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1 **Highly drug-resistant *Salmonella* Kentucky ST198-X1 in the Mediterranean basin: a**
2 **microbiological study**

3

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17

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19

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23

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25

26

27 **SUMMARY (253)**

28 **Background**

29 *Salmonella* is a major food-borne pathogen found worldwide, which can cause life-
30 threatening infections. Ciprofloxacin and extended-spectrum cephalosporins (ESCs) are the
31 drugs of choice for severe *Salmonella* infections. We previously reported a ciprofloxacin-
32 resistant *S. enterica* serotype Kentucky strain (*Salmonella* Kentucky ST198-X1 CIP^R) that
33 emerged in Egypt and spread throughout Africa and the Middle East from 2002 to 2008.

34

35 **Methods**

36 Data for *Salmonella* Kentucky collected by the French national *Salmonella* laboratory
37 surveillance system from 2000 to 2011 and by two sites in Casablanca, Morocco, from 2003
38 to 2011 were analysed. Isolates displaying resistance to ESCs and/or with decreased
39 susceptibility to carbapenems were studied by *Xba*I pulsed-field gel electrophoresis and by
40 multilocus sequence typing. The mechanisms of resistance to antimicrobial drugs were
41 identified.

42

43 **Findings**

44 Isolations of *Salmonella* Kentucky ST198-X1 CIP^R have recently increased in frequency (376
45 isolates for 2009-2011 versus 200 for 2000-2008) in France, and the geographic area in which
46 infections occur has expanded to include the Indian subcontinent and South-East Asia. We
47 have observed multiple acquisitions of extended-spectrum β -lactamase (CTX-M-1, CTX-M-
48 15), plasmid-encoded cephalosporinase (CMY-2), or carbapenemase (OXA-48, VIM-2) genes
49 by *Salmonella* Kentucky ST198-X1 CIP^R isolates from the Mediterranean area since 2009.
50 Many of these highly drug-resistant *Salmonella* isolates are also resistant to most
51 aminoglycosides (*armA* gene) and to azithromycin (*mph(A)* gene).

52 **Panel: Research in context**

53

54 **Systematic review**

55 We searched PubMed for articles published up to January 30, 2013, with the search terms
56 “Salmonella” and “carbapenemases” or “carbapenems” or “NDM-1”. No language
57 restrictions were used. We identified only five studies describing various sporadic *Salmonella*
58 spp. isolates resistant to carbapenems. None of these isolates was also resistant to
59 fluoroquinolones. Two of these studies concerned isolates resistant to carbapenems due to
60 mechanisms other than carbapenemase production: two clinical isolates of serotype Wien,
61 which had lost a porin and produced cephamycinase CMY-4, in Tunisia in 2001, and one
62 clinical isolate of serotype Typhimurium, which had lost two porins and produced
63 cephamycinase CMY-2, in Taiwan in 2010.^{20,21} The first carbapenemase producer was a
64 clinical isolate of serotype Cubana, which produced carbapenemase KPC-2 and was obtained
65 in the US in 1998.^{22,23} In 2011 and 2012, the first two clinical isolates of NDM-1-producing
66 *Salmonella* of serotypes Senftenberg and Westhampton were reported, isolated from patients
67 returning from India.^{24,25} In 2012, the first carbapenemase (VIM-1)-producing *S. enterica*
68 isolates were isolated from food animals in Europe.²⁶

69

70 **Interpretation**

71 This report confirms the emergence of highly drug-resistant *Salmonella* Kentucky, a potential
72 risk to Public Health, in the Mediterranean basin. This ciprofloxacin-resistant *Salmonella*
73 Kentucky ST198-X1 strain, which is increasingly frequently isolated, has recently acquired β -
74 lactamases (CTX-M ESBLs, CMY-2 AmpC, and VIM-2 and OXA-48 carbapenemases)
75 encoding resistance to extended-spectrum cephalosporins and carbapenems. Further efforts
76 are required from national and international health, food and agricultural authorities, to

77 control the spread of this highly drug-resistant strain in humans and food animals. We
78 propose the inclusion of ciprofloxacin-resistant *Salmonella* Kentucky as a new target strain, in
79 national programmes for the control of *Salmonella* in poultry.

80

81 **Funding**

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83 the French Government “Investissement d'Avenir” programme.

84

85

86 **Box**

87 On October 14th 2009, a 69-year-old woman living in western France was hospitalised for an
88 upper respiratory tract infection, fever and diarrhoea. The symptoms began during a holiday
89 in Egypt (September 19th to October 2nd, 2009). The patient's clinical history included a high-
90 grade follicular lymphoma in 2003, treated by chemotherapy and allogeneic transplantation,
91 in remission since 2005. The patient had had repetitive respiratory infections due to sequellar
92 hypogammaglobulinaemia. Her last hospital admission was for right hemicolectomy surgery
93 in 2007. One day after admission, a *S. enterica* serotype Saintpaul isolate that was resistant to
94 ampicillin, susceptible to ESCs and had intermediate resistance to imipemem (MIC 3 mg/L)
95 was obtained from blood and stool cultures (Tables 2 & 3). Treatment with 1 g/day
96 ciprofloxacin was administered for 10 days. The patient was given a blood transfusion (two
97 units) and an intravenous polyclonal immunoglobulin perfusion and rapidly recovered. One
98 month later, the patient presented a new episode of febrile bronchial and diarrhoeal infection,
99 which was treated with 1 g/d ceftriaxone for five days. No bacteriological testing was
100 performed and the patient recovered slowly, with persistent digestive disorders. A new stool
101 culture was performed on December 16th 2009, and was positive for *Salmonella* Kentucky
102 CIP^R, resistant to ESCs, cotrimoxazole and azithromycin, but susceptible to imipenem
103 (Tables 2 & 3). No antimicrobial agents were given, but a series of stool samples was
104 collected over time and cultured, to follow the elimination of the *Salmonella* strains.
105 *Salmonella* Kentucky CIP^R was isolated in January 2010 and January 2011 (Tables 2 & 3);
106 additional stool cultures for *Salmonella* in March and April 2011 were also positive (isolates
107 not sent to FNRC-Salm), despite the patient being free from digestive disorders.

108

109

110 INTRODUCTION

111 Antimicrobial drug-resistant bacteria are a serious challenge for the clinical care of patients
112 and for Public Health in the 21st century.¹ The Gram-negative “superbugs”, such as those
113 resistant to extended-spectrum cephalosporins (ESCs) due to the production of either
114 extended-spectrum β -lactamases (ESBLs) or cephamycinases (AmpC), seem to have now
115 eclipsed Gram-positive “superbugs” (i.e., methicillin-resistant *Staphylococcus aureus* and
116 vancomycin-resistant *Enterococcus* spp). Furthermore, the recent emergence of
117 Enterobacteriaceae resistant to all β -lactam antibiotics, including ESCs and carbapenems, is
118 of particular concern, because carbapenems are, in many cases the last option available for
119 treating serious infection with ESC-resistant Gram-negative bacteria. Indeed, the development
120 pipeline for new antimicrobial drugs with bactericidal activity against Gram-negative bacteria
121 has now run dry.^{2,3}

122
123 In a 2004 report entitled “Bad Bugs, No Drugs”, the Infectious Diseases Society of America
124 (IDSA) imagined a catastrophic scenario with an explosive epidemic of 220,000 cases and
125 1,730 deaths caused by a multidrug-resistant non-typhoidal *Salmonella*, resistant, in
126 particular, to both ESCs and fluoroquinolones. This choice was based on the following
127 observations (i) *Salmonella* is a prevalent zoonotic agent causing an estimated 1.7 million
128 infections, resulting in 2,800 deaths per year in high-income regions of North America in
129 2006,⁴ (ii) *Salmonella* can cause major food-borne outbreaks, such as that in the US in 1994
130 associated with manufactured ice cream contaminated with *Salmonella enterica* serotype
131 Enteritidis, which caused sickness in an estimated 224,000 people,⁵ (iii) fluoroquinolones,
132 including ciprofloxacin, and ESCs are the drugs of choice for treating severe *Salmonella*
133 infections and for people at risk of such infections (infants, the elderly and

134 immunocompromised patients), and (iv) infections with drug-resistant *Salmonella* are
135 associated with higher morbidity and mortality.⁶
136
137 We previously reported the international emergence of a multidrug-resistant *S. enterica*
138 serotype Kentucky (*Salmonella* Kentucky) strain, identified as being multilocus sequence
139 type (MLST) ST198 and as belonging to *Xba*I pulsed-field gel electrophoresis (PFGE) cluster
140 X1.⁷ *Salmonella* Kentucky ST198-X1 isolates were resistant to several antimicrobial drugs,
141 including ciprofloxacin (minimal inhibitory concentration [MIC] \geq 4 mg/L), which is a very
142 unusual resistance trait in *Salmonella*.^{8,9} The first ciprofloxacin-resistant *Salmonella*
143 Kentucky (*Salmonella* Kentucky CIP^R) to be identified was isolated from a French tourist
144 who visited Egypt in 2002. From then until 2008, the *Salmonella* surveillance systems in
145 France, England, and Denmark detected 489 cases of infection with this strain in people who
146 had travelled to or stayed in Africa or the Middle East.⁷ Hospitalisation was more frequent
147 among patients infected with CIP^R Kentucky (mean age, 36 years) than among those infected
148 with Kentucky strains susceptible to ciprofloxacin.⁷
149
150 All *Salmonella* Kentucky CIP^R isolates in our survey were susceptible to ESCs. However, one
151 case report described a Belgian traveller infected with *Salmonella* Kentucky CIP^R during a
152 trip to Libya in 2005, who required treatment with meropenem due to ESC resistance (CTX-
153 M-1 ESBL production) after multiple treatment failures for a severe infection.¹⁰
154 The aim of this study was to monitor recent trends in the global epidemiology and
155 antimicrobial resistance of the *Salmonella* Kentucky ST198-X1 CIP^R strain. The work was
156 conducted in parallel in France, where this infection occurred mostly in travellers or migrants,
157 and in Morocco, where most of the French travellers or migrants had acquired the infection.

158 This study identified highly drug-resistant (HDR) isolates, present in both France and
159 Morocco since 2009. These CIP^R isolates acquired in the Mediterranean area produce various
160 carbapenemases, cephamycinase, or ESBLs. This report indicates that *Salmonella* has taken a
161 major step towards panresistance and suggests that the catastrophic scenario imagined by the
162 IDSA might become all too real in the near future.
163

164 **MATERIALS & METHODS**

165

166 **Data for human *Salmonella* infections**

167 *France*

168 We used data from the French National Reference Centre for *Salmonella* (FNRC-Salm),
169 established since 1947. During the 2000s, the FNRC-Salm network included a stable number
170 of approximately 1,400 hospital and private clinical laboratories. In 2008, an unpublished
171 survey of all French clinical laboratories ($n=3,375$, response rate of 95%) estimated that about
172 65% of all human *Salmonella* isolates in France were reported to the FNRC-Salm. Basic
173 epidemiological data (date and site of isolation, sex and age of the patient, and international
174 travel) were recorded for each isolate. From 2000 to 2011, 128,836 serotyped *Salmonella*
175 isolates were registered at the FNRC-Salm, including 954 non-repeated *Salmonella* Kentucky
176 isolates (0.7% of all *Salmonella* isolates).

177

178 *Morocco*

179 We used 2003-2011 data from two sites in Casablanca, the largest city in Morocco. The first
180 site was the Microbiology Laboratory of the University Hospital Centre Ibn Rochd (UHCIR),
181 Casablanca, a 1,700-bed teaching hospital. The second site was the Pasteur Institute of
182 Morocco (PIM), which receive clinical strains of *Salmonella* for serotyping from private
183 laboratories. Between 2003 and 2011, 226 *Salmonella* isolates were obtained and serotyped,
184 including 30 non-repeated *Salmonella* Kentucky isolates (12.8% of all *Salmonella* isolates).

185

186 **Microbiological investigations**

187 *Bacterial isolates*

188 All but two (which could not be subcultured) of the 954 *Salmonella* Kentucky isolates
189 obtained from humans between 2000 and 2011 in France were included in this study. Thirty
190 (26 from UHCIR and 4 from PIM) *Salmonella* Kentucky isolates collected from humans in
191 Casablanca, Morocco between 2003 and 2011 were also studied. One additional isolate from
192 the FNRC-Salm was studied: one of serotype Saintpaul isolated from a patient co-infected
193 with *Salmonella* Kentucky in 2009.

194

195 *Antimicrobial susceptibility testing*

196 Antimicrobial susceptibility testing (AST) was performed on all *Salmonella* isolates, by the
197 disk diffusion method with a panel of 32 antimicrobial agents (Bio-Rad, Marnes-La-Coquette,
198 France).⁷ The MICs of ceftriaxone, ceftazidime, imipenem, ertapenem, meropenem,
199 ciprofloxacin, azithromycin, colistin, and tigecycline were determined by Etests (AB Biodisk,
200 Solna, Sweden). Results were interpreted with the Antibiogram Committee of the French
201 Society for Microbiology (CA-SFM) (www.sfm-microbiologie.org/) breakpoints. In
202 particular, susceptible isolates were defined as having a MIC ≤ 0.5 mg/L for ciprofloxacin,
203 and resistant isolates were defined as having a MIC > 1 mg/L for ciprofloxacin, regardless of
204 isolate source (i.e., intestinal or extraintestinal). Isolates were defined as highly drug-resistant
205 if they were resistant to at least four antibiotic classes, including both fluoroquinolones (i.e.,
206 ciprofloxacin) and ESCs (i.e., ceftriaxone and/or ceftazidime).

207

208 *Molecular typing*

209 PulseNet standard pulsed-field gel electrophoresis (PFGE) of *Xba*I-digested chromosomal
210 DNA and multilocus sequence typing (MLST) were performed as previously described.⁷

211

212 *Determination of resistance mechanisms*

213 The presence of beta-lactam resistance genes (*bla*_{TEM}, *bla*_{SHV}, *bla*_{OXA-1} group, *bla*_{CMY}, *bla*_{CTX-}
214 *M*, *bla*_{OXA-48}, *bla*_{VIM}, *bla*_{NDM}, and *bla*_{KPC}), plasmid-mediated quinolone resistance genes, (*qnrA*,
215 *qnrB*, *qnrS*, *qnrD*, *aacA4-cr* (also known as *aac(6')-Ib-cr*) and *qepA*), macrolide resistance
216 genes (*ermA*, *ermB*, *ermC*, *mph(A)*, *ereA*, *ereB*, *mrsA*, *mrsB*, *mefA*, and *mefE*),
217 aminoglycoside resistance genes (*armA*, *rmtA*, *rmtB*, *rmtC*, *rmtD*, and *npmA*), class 1 integron
218 gene cassettes and *Salmonella* genomic island 1 (SGI1) was assessed by PCR, as previously
219 described.^{7,11-14}

220

221 The quinolone resistance-determining region (QRDR) of *gyrA*, *gyrB*, *parC* and *parE*
222 (encoding subunits of the DNA gyrase and the topoisomerase IV) was sequenced, as
223 previously described.⁷ The nucleotide and deduced amino-acid sequences were analysed and
224 compared with sequences available from the National Center for Biotechnology Information
225 website (<http://www.ncbi.nlm.nih.gov>).

226

227 We assessed resistance transfer by mating, with ESBL, cephamycinase and carbapenemase
228 producers, using liquid and solid media, with *E. coli* K-12 BM14 resistant to sodium azide as
229 the recipient strain. Transconjugants were selected on Drigalski agar (Bio-Rad) supplemented
230 with ceftriaxone (4 mg/L), ceftazidime (16 mg/L), or imipenem (3 mg/L) plus sodium azide
231 (500 mg/L). Three *E. coli* transconjugants were arbitrarily selected in each experiment. We
232 used S1 nuclease treatment and PFGE to determine the sizes of bacterial plasmids accurately,
233 and PCR-based replicon typing analysis was performed, as previously described.¹⁵

234

235 **RESULTS**

236

237 **Occurrence of *Salmonella* Kentucky CIP^R in humans**

238 *France*

239 Of the 497 isolates of *Salmonella* Kentucky obtained in France between 2000 and 2008, 200
240 (40.2%) were resistant to ciprofloxacin (previously reported in reference 7). For the period
241 2009-2011, 376 (82.6%) of the 455 *Salmonella* Kentucky tested were CIP^R (Figure). This
242 near doubling of the number of *Salmonella* Kentucky CIP^R isolates obtained, in a third of the
243 time, with a stable network of laboratories, against a backdrop of a general decrease in the
244 number of isolations of *Salmonella* ($\approx 11,000$ clinical isolates received per year during the
245 period 2000-2008 vs $\approx 10,000$ during the period 2009-2011), indicates that this *Salmonella*
246 Kentucky CIP^R strain continued to circulate and spread.

247

248 Travel information was available for 371 patients (64.5%) infected with CIP^R Kentucky
249 during the period 2000-2011 (Table 1). Of these 371 patients, 338 (91.1%) had travelled
250 internationally in the 15 days before the onset of illness, whereas the remaining 33 patients
251 had not. Most of the patients seen between 2002 and 2005 had travelled to North-East or East
252 Africa. Since 2006, patients have been reporting travel to North-East and East Africa, North
253 Africa, West Africa, and the Middle East. Since 2009, the area of infection has extended to
254 include India.

255

256

257

258 *Morocco*

259 Of the 30 clinical isolates of *Salmonella* Kentucky obtained in Casablanca between 2003 and
260 2011, 19 (63.3%) were CIP^R. The first *Salmonella* Kentucky CIP^R isolate was obtained in
261 2006 and the annual number of isolates obtained has since fluctuated between one and eight
262 (2007, *n*=1; 2008, *n*=5; 2009, *n*=2; 2010, *n*=8; 2011, *n*=2).

263

264 **Recent trends in the antimicrobial resistance of *Salmonella* Kentucky**

265 *Emergence of CIP^R-ESC^R Salmonella Kentucky in the Mediterranean area since 2009*

266 Based on the FNRC-Salm 2000-2011 data, the first *Salmonella* Kentucky isolate resistant to
267 ESCs (ESC^R) was isolated in 2009 (Figure). From 2009 to 2011, 10 *Salmonella* Kentucky
268 ESC^R isolates (2.2% of all *Salmonella* Kentucky during this period) in total were identified:
269 six were susceptible to ciprofloxacin and had a cephamycinase-like profile and four were
270 resistant to both ciprofloxacin and ESCs. The four CIP^R-ESC^R isolates were acquired in
271 Algeria, Morocco, Egypt, and Turkey (Tables 2 & 3). They produced the cephamycinase
272 CMY-2 (*n*=2) or the ESBLs CTX-M-1 (*n*=1) or CTX-M-15 (*n*=1), encoded by 90 to 200 kb
273 plasmids from the IncI1, IncL/M or IncA/C incompatibility groups.

274

275 *Two Salmonella strains producing carbapenemase OXA-48 in a traveller returning from*

276 *Egypt in 2009*

277 One of the four *Salmonella* Kentucky CIP^R-ESC^R isolates detected since 2009, #09-9322 (see
278 previous section), was isolated from a patient co-infected with another serotype of
279 *Salmonella*, Saintpaul, which produced a carbapenamase not present in #09-9322, but
280 subsequently found in one of the three sequential *Salmonella* Kentucky isolates from the same
281 patient (box and Tables 2 & 3). The serotype Saintpaul isolate was found to contain the
282 *bla*_{OXA-48} carbapenemase gene on an IncL/M plasmid of about 70 kb. The three sequential

283 *Salmonella* Kentucky CIP^R isolates belonged to the ST198-X1 strain, and carried the *gyrA*
284 and *parC* mutations previously encountered in Kentucky isolates from Egypt and West
285 Africa.⁷ The three isolates also contained the phosphotransferase *mph(A)* gene conferring
286 high-level resistance to azithromycin. The three isolates presented different resistance
287 profiles, due to the acquisition/loss of various R plasmids and also, probably, due to IS26
288 rearrangements of the SGI1.⁷ The first isolate was resistant to ESCs due to the presence of the
289 *bla*_{CMY-2} gene, whereas the most recent isolate, collected one year later, contained the *bla*_{OXA-}
290 ₄₈ carbapenemase gene. All four isolates were susceptible to colistin and tigecycline.

291

292 *Highly drug-resistant Salmonella Kentucky isolates producing VIM-2 in Morocco in 2010*

293 Five of the 30 *Salmonella* Kentucky isolates obtained in Casablanca, Morocco, between 2003
294 and 2011 (16.6%) were ESC^R. These five *Salmonella* Kentucky ST198-X1 ESC^R-CIP^R
295 isolates had decreased susceptibility to imipenem (MIC range, 1-3 mg/L). They all contained
296 the *bla*_{VIM-2} gene within In58,¹⁶ itself carried on a 30-kb plasmid. Three isolates originated
297 from patients hospitalised in three different reanimation wards (one blood culture, two urine
298 cultures) of the UHCIR during January 2010, the other two isolates being obtained from stool
299 cultures performed at the PIM in January and August 2010.

300

301

302 **DISCUSSION**

303 We report a new step towards pan-antimicrobial resistance in *Salmonella*, a major foodborne
304 pathogen found worldwide, which can cause life-threatening infections. The *Salmonella*
305 Kentucky ST198-X1 isolates reported here are resistant to both fluoroquinolones and ESCs
306 (except for the OXA-48-producing strain), and some also display full or intermediate
307 resistance to carbapenems. Many are also resistant to most aminoglycosides (*armA* gene) and
308 to azithromycin (*mph(A)* gene). *Salmonella* Kentucky ST198-X1 is a particularly successful
309 strain that has accumulated various chromosomal resistance determinants since the mid-
310 1990s, with the integration of the *Salmonella* genomic island 1 (encoding resistance to
311 multiple antimicrobial drugs, including amoxicillin, gentamicin, and sulfonamides), followed
312 by cumulative mutations in the *gyrA* and *parC* genes, leading to resistance to nalidixic acid,
313 and then to ciprofloxacin, in 2002. This strain was mostly identified in Egypt before 2005,⁷
314 but has since spread rapidly throughout Africa and the Middle East. The slight decrease in
315 isolation rates for this strain in 2011 probably resulted from the “Arab Spring”, which may
316 have discouraged travel to the area in which this strain is endemic. Thus, 150 *Salmonella*
317 Kentucky CIP^R isolates were obtained at the FNRC-Salm in 2012 (data not shown), a number
318 similar to that obtained in 2010. The *Salmonella* Kentucky CIP^R strain was first identified in
319 the Indian subcontinent in 2009, and a pattern of current spread across Asia is also suggested
320 by the isolation of two *Salmonella* Kentucky CIP^R isolates from French patients reporting
321 travel to Vietnam and Indonesia in 2012 (data not shown). As the geographic spread of this
322 strain has been predicted by a French surveillance system, it may be partially biased by the
323 preferred destinations of French travellers and particular migrant populations with historical
324 links to France. Where possible, these data should be confirmed by local studies.

325

326 This epidemic was previously associated with a livestock (autochthonous poultry) reservoir of
327 this *Salmonella* Kentucky CIP^R strain in Africa. It was suggested that the common use of
328 fluoroquinolones in poultry and the lack of both laboratory-based surveillance of infections
329 and control measures in the countries in which this strain circulates played a role in the rapid
330 spread of this strain after 2002.⁷ A survey performed on 92 poultry farms in Sudan, East
331 Africa, in 2008 revealed that enrofloxacin, a fluoroquinolone, was commonly added to the
332 drinking water on 14% of the farms surveyed.¹⁷ Both here and in our previous study, ~11% of
333 the patients reported no history of travel outside Europe, suggesting that these infections may
334 have resulted from the consumption of contaminated foods or secondary contamination in
335 Europe. Indeed, contaminated spices from North Africa have previously been identified in
336 France and the US.⁷ This strain also seems to have become established in some European
337 flocks, another major source of concern. In 2010, *Salmonella* Kentucky CIP^R isolates were
338 found in turkey meat products in Germany and in turkey meat or flocks in Poland.^{18,19} One of
339 the *Salmonella* Kentucky CIP^R isolates recovered from a flock in Poland in 2010 was also
340 resistant to ESCs, due to the production of a CTX-M ESBL.¹⁹

341

342 The diversity of the recently acquired β -lactamases (CTX-M ESBLs, CMY-2 AmpC, and
343 VIM-2 and OXA-48 carbapenemases) suggests that the increasingly common *Salmonella*
344 Kentucky ST198-X1 CIP^R strain has been “collecting” genes for resistance to ESCs and
345 carbapenems. Resistance to carbapenems is otherwise extremely rare in *Salmonella* spp.
346 (panel). The simultaneous presence of ESCs and carbapenem determinants (CMY-2 and
347 OXA-48) was even documented in this study in *Salmonella* Kentucky ST198-X1 CIP^R
348 isolated from a single patient.

349

350 A similar scenario, but without the acquisition of carbapenemase, occurred in Taiwan for *S.*
351 *enterica* serotype Choleraesuis (*Salmonella* Choleraesuis), a serotype acquired from pigs and
352 associated with extraintestinal infection in humans.⁸ The first CIP^R isolates appeared in 2000
353 and, in the third quarter of 2001, 60% of the *Salmonella* Choleraesuis isolates from humans
354 were CIP^R.⁸ This trait was attributed to the use of enrofloxacin in pigs. Additional resistance
355 to ESCs mediated by the cephamycinase CMY-2 has appeared since 2002.²⁶ This enzyme is
356 frequent in many *Salmonella* serotypes, including Newport in the US, where its emergence
357 has been associated with the use of ceftiofur, an ESC licensed for use in cattle, pigs, and other
358 food animals.²⁷ Unlike *Salmonella* Choleraesuis CIP^R and Newport ESC^R, *Salmonella*
359 Kentucky ST198-X1 CIP^R is not restricted to a single country or region, rendering control
360 measures in livestock more difficult.

361

362 We found that *Salmonella* Kentucky ST198-X1 had a broad geographic distribution,
363 overlapping with that of certain plasmid-borne carbapenemases, such as OXA-48 and
364 VIM.^{12,16} This makes it likely that carbapenemase-producing *Salmonella* will become more
365 frequent in the Mediterranean area in the near future, particularly if such carbapenemase
366 producers become established in livestock, as previously observed for ESBL- and
367 cephamycinase-producing *Salmonella* in industrialised countries.²⁷⁻²⁹ Indeed, isolation of the
368 VIM-1-producing *S. enterica* serotype Infantis from two pig farms and one poultry farm in
369 Germany was reported in 2012.²⁵

370

371 Another issue is the difficulty of phenotypic detection for several carbapenemase producers.¹²
372 This problem is particularly difficult for OXA-48, which weakly hydrolyses carbapenems but
373 not ESCs in the absence of additional ESBL and/or cephamycinase and permeability defects.
374 Indeed, carbapenem MICs were found to be low for the carbapenemase producers. Two

375 isolates, one OXA-48-positive and one VIM-2-positive Kentucky isolate, were even classified
376 as susceptible to the three carbapenems tested, on the basis of the CLSI or CA-SFM
377 breakpoints. The use of rapid diagnostic tests, such as the recently developed Carba NP test,
378 would facilitate the early detection of carbapenemase producers.³⁰

379

380 In conclusion, this report highlights the recent emergence of HDR *Salmonella* and the need to
381 screen *Salmonella* isolated either from humans or food-producing animals for carbapenemase
382 producers. The main types of carbapenemase (KPC, OXA-48, NDM, VIM) have now been
383 identified in *Salmonella*, and half of these enzymes have been found in the *Salmonella*
384 Kentucky ST198-X1 strain. National and international health, food and agricultural
385 authorities need to recognise rapidly the potential risk to Public Health posed by *Salmonella*
386 Kentucky ST198-X1 CIP^R, so that *Salmonella* Kentucky CIP^R can be included, as a new
387 targeted strain, in current national programmes for the control of *Salmonella* in poultry.

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389 **AUTHOR CONTRIBUTIONS**

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391 Conceived and designed the experiments: SLH and FXW. Performed the experiments: DH,
392 LS, DE, VG. Contributed reagents/materials/analysis tools: BB, KZ. Analysed the data: SLH
393 and FXW. Wrote the paper: SLH and FXW. Reviewed, critiqued and offered comments on
394 the text: DH, BB, KZ.

395

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397

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409 **CONFLICTS OF INTEREST**

410 All authors declare that they have no competing interests or conflicts of interest.

411

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Table 1: Countries visited by patients infected with *S. enterica* serotype Kentucky resistant to ciprofloxacin in the 15 days before the onset of illness (data from the French National Reference Centre for *Salmonella*)

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| Country | 2002-2005 | 2006-2008 | 2009-2011 | Total |
|----------------------|-----------|------------|------------|------------|
| Africa | | | | |
| Not specified | | 3 | 2 | 5 |
| Algeria | | 9 | 60 | 69 |
| Cameroon | | 2 | 1 | 3 |
| Djibouti | | 1 | 2 | 3 |
| Egypt | 11 | 11 | 7 | 29 |
| Ethiopia | | | 2 | 2 |
| Ivory Coast | | | 6 | 6 |
| Kenya | 2 | 1 | | 3 |
| Libya | | 2 | 1 | 3 |
| Mauritania | | | 2 | 2 |
| Morocco | | 69 | 78 | 147 |
| Senegal | | | 7 | 7 |
| Sudan | 1 | | | 1 |
| Tanzania | 1 | 2 | | 3 |
| Tunisia | | 5 | 21 | 26 |
| Middle East | | | | |
| Iran | | 1 | | 1 |
| Iraq | | | 1 | 1 |
| Israel | | | 1 | 1 |
| Lebanon | | 2 | 2 | 4 |
| Saudi Arabia | | 1 | | 1 |
| Syria | | | 1 | 1 |
| Turkey | | 2 | 2 | 4 |
| Asia | | | | |
| India | | | 8 | 8 |
| North America | | | | |
| Canada | | | 1 | 1 |
| Europe | | | | |
| France [†] | | 6 | 27 | 33 |
| Croatia | | | 1 | 1 |
| Greece | | | 1 | 1 |
| Spain | | | 5 | 5 |
| Total | 15 | 117 | 239 | 371 |

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[†]France is indicated as the country of infection in cases of notification of an absence of international travel for up to 2 months before the onset of symptoms

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Table 2: Antimicrobial drug-resistant *Salmonella* isolates included in this study

| Isolate | Serotype | Date of isolation | Source ^a | Country of infection | Antimicrobial resistance profiles ^b | MLST/ PFGE | SGII | MIC (mg/L) ^c | | | | | | | | | |
|--|-----------|-------------------|---------------------|----------------------|--|------------|------|-------------------------|------|------|-------|-------|-------|-----|------|------|--|
| | | | | | | | | Cro | Caz | IMP | ETP | MEM | CIP | Azi | CST | TGC | |
| Isolates recovered through the French national <i>Salmonella</i> surveillance system | | | | | | | | | | | | | | | | | |
| 09-8391 | Kentucky | 02 Nov 09 | F, 65y, stool, H | Morocco | A Cro Caz Fox Nal CIP | ST198/X1e | + | 64 | 48 | 0.38 | 0.064 | 0.064 | 32 | 8 | 0.25 | 0.5 | |
| 09-9322 | Kentucky | 16 Dec 09 | F, 70y, stool, N | Egypt | A Cro Caz Fox S Sp K T N Chl Sul Tmp Nal CIP Azi | ST198/X1w | + | 24 | 64 | 0.5 | 0.023 | 0.047 | 12 | 128 | 0.19 | 0.38 | |
| 10-0720 | Kentucky | 31 Jan 10 | F, 25y, stool, H | Turkey | A Cro S Sp G Sul Te Nal CIP | ST198/X1b | + | 64 | 4 | 0.25 | 0.016 | 0.064 | 16 | 4 | 0.25 | 1 | |
| 10-5456 | Kentucky | 13 Aug 10 | F, 7y, stool, H | Algeria | A Cro Caz S Sp K T N G Ak Chl Sul Tmp Nal Cip Azi | ST198/X1a | + | >256 | >256 | 0.38 | 0.023 | 0.047 | 12 | 32 | 0.25 | 0.5 | |
| Isolates recovered through the survey in Casablanca, Morocco | | | | | | | | | | | | | | | | | |
| 10-1923 | Kentucky | 04 Jan 10 | M, 25y, urine, H | Morocco | A Cro Caz Fox IMP* S Sp K T G Sul Te Nal CIP | ST198/X1j | + | 256 | 192 | 3 | 1.5 | 0.25 | 12 | 4 | 0.25 | 1 | |
| 10-1922 | Kentucky | 07 Jan 10 | M, 20y, blood, H | Morocco | A Cro Caz Fox IMP* S Sp K T N G Ak Is Sul Te Nal CIP | ST198/X1m | + | 24 | 24 | 3 | 0.5 | 0.25 | 12 | 6 | 0.25 | 1 | |
| 10-1924 | Kentucky | 21 Jan 10 | M, 92y, urine, H | Morocco | A Cro Caz Fox IMP* S Sp K T N G Sul Te Nal CIP | ST198/X1j | + | 256 | 96 | 3 | 3 | 1 | 16 | 6 | 0.25 | 1 | |
| 10-1925 | Kentucky | 24 Jan 10 | M, >18y, stool, N | Morocco | A Cro Caz Fox S Sp K T N G Ak Is Sul Te Nal CIP | ST198/X1j | + | 32 | 24 | 1 | 0.19 | 0.25 | 8 | 4 | 0.25 | 0.75 | |
| 10-1926 | Kentucky | 25 Aug 10 | M, >18y, stool, N | Morocco | A Cro Caz Fox IMP* S Sp K T G Sul Te Nal CIP | ST198/X1j | + | >256 | 48 | 2 | 0.75 | 1 | 8 | 4 | 0.5 | 1 | |
| Isolates recovered from a single patient ^d | | | | | | | | | | | | | | | | | |
| 09-7981 | Saintpaul | 16 Oct 09 | F, 69y, blood, H | Egypt | A IMP* | ST1670 | - | 1.5 | 2 | 3 | 1 | 1.5 | 0.023 | 2 | 0.25 | 0.38 | |
| 10-0305 | Kentucky | 07 Jan 10 | F, 70y, stool, N | Egypt | K Chl Tmp Nal CIP Azi | ST198/X1w | + | 0.094 | 0.50 | 0.38 | 0.008 | 0.023 | 12 | 48 | 0.19 | 0.5 | |
| 11-0664 | Kentucky | 28 Jan 11 | F, 71y, stool, N | Egypt | A Nal CIP Azi | ST198/X1w | + | 0.125 | 0.25 | 0.75 | 0.5 | 0.19 | 8 | 32 | 0.50 | 0.50 | |

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^aF, female; M, male; y, years (age); H, hospitalised; N, not hospitalised

^bA, amoxicillin; Cro, ceftriaxone; Caz, ceftazidime; Fox, cefoxitin; IMP, imipenem (*, intermediate resistance according to CA-SFM, resistance according to CLSI); ETP, ertapenem; MEM, meropenem; S, streptomycin; Sp, spectinomycin; K, kanamycin; T, tobramycin; N, netilmicin; G, gentamicin; Ak, amikacin; Is, isepamicin; Chl, chloramphenicol; Sul, sulfamethoxazole; Tmp, trimethoprim; Nal, nalidixic acid; Cip, ciprofloxacin; Azi, azithromycin; CST, colistin; TGC, tigecycline

^cCA-SFM and CLSI (M100 S22) breakpoints for carbapenems: IMP and MEM (CA-SFM, S ≤ 2 mg/L, R > 8 mg/L; CLSI, S ≤ 1 mg/L, R ≥ 4 mg/L); ETP (CA-SFM, S ≤ 0.5 mg/L, R > 1 mg/L; CLSI, S ≤ 0.5 mg/L, R ≥ 2 mg/L). For categorisation, Etest MICs between standard dilutions were rounded up to the next two-fold dilution

^dIsolate 09-9322 recovered by the French national surveillance system was also isolated from this single patient who had travelled to Egypt

515 **Table 3:** Mechanisms of resistance to antimicrobial drugs in the antimicrobial drug-resistant *Salmonella* isolates included in this study
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| Isolate | Serotype | Main determinants of resistance to: (incompatibility group, plasmid size) | | | | | | Class 1 integrons | |
|--|-----------|--|--|--------------------|----------|------|---------------------|-----------------------------|---|
| | | ESCs | Carbapenems | Ciprofloxacin | | | Azi | | Aminoglycosides |
| | | | | GyrA | ParC | PMQR | | | |
| Isolates recovered through the French national <i>Salmonella</i> surveillance system | | | | | | | | | |
| 09-8391 | Kentucky | <i>bla</i> _{CMY-2} (IncII, 90 kb) | - | Ser83Phe, Asp87Asn | Ser80Ile | | | - | - |
| 09-9322 | Kentucky | <i>bla</i> _{CMY-2} (IncII, 90 kb; IncA/C, 200 kb) | - | Ser83Phe, Asp87Gly | Ser80Ile | | <i>mph</i> (A) (NT) | | 1.8 kb (<i>dfrA12</i> , <i>aadA2</i>) |
| 10-0720 | Kentucky | <i>bla</i> _{CTX-M-1} (IncII, 90 kb) | - | Ser83Phe, Asp87Asn | Ser80Ile | | - | | 1.5 kb (<i>aacA5</i> , <i>aadA7</i>) |
| 10-5456 | Kentucky | <i>bla</i> _{CTX-M-15} (IncL/M, 90 kb) | - | Ser83Phe, Asp87Asn | Ser80Ile | | <i>mph</i> (A) (NT) | <i>armA</i> (IncL/M, 90 kb) | 1.8 kb (<i>dfrA12</i> , <i>aadA2</i>) |
| Isolates recovered through the survey in Casablanca, Morocco | | | | | | | | | |
| 10-1923 | Kentucky | - | <i>bla</i> _{VIM-2} (UT, 30 kb) | Ser83Phe, Asp87Gly | Ser80Ile | | - | | 1.5 kb (<i>aacA5</i> , <i>aadA7</i>), 3 kb (<i>aacA7</i> , <i>bla</i> _{VIM-2} , <i>aacC1</i> , <i>aacA4</i>) |
| 10-1922 | Kentucky | - | <i>bla</i> _{VIM-2} (IncW, 30 kb) | Ser83Phe, Asp87Gly | Ser80Ile | | - | | 1.5 kb (<i>aacA5</i> , <i>aadA7</i>), 3 kb (<i>aacA7</i> , <i>bla</i> _{VIM-2} , <i>aacC1</i> , <i>aacA4</i>) |
| 10-1924 | Kentucky | - | <i>bla</i> _{VIM-2} (IncW) | Ser83Phe, Asp87Gly | Ser80Ile | | - | | 1.5 kb (<i>aacA5</i> , <i>aadA7</i>), 3 kb (<i>aacA7</i> , <i>bla</i> _{VIM-2} , <i>aacC1</i> , <i>aacA4</i>) |
| 10-1925 | Kentucky | - | <i>bla</i> _{VIM-2} (IncW) | Ser83Phe, Asp87Gly | Ser80Ile | | - | | 1.5 kb (<i>aacA5</i> , <i>aadA7</i>), 3 kb (<i>aacA7</i> , <i>bla</i> _{VIM-2} , <i>aacC1</i> , <i>aacA4</i>) |
| 10-1926 | Kentucky | - | <i>bla</i> _{VIM-2} (IncW) | Ser83Phe, Asp87Gly | Ser80Ile | | - | | 1.5 kb (<i>aacA5</i> , <i>aadA7</i>), 3 kb (<i>aacA7</i> , <i>bla</i> _{VIM-2} , <i>aacC1</i> , <i>aacA4</i>) |
| Isolates recovered from a single patient [‡] | | | | | | | | | |
| 09-7981 | Saintpaul | - | <i>bla</i> _{OXA-48} (IncL/M, 70 kb) | WT | WT | | | - | - |
| 10-0305 | Kentucky | - | - | Ser83Phe, Asp87Gly | Ser80Ile | | <i>mph</i> (A) (NT) | | 1.8 kb (<i>dfrA12</i> , <i>aadA2</i>) |
| 11-0664 | Kentucky | - | <i>bla</i> _{OXA-48} (NT) | Ser83Phe, Asp87Gly | Ser80Ile | | <i>mph</i> (A) (NT) | - | - |

517 NT, not transferable; UT, untypeable

518 [‡]Isolate 09-9322 recovered by the French national surveillance system was also isolated from this single patient who had travelled to Egypt.
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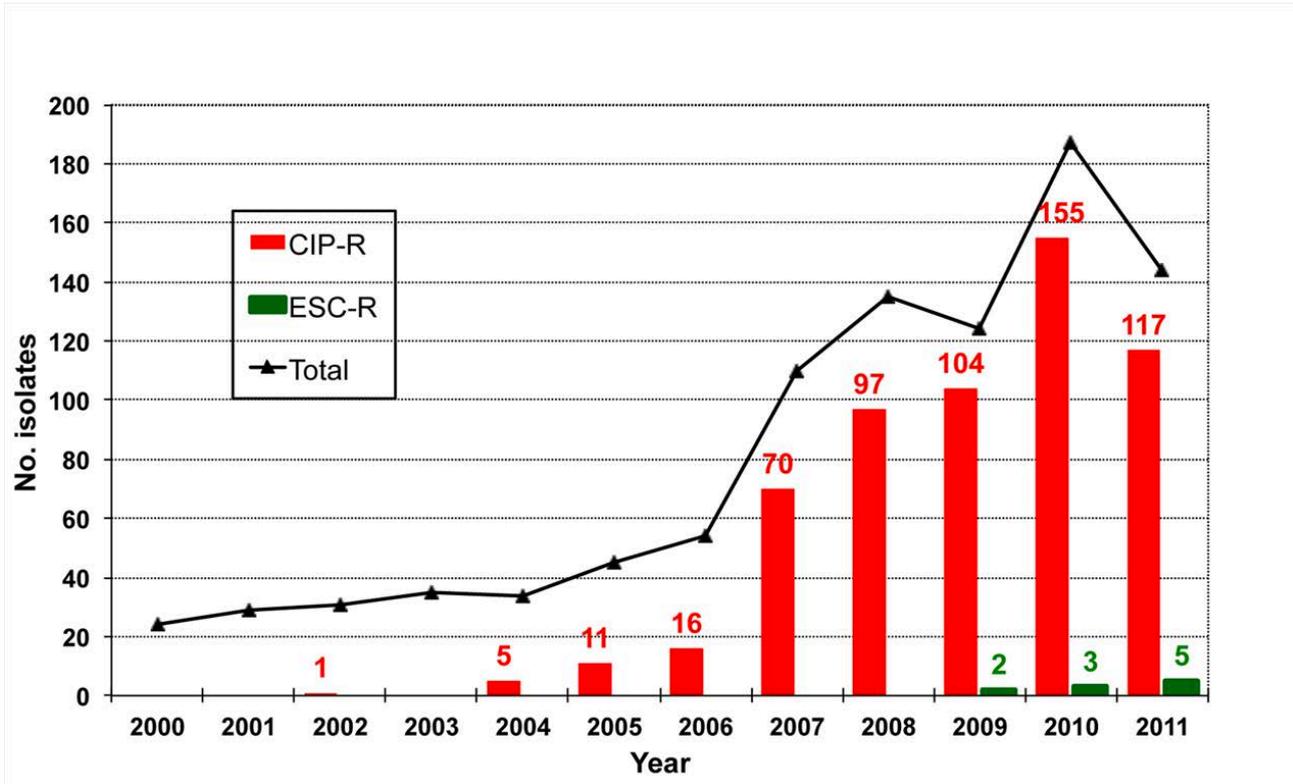


Figure 1. Human *S. enterica* serotype Kentucky isolates identified at the French National Reference Centre for *Salmonella* between 2000 and 2011

The total annual number of *S. enterica* serotype Kentucky isolates is indicated by a black triangle. The annual number of these isolates resistant to ciprofloxacin (CIP-R) is indicated in red, and that of isolates resistant to extended-spectrum cephalosporins (ESC-R) is shown in green. During this period, the total number of *Salmonella* spp. registered at the French National Reference Centre was 128,836 (2000, $n=12,883$; 2001, $n=12,601$; 2002, $n=11,775$; 2003, $n=10,472$; 2004, $n=10,589$; 2005, $n=11,439$; 2006, $n=10,154$; 2007, $n=8,124$; 2008, $n=10,378$; 2009, $n=9,947$; 2010, $n=9,405$; 2011, $n=11,069$).