion for strain 05-8560, and a 91 bp deletion for strain 02-8141 (Figure 1). The role of these mutations in upregulating acrAB and tolC expression, and consecutive enhanced efflux-mediated resistance, was further assessed by: (i) complementing with the wild-type ramR gene (using plasmid pRamR Abouzeed et al., 2008); (ii) determining the MICs of ciprofloxacin and unrelated antibiotic florfenicol shown to be substrate of AcrAB-TolC (Baucheron et al., 2002); and (iii) measuring expression of ramA, acrA, and tolC by qRT-PCR (Giraud et al., 2013). The results shown in Table 3 are in agreement with data published previously for other S. enterica serovars (Abouzeed et al., 2008; Kehrenberg et al., 2009), i.e. ramR mutations observed account for a 2- to 4- fold increased resistance level by active efflux through enhanced expression of AcrAB-TolC. As also observed in previous studies, the effect of such mutations on ramA transcription level was significantly higher than on acrA or tolC transcription levels. It is somehow expected considering the direct local repressor activity of RamR on ramA transcription and the distant RamA transcriptional activator activity on acrAB and tolC (Abouzeed et al., 2008; Baucheron et al., 2012; Giraud et al., 2013).

Non-target mutations as assessed in this study confirm they are infrequent in Salmonella spp. but seem nevertheless
### Table 3 | Characteristics of the *Salmonella enterica* serovar Kentucky ST198 strains carrying ramR mutations.

| Strain         | Source  | Geographic origin | Antimicrobial resistance profilea | PFGE type (variant)b | MIC of indicated antibiotic (µg/ml) | Substitution(s) in the QRDR of: ramR | Mutation in ramR | Transcription levels of: ramA acrA tolC |
|----------------|---------|-------------------|----------------------------------|---------------------|------------------------------------|--------------------------------------|-----------------|--------------------------------------|
|                |         |                   |                                  |                     | NAL CIP FFCc | Gyra ParC                        |                                     |                 | ramaA acrA tolC                        |
| **MDR STRAINS**|         |                   |                                  |                     |       |                                |                                     |                 |                                      |
| 05-8560        | Human   | Tunisia            | AMX STR SPT GEN SUL TET NAL CIP  | XKEN-1d             | >1024 16 16 S83F, D87Y S80I 1 bp insertion (position 506) | 24.6 7.2 2.6 |
| 05-8560(pRamR) |         |                   |                                  |                     | >1024 4 4 |                                |                                     |                 | 2.4 1.7 1.7                           |
| 02-8141        | Human   | Egypt              | AMX STR SPT GEN SUL TET NAL      | XKEN-1m             | 512 0.50 16 S83F – 91 bp insertion (position 42) | 106.1 10.4 7.8 |
| 02-8141(pRamR) |         |                   |                                  |                     | 512 0.125 8 |                                |                                     |                 | 1.6 1.1 1.2                           |
| 02-2818        | Human   | Egypt              | AMX STR SPT GEN SUL TET NAL      | XKEN-1i             | 512 0.50 16 S83F – 4 bp duplication (position 508) | 29.1 5.3 4.7 |
| 02-2818(pRamR) |         |                   |                                  |                     | 256 0.25 4 |                                |                                     |                 | 1.9 0.9 1.6                           |
| 02-9866        | Human   | Egypt              | AMX STR SPT GEN SUL TET NAL CIP  | XKEN-1a             | >1024 8 4 S83F, D87N S80I – | 2.9 1.2 1.6 |
| 02-9866(pRamR) |         |                   |                                  |                     | >1024 4 4 |                                |                                     |                 | 1.8 1.6 2.4                           |
| **REFERENCE STRAIN**|         |                   |                                  |                     |       |                                |                                     |                 |                                      |
| 98K            | Chicken | USA                | Susceptible                      | XKEN-4              | – 1 0.004 2 – – – | 1.0 1.0 1.0 |
| 98K(pRamR)     |         |                   |                                  |                     | 1 0.004 2 |                                |                                     |                 | 2.1 1.3 1.5                           |

*AMX, amoxycillin; STR, streptomycin; SPT, spectinomycin; GEN, gentamicin; SUL, sulfonamides; TET, tetracycline; NAL, nalidixic acid; CIP, ciprofloxacin.

Ks: subgroup of SGI1-K.

FFC, florfenicol.
mostly restricted to the ram regulatory region. Most mutations in the ramR-ramA region reported to date, as also shown in this study, are distinct and found in single isolates. To our knowledge only independent isolates of the epidemic ciprofloxacin-resistant serovar Typhimurium DT204 clone from the 1990s have been shown to carry the same mutation in ramR consisting of an insertion by an IS1 element (Abouzeed et al., 2008). We may nevertheless expect that the further global spread of ciprofloxacin-resistant serovar Kentucky ST198 and its resistance evolution will possibly, like in the case of serovar Typhimurium DT204, result in successful ramR-mutation-carrying subclones.

ACKNOWLEDGMENTS
We are grateful to Isabelle Monchaux and Laetitia Fabre for excellent technical assistance. We would like to thank all corresponding laboratories of the French National Reference Center for E. coli, Shigella, and Salmonella. The French National Reference Center for E. coli, Shigella, and Salmonella is funded by the Institut Pasteur and the Institut de Veille Sanitaire.

REFERENCES
Abouzeed, Y. M., Baucheron, S., and Cloeckaert, A. (2008). ramR mutations involved in efflux-mediated multidrug resistance in Salmonella enterica serovar Typhimurium. Antimicrob. Agents Chemother. 52, 2428–2434. doi: 10.1128/AAC.00848-08
Akiyama, T., and Khan, A. A. (2012). Molecular characterization of strains of fluoroquinolone-resistant resistant Salmonella enterica serovar Schwarzenberg carrying multidrug resistance isolated from imported foods. J. Antimicrob. Chemother. 67, 101–110. doi: 10.1093/jac/dkr414
Baucheron, S., Chaslus-Dancla, E., and Cloeckaert, A. (2004). Role of ToIC and parC mutation in high-level fluoroquinolone resistance in Salmonella enterica serotype Typhimurium DT204. J. Antimicrob. Chemother. 53, 657–659. doi: 10.1093/jac/dkh122
Baucheron, S., Coste, F., Canepa, S., Maurel, M. C., Giraud, E., Culard, F., et al. (2012). Binding of the RamR repressor to wild-type and mutated promoters of the ramA gene involved in efflux-mediated multidrug resistance in Salmonella enterica serovar Typhimurium. Antimicrob. Agents Chemother. 56, 942–948. doi: 10.1128/AAC.05444-11
Baucheron, S., Imberechts, H., Chaslus-Dancla, E., and Cloeckaert, A. (2002). The AcrB multidrug transporter plays a major role in high-level fluoroquinolone resistance in Salmonella enterica serovar Typhimurium phage type DT204. Microb. Drug Resist. 8, 281–289. doi: 10.1089/1076629026046943
Boyd, D. A., Peters, G. A., Cloeckaert, A., Boundedre, K. S., Chaslus-Dancla, E., Imberechts, H., et al. (2001). Complete nucleotide sequence of a 43-kilobase genomic island associated with the multidrug resistance region of Salmonella enterica serovar Typhimurium DT104 and its identification in phage type DT120 and serovar Agona. J. Bacteriol. 183, 5725–5732. doi: 10.1128/JB.183.19.5725-5732.2001
Chu, C., Su, L. H., Chu, C. H., Baucheron, S., Cloeckaert, A., and Chiu, C. H. (2005). Resistance to fluoroquinolones linked to gyrA and parC mutations and overexpression of acrAB efflux pump in Salmonella enterica serotype Choleraesuis. Microb. Drug Resist. 11, 248–253. doi: 10.1089/mdr.2005.11.248
Cloeckaert, A., and Chaslus-Dancla, E. (2001). Mechanisms of quinolone resistance in Salmonella. Vet. Res. 32, 291–300. doi: 10.1051/vetres:2001105
Cloeckaert, A., and Schwarz, S. (2001). Molecular characterization, spread and evolution of multidrug resistance in Salmonella enterica typhimurium DT104. Vet. Res. 32, 301–310. doi: 10.1051/vetres:20001126
Doublet, B., Praud, K., Bertrand, S., Collard, J. M., Weill, F. X., and Cloeckaert, A. (2008). Novel insertion sequence- and transposon-mediated genetic rearrangements in genomic island SGH1 of Salmonella enterica serovar Kentucky. Antimicrob. Agents Chemother. 52, 3745–3754. doi: 10.1128/AAC.00525-08
Giraud, E., Baucheron, S., and Cloeckaert, A. (2006). Resistance to fluoroquinolones in Salmonella: emerging mechanisms and resistance prevention strategies. Microbes Infect. 8, 1937–1944. doi: 10.1016/j.micinf.2005.12.025
Giraud, E., Baucheron, S., Virlogeux-Payant, L., Nishino, K., and Cloeckaert, A. (2013). Effects of natural mutations in the ramA locus on invasiveness of epidemic fluoroquinolone-resistant Salmonella enterica serovar Typhimurium isolates. J. Infect. Dis. 207, 794–802. doi: 10.1093/infdis/jis755
Hentschke, M., Christner, M., Sobottka, L., Apfelbacher, M., and Rohde, H. (2010). Combined ramR mutation and presence of a Tn1721-associated tet(A) variant in a clinical isolate of Salmonella enterica serovar Harad resistant to tigecycline. Antimicrob. Agents Chemother. 54, 1319–1322. doi: 10.1128/AAC.00993-09
Kehrenberg, C., Cloeckaert, A., Klein, G., and Schwarz, S. (2009). Decreased fluoroquinolone susceptibility in mutants of Salmonella serovars other than Typhimurium: detection of novel mutations involved in modulated expression of ramA and sax5. J. Antimicrob. Chemother. 64, 1175–1180. doi: 10.1093/jac/dkp347
Le Hello, S., Hendrikson, R. S., Doublet, B., Fisher, L., Nielsen, E. M., Whichard, J. M., et al. (2011). International spread of an epidemic population of Salmonella enterica serotype Kentucky ST198 resistant to ciprofloxacin. J. Infect. Dis. 204, 675–684. doi: 10.1093/infdis/jir409
Nikaido, E., Yamaguchi, A., and Nishino, K. (2008). AcrAB multidrug efflux pump regulation in Salmonella enterica serovar Typhimurium by RamA in response to environmental signals. J. Biol. Chem. 283, 22445–22453. doi: 10.1074/jbc.M804544200

FIGURE 1 | Mutations detected in the ramR-ramA region relative to the genome sequence of S. enterica serovar Kentucky strain CDC 191 (GenBank: ABEIO10000021).
Olliver, A., Vallé, M., Chaslus-Dancla, E., and Cloeckaert, A. (2005). Overexpression of the multidrug efflux operon acrEF by insertion activation with IS1 or IS10 elements in Salmonella enterica serovar typhimurium DT204 acrB mutants selected with fluoroquinolones. Antimicrob. Agents Chemother. 49, 289–301. doi: 10.1128/AAC.49.1.289-301.2005

Piddock, L. J. V. (2002). Fluoroquinolone resistance in Salmonella serovars isolated from humans and food animals. FEMS Microbiol. Rev. 26, 3–16.

Velge, P., Cloeckaert, A., and Barrow, P. (2005). Emergence of Salmonella epidemics: the problems related to Salmonella enterica serotype Enteritidis and multiple antibiotic resistance in other major serotypes. Vet. Res. 36, 267–288. doi: 10.1051vetres:2005005

Weill, F. X., Bertrand, S., Guessner, F., Baucheron, S., Cloeckaert, A., and Grimont, P. A. (2006). Ciprofloxacin-resistant Salmonella Kentucky in travelers. Emerg. Infect. Dis. 12, 1611–1612. doi: 10.3201/eid1210.060589

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received: 21 June 2013; accepted: 09 July 2013; published online: 31 July 2013.

Citation: Baucheron S, Le Hello S, Doublet B, Giraud E, Weill F-X and Cloeckaert A (2013) ramR mutations affecting fluoroquinolone susceptibility in epidemic multidrug-resistant Salmonella enterica serovar Kentucky ST198. Front. Microbiol. 4:213. doi: 10.3389/fmicb.2013.00213

This article was submitted to Frontiers in Antimicrobials, Resistance and Chemotherapy, a specialty of Frontiers in Microbiology.

Copyright © 2013 Baucheron, Le Hello, Doublet, Giraud, Weill and Cloeckaert. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) or licensor are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.