

1 **Global dissemination patterns of common gene cassette arrays in class 1 integrons**

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Abbreviations: MGEs, mobile genetic elements; 5'-CS, 5'-conserved segment; 3'-CS, 3'-conserved segment; ISCRI, insertion sequence common region; HGT, horizontal gene transfer; orf, open reading frame.

27 **Summary**

28 Integrons are genetic elements that contain a site-specific recombination system able to
29 capture, express and exchange gene cassettes. Mobile integrons are widespread and
30 often confer resistance to multiple antibiotics, due to the expression of the arrays of
31 gene cassettes they carry. Although more than 300 cassette arrays have been described,
32 less than 10 array compositions prevail in the reports related with class 1 integrons.
33 These common arrays are found in a broad variety of hosts and environments,
34 highlighting the high level of horizontal dissemination of these elements among
35 bacterial populations and species. Clonal expansion also contributes to the current
36 prevalence of and inter-regional spread of integron-carrying bacterial species. Here we
37 review the dissemination pattern of common cassette arrays with a focus on the
38 bacterial species, the geographical dispersal pattern and the environments in which they
39 reside. Conserved arrays of gene cassettes are found in at least 74 countries and 72
40 species present in different environments. The factors governing the further spread and
41 population dynamics of these cassette arrays remain to be determined.

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61 **Introduction**

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63 Integrons are genetic elements that contain a site-specific recombination system able to
64 capture, express and exchange specific DNA elements, called gene cassettes (Hall &
65 Collis, 1995). Gene cassettes are genetic units that include a single *open reading frame*
66 (orf), usually without promoter, and a specific recombination site, *attC* (Domingues *et*
67 *al.*, 2012a; Recchia & Hall, 1995).

68 Integrons are present in approx. 10% of the bacterial genomes sequenced, and
69 contribute to genomic plasticity and environmental adaptation of bacteria (Boucher *et*
70 *al.*, 2007). In fact, integrons can be considered one of the major genetic carriers of and
71 vectors for dissemination of antibiotic resistance determinants in bacteria (Cambray *et*
72 *al.*, 2010). Integrons have been classified according to their genomic context as either
73 mobile integrons, whenever they are associated with transposons, or chromosomal
74 integrons, when located in the bacterial chromosome (Cambray *et al.*, 2010; Mazel,
75 2006). Mobile integrons are mainly found in Gram-negative bacteria, though a few
76 studies have also reported their presence among Gram-positive species (Cambray *et al.*,
77 2010; Domingues *et al.*, 2012a). The genetic relatedness of the integrase gene of the
78 mobile integrons is used to group them into distinct classes (Boucher *et al.*, 2007;
79 Stokes & Hall, 1989). Based on the nucleotide sequence of the integrase, five classes of
80 mobile integrons have been described (Cambray *et al.*, 2010). Class 1 integrons were
81 described in 1989 (Stokes & Hall, 1989), and are reported as the most common and
82 widespread, especially in clinical settings. This class mainly carries antimicrobial
83 resistance genes and it is highly disseminated due to the close association with
84 transposons, often embedded in conjugative plasmids (Cambray *et al.*, 2010).

85 All integrons consist of three essential elements, the *intI* integrase gene, which encodes
86 the IntI protein responsible for the site-specific recombination of gene cassettes, the
87 adjacent recombination site *attI* and the gene cassette promoter P_c (previously called
88 P_{ANT}) (Hall & Collis, 1998), although the presence of the promoter has not been shown
89 in all classes (Boucher *et al.*, 2007). An additional promoter, P₂, is present in some
90 integrons (Collis & Hall, 1995).

91 The complete integron is not considered to be a mobile element itself as it lacks
92 functions for self-mobility. However, the individual gene cassettes are considered
93 mobile within integrons (Mazel, 2006). Furthermore, integrons are often embedded in
94 larger mobile genetic elements (MGEs) such as transposons and plasmids which

95 mediate horizontal dissemination of the integrons (Domingues *et al.*, 2012a; Fluit &
96 Schmitz, 1999; Gombac *et al.*, 2002). The functions, abundance and selection of MGEs
97 in bacterial communities are therefore important for further integron dispersal and
98 bacterial evolution (Aminov, 2011; Wright *et al.*, 2008). This ability of broad and rapid
99 dispersal has critical clinical implications, as the majority of the gene cassettes in
100 examined mobile integrons encode antimicrobial resistance (Partridge *et al.*, 2009;
101 Recchia & Hall, 1995).

102 Integrons with identical gene cassette arrays are found in different species from diverse
103 environments and geographic locations. Here, we review the occurrence and
104 dissemination pattern of some of the most common gene cassette arrays (Partridge *et al.*,
105 2009) found in mobile integrons belonging to class 1.

106

107 **Class 1 integrons**

108 Class 1 integrons have usually three distinct genetic regions: two highly conserved
109 regions, the 5'-conserved segment (5'-CS) and the 3'-conserved segment (3'-CS),
110 flanking the central but variable region where the gene cassettes are located (Stokes &
111 Hall, 1989); these integrons have been designated classic class 1 integrons. The 5'-CS
112 includes the *intI1* gene, the *attI1* site and the promoters P_c, and P2 when present. The 3'-
113 CS consists of the *qacEΔ1* gene, which encodes an incomplete version of a protein that
114 mediates resistance to certain detergents, the *sulI* gene, encoding resistance to
115 sulphonamides, and an open reading frame, *orf5*, of unknown function (Figure 1). The
116 central variable region can have different numbers and types of gene cassettes resulting
117 in integrons with diverse compositions of gene cassette arrays. The variable region of
118 class 1 integrons is often targeted in PCR with a pair of primers called 5'-CS and 3'-CS,
119 which bind in the conserved regions of this class (Levesque *et al.*, 1995). The size of the
120 amplicon of each cassette array described in this manuscript refers to the PCR product
121 obtained with this primer pair. It is noted that several other primer pairs have been
122 developed and the PCR amplicon produced by these can have different sizes although
123 they target the same arrays (Ajiboye *et al.*, 2009; Sandvang *et al.*, 1998; White *et al.*,
124 2000).

125 Although this is the most commonly described structure of class 1 integrons, other
126 structures have been identified: such as the integrons without a 3'-CS (Dawes *et al.*,
127 2010; Pan *et al.*, 2006), and others with more complex structures. The term complex
128 class 1 integrons has been used for the ones that includes ISCR1 (Insertion Sequence

129 Common Region), partial duplications of the 3'-CS and an addition ISCR1-associated
130 region that usually carries a non-cassette resistance gene (Bennett, 2008; Toleman *et al.*,
131 2006a, b).

132

133 **Gene cassettes**

134 Numerous combinations of gene cassettes have been reported (Partridge *et al.*, 2009). A
135 number is assigned to each new integron based on the cassette array and its unique
136 nucleotide and amino acid sequence. A list of numbered class 1 integrons is available
137 from the INTEGRALL database (<http://integrall.bio.ua.pt/>) (Moura *et al.*, 2009). So far
138 more than 1050 gene cassette arrays with single or multiple nucleotide differences have
139 been identified in class 1 integrons (database last accessed on 17 November 2014). It is
140 noted that the INTEGRALL database primary focuses on gene cassette compositions
141 whereas early integron numbers also indicate the structure beyond the last cassette
142 (Partridge *et al.*, 2002). Thus the taxonomy of integrons has changed over time and may
143 or may not consider both the gene cassettes and the characteristics of the flanking DNA
144 (e.g. defective Tn402 sequences). Unfortunately, the non-uniform taxonomy has also
145 led to a lack of full oversight in the designation of gene cassettes. For instance, some
146 identical gene cassette compositions appear in different studies with different
147 designations, as the same gene has been named differently. Additionally, the same name
148 has also been attributed to different genes. This lack of consistency can be confusing in
149 the case of naming gene cassettes of unknown function. A new nomenclature for these
150 *orf* cassettes was proposed. The designation *gcu* (gene cassette of unknown function)
151 was proposed to refer to cassettes with an *attC* site but with unknown function
152 (Partridge *et al.*, 2009). Some examples of inconsistencies in the naming of gene
153 cassettes are given in Table 1 (Du *et al.*, 2005; Partridge & Hall, 2005; Partridge *et al.*,
154 2009; Ramirez & Tolmasky, 2010). Furthermore, most of the published studies do not
155 provide the specific nucleotide sequence of the described genes. This practice also
156 hampers the correct identification of the arrays considered.

157

158 Common gene cassette arrays

159 According to Partridge and colleagues (Partridge *et al.*, 2009), the single gene cassettes
160 *aadB*, *dfrA7*, *aadA1a*, *aadA2*, *blaP1* [now called *bla_{CARB-2}* (www.lahey.org/Studies -
161 accessed on 17 November 2014)], and the arrays *dfrA1-gcuC*, *dfrA1-aadA1a*, *dfrA17-*

162 *aadA5* and *dfrA12-gcuF-aadA2* were the most common ones reported in class 1
163 integrons surrounded by the 5'-CS and 3'-CS regions (see further description below).

164 There is no standard system available to indicate nucleotide variants of gene cassettes.
165 For the purpose of this review, we assume, like these authors, that the gene cassettes are
166 only different (for the purpose of classification) if their nucleotide sequence differs by
167 more than 2%. An exception was made for *bla_{CARB-2}* cassettes for which a single
168 nucleotide change, resulting in an amino acid change, lead to classification as a different
169 gene (www.lahey.org/Studies - accessed on 07 April 2015). Below we list key
170 characteristics of commonly occurring gene cassette arrays identified by Partridge and
171 colleagues (Partridge *et al.*, 2009), before a closer examination of their species,
172 geographical and environmental distribution.

173 Information on the distribution of each cassette array was collected from Pubmed,
174 GenBank and INTEGRALL databases using the designation of each gene cassette or
175 cassette array as the search term. In Pubmed, the term “integron” was added to the
176 search, together with each cassette/array. For each gene, additional search with the
177 alternative names given to the same cassette were performed. For example, for the
178 cassette array “*dfrA17-aadA5*” the searches performed in Pubmed were: “*dfrA17* AND
179 integron”, “*dfr17* AND integron”, “*dhfrXVII* AND integron”, “*aadA5* AND integron”,
180 “*ant(3′)-Ie* AND integron”, “*dfrA17-aadA5* AND integron”, “*dfr17-aadA5* AND
181 integron”, “*dhfrXVII-aadA5* AND integron”, “*dfrA17- ant(3′)-Ie* AND integron”,
182 “*dfr17- ant(3′)-Ie* AND integron”, and “*dhfrXVII- ant(3′)-Ie* AND integron”.

183 The references that are used as examples in this manuscript include studies that have
184 determined the cassette array by nucleotide sequence, size of the PCR amplicon and
185 restriction analysis, PCR amplification of the gene cassettes with specific primers,
186 and/or Southern blot hybridization, except for *bla_{CARB-2}*, where only studies that
187 performed nucleotide sequence were included.

188

189

190 *aadB*: the *aadB* gene encodes an aminoglycoside 2"-adenylyltransferase conferring
191 resistance to dibekacin, gentamicin, kanamycin, sisomicin and tobramycin (Shaw *et al.*,
192 1993). The *aadB* gene cassette is 591 bp long (Recchia & Hall, 1995), and the PCR
193 amplicon is 744 bp. This gene cassette was first identified in the variable region of a
194 class 1 integron in an Australian clinical isolate of *Escherichia coli* (isolated in 1978)
195 and first described in 1986 (Cameron *et al.*, 1986; Stokes & Hall, 1989). This was later

196 shown to be embedded in the variable region of a complex class 1 integron, with
197 duplication of the 3'-CS (Hall & Stokes, 1990).

198

199 *dfrA7*: the *dfrA7* gene encodes a type VII dihydrofolate reductase, conferring
200 trimethoprim resistance (Roberts *et al.*, 2012; van Hoek *et al.*, 2011). The PCR
201 amplicon obtained with this cassette is 770 bp long, while the cassette itself is 617 bp
202 long (Recchia & Hall, 1995). The first report of this gene as part of a class 1 integron
203 dates to 1993 (Sundstrom *et al.*, 1993), when it was described to be located on plasmids
204 from *E. coli* isolated in Sweden in 1974 (Tennhammar-Ekman & Skold, 1979) and Sri
205 Lanka in 1981 (Sundstrom *et al.*, 1987).

206

207 *aadA1a*: the *aadA1a* gene encodes an aminoglycoside 3"-adenylyltransferase,
208 associated with resistance to spectinomycin and streptomycin (Ramirez & Tolmasky,
209 2010). The cassette is 856 bp long (Recchia & Hall, 1995). A class 1 integron with this
210 cassette will produce a PCR amplicon of 1009 bp. The *aadA1* gene has been associated
211 with the Tn21 transposon for many years (Liebert *et al.*, 1999); the first strain known to
212 carry it was *Shigella flexneri*, isolated in Japan in the late 1950s (Nakaya *et al.*, 1960).
213 In 1989, when integrons were first described, this gene was found to be associated with
214 a class 1 integron (Stokes & Hall, 1989).

215

216 *aadA2*: the *aadA2* gene encodes an aminoglycoside 3"-adenylyltransferase that confers
217 resistance to spectinomycin and streptomycin (Ramirez & Tolmasky, 2010). The *aadA2*
218 gene cassette is 856 bp long (Recchia & Hall, 1995) and the PCR amplicon is 1009 bp
219 long. The first report of a class 1 integron with this single cassette dates back to 1995,
220 and refers to a clinical isolate of *Pseudomonas aeruginosa* isolated in Japan in 1965
221 (Kazama *et al.*, 1995). Besides the classic class 1 integron, the widely disseminated
222 *aadA2* gene cassette is also present in complex class 1 integrons, such as in the
223 *Salmonella* resistance island SGII and some of the variants (Boyd *et al.*, 2002; Boyd *et*
224 *al.*, 2008).

225

226 *bla_{CARB-2}*: the β -lactamase encoded by the *bla_{CARB-2}* gene confers resistance to
227 penicillins including carbenicillin (Matthew & Sykes, 1977). The cassette is 1044 bp
228 (Recchia & Hall, 1995) and the PCR amplicon is 1197 bp long. The first report of the
229 integron-borne *bla_{CARB-2}* gene cassette was published in 1991 in a plasmid from a *P.*

230 *aeruginosa* (Huovinen & Jacoby, 1991) isolate collected years before (Levesque &
231 Jacoby, 1988). The composition of this gene cassette is not always known in detail
232 (Soufi *et al.*, 2012; Van *et al.*, 2007). The *bla*_{CARB-2} cassette is often found adjacent to a
233 5'-CS fused to the *groEL* gene in the integron of the *Salmonella enterica* genomic
234 islands SGI1, which can also include *ISCR1* (Boyd *et al.*, 2001; Doublet *et al.*, 2004). In
235 addition, this cassette can also be part of complex class 1 integrons, such as the one
236 inserted in the *S. enterica* islands SGI1-A and SGI1-G (Doublet *et al.*, 2004).

237

238 *dfrA1-gcuC*: the *dfrA1* cassette is a dihydrofolate reductase type I, conferring
239 trimethoprim resistance (Roberts *et al.*, 2012; van Hoek *et al.*, 2011); the *gcuC* cassette
240 is a hypothetical protein of unknown function. Whereas the gene cassette *dfrA1* is 577
241 bp long (Recchia & Hall, 1995), the *gcuC* is 512 bp long (Partridge *et al.*, 2009), and
242 the gene cassette array composed by these two cassettes produces a PCR amplicon of
243 1242 bp. This class 1 integron array was first reported in 1990 (amplicon size 1236 bp),
244 in the plasmid pLMO150 extracted from an Enterobacterium (Sundstrom & Skold,
245 1990). This particular cassette array can also be part of the genomic island SGI1, being
246 embedded in a complex class 1 integron in this case (Boyd *et al.*, 2008).

247

248 *dfrA1-aadA1a*: as previously mentioned, the *dfrA1* gene encodes a dihydrofolate
249 reductase type I, conferring resistance to trimethoprim (Roberts *et al.*, 2012; van Hoek
250 *et al.*, 2011); and the *aadA1a* gene encodes the enzyme aminoglycoside 3"-
251 adenylyltransferase associated with resistance to spectinomycin and streptomycin
252 (Ramirez & Tolmasky, 2010). The individual sizes of the cassettes *dfrA1* and *aadA1a*
253 are, as mentioned before, 577 bp and 856 bp, respectively (Recchia & Hall, 1995); the
254 *dfrA1-aadA1a* array PCR amplicon is 1586 bp long. The first report of this class 1
255 integron array dates from 1990, in the plasmid pLMO229 of an Enterobacterium
256 (Sundstrom & Skold, 1990)

257

258 *dfrA17-aadA5*: the *dfrA17* gene encodes a dihydrofolate reductase type XVII, also
259 conferring trimethoprim resistance (Roberts *et al.*, 2012; van Hoek *et al.*, 2011); an
260 aminoglycoside 3"-adenylyltransferase, associated with spectinomycin and
261 streptomycin resistance, is encoded by the *aadA5* gene (Ramirez & Tolmasky, 2010).
262 The PCR product obtained from the amplification of a classic class 1 integron
263 composed by the array *dfrA17-aadA5* is 1664 bp; the *dfrA17* and *aadA5* cassettes are

264 616 bp and 895 bp long, respectively (Partridge *et al.*, 2009). This gene cassette array
265 was reported for the first time in 2000, in the chromosome of a clinical *E. coli* isolate
266 collected in Australia in 1998 (White *et al.*, 2000). It is noted that the White *et al.* paper
267 does not suggest the *aadA5* gene confer streptomycin resistance. However, reports
268 studying the gene when present in other arrays suggest so (Sandvang, 1999).

269

270 *dfrA12-gcuF-aadA2*: the *dfrA12* gene encodes a type XII dihydrofolate reductase,
271 which confers trimethoprim resistance (Roberts *et al.*, 2012; van Hoek *et al.*, 2011); the
272 *gcuF* gene encodes a hypothetical protein of unknown function; and the *aadA2* gene, as
273 mentioned before, encodes an aminoglycoside 3"-adenyltransferase, associated with
274 spectinomycin and streptomycin resistance (Ramirez & Tolmasky, 2010). The array
275 composed by these three gene cassettes produces a PCR amplicon of 1913 bp. The
276 *dfrA12* cassette is 584 bp long, the *gcuF* cassette is 320 bp long and the *aadA2* cassette
277 is 856 bp (Partridge *et al.*, 2009; Recchia & Hall, 1995). The first report of a classic
278 class 1 integron with this cassette array dates back to 1993, when it was identified in the
279 plasmid of a clinical *E. coli* isolate originally collected in Finland in the 1980's
280 (Heikkila *et al.*, 1993).

281

282 **Bacterial species distribution**

283 The nine commonly occurring gene cassette arrays (Partridge *et al.*, 2009) considered in
284 this review have altogether been reported in at least 72 bacterial species (Table 2). They
285 are predominately found in class 1 integrons from Gram-negative bacterial species, as is
286 also the case for mobile integrons in general. However, a few arrays, specifically
287 *aadA1a*, *aadA2*, *dfrA17-aadA5*, and *dfrA12-gcuF-aadA2*, have also been detected in
288 Gram-positive bacteria.

289 Some bacterial species seem more likely to carry integrons than others. For instance,
290 more than six of the arrays have been found in bacteria belonging to the species
291 *Acinetobacter baumannii*, *E. coli*, *Klebsiella pneumoniae*, *Proteus mirabilis* and *S.*
292 *enterica*. In contrast, only one type of array has been described in the species
293 *Citrobacter braakii*, *Pseudomonas putida*, *Serratia liquefaciens* and *Vibrio*
294 *alginolyticus*. The species carrying the broader set of arrays are all known nosocomial
295 pathogens, often exposed to diverse antibiotic classes, and they are present in the same
296 environments. Thus, they are expected to have opportunities for physical contact and

297 horizontal exchange as well as being under strong positive selection for the resistance
298 traits encoded by the particular gene cassette compositions considered here.

299 Among the reviewed arrays, *aadA1a*, *aadA2* and *dfrA12-gcuF-aadA2* are present in a
300 diverse range of bacterial species (>30), while *aadB* and *bla_{CARB-2}* are restricted to a
301 smaller number of species and seem to have preference for *Enterobacteriaceae* and *S.*
302 *enterica*, respectively.

303 Further studies should be conducted to better understand to what extent gene cassette
304 distribution patterns are limited by host species and environmental factors. As integrons
305 are frequently genetically linked to MGEs, consideration of the host ranges of linked
306 MGE and the impact of linked selection is essential in this context. See below for a
307 further discussion on limitations in studies due to biased or limited sampling or
308 publication effort.

309

310 **Geographical dissemination**

311 Class 1 integrons are globally disseminated. Class 1 integrons carrying the nine
312 common arrays considered here have been described in at least 73 countries (Table 3)
313 belonging to all continents, with the exception of Antarctica. However, some of the
314 gene cassette arrays considered appear (based on published literature) to have a
315 continent-related prevalence. For instance, the *dfrA1-gcuC* array is mostly reported in
316 Asia, while the *aadB* cassette is mainly reported in European countries. We can find
317 reports of all nine arrays in China, Malaysia, Tunisia and the United States. Other
318 countries, such as Austria and Zimbabwe, have so far reported bacteria with only one
319 type of the common arrays. If the geographical distribution pattern reflects a true
320 distribution or a biased or limited sampling or publication effort is yet not known.

321 More studies are needed to understand the causal factors determining the initial events
322 creating the particular gene cassette array as well as the population dynamic factors
323 resulting in the currently observed global dissemination patterns of antibiotic resistance
324 genes associated with class 1 integrons. Particularly, there is a need to better understand
325 the interplay between various population genetic processes (e.g. selection from
326 antibiotic usage, co-selection, vectors, genetic drift, dispersal) in determining further
327 geographic dissemination of these integrons. The effects of various antibiotic usage
328 levels and patterns in different countries must also be considered in this context.

329

330 **Environmental distribution**

331 As expected from the dissemination patterns of antimicrobial resistance in general,
332 resistance-encoding gene cassette arrays are mostly reported in bacteria isolated from
333 human clinical settings. Nonetheless, there are an increasing number of studies
334 describing the presence of gene cassette arrays in other environments. Humans are in
335 contact with animals, animal food products and other environmental sources of
336 integrons, and can both be recipients of and donors of integron-carrying bacteria or
337 genetic material (Stokes & Gillings, 2011). The flow of integrons and gene cassettes
338 between environments is a spatially and temporally variable, and may be best explained
339 as a multidimensional process. The specific events of gene exchange and directions will
340 depend on a multitude of factors, such as the encoded trait(s) and genetic composition
341 of the integron, the mobility of the genetic region it is embedded in, randomness and
342 chance dispersal, and the characteristics of the host and environmental conditions,
343 including selection of the host bacterium for integron encoded traits. Examples of the
344 many clinical and environmental sources in which the arrays are found are given in
345 Table 4.

346 Importantly, integrons have been detected in locations where a selective advantage of
347 carrying antibiotic resistance traits to pharmaceutically-produced antibiotics is not
348 expected, such as in wild animals (Power *et al.*, 2013) and in remote rural communities
349 with minimal consumption of antibiotics (Pallecchi *et al.*, 2007). An association
350 between the presence of class 1 integrons and urbanization has not been found in a
351 Patagonian island (Nardelli *et al.*, 2012). On the other hand, a recent study suggested
352 that human activities are a major source of class 1 integrons, which end up in the
353 environment (Stalder *et al.*, 2014). Power and colleagues (Power *et al.*, 2013) provided
354 evidence for the transfer of class 1 integrons from humans to captive rock wallabies.
355 These wallabies were later released, resulting in an opportunity to further spread the
356 integrons into wild populations of wallabies and their natural environments. Other
357 studies suggest that animals transmit antibiotic resistance to humans. For example,
358 although not integron-based, Harrison and collaborators (Harrison *et al.*, 2013)
359 suggested the transmission of methicillin-resistant *Staphylococcus aureus* from
360 livestock to humans.

361

362

363 **Observational bias and other limitations in studies**

364 It is emphasized that the species, geographical and environmental distribution patterns
365 of class 1 integrons examined here do not represent the actual prevalence pattern.
366 Limitations in experimental design, sampling and reporting will lead to observational
367 bias, and dominance of studies from research-oriented countries and particular clinical
368 environments in the published scientific literature. The urgency of communicating
369 clinical resistance developments creates a positive publication bias in the scientific
370 literature on the presence of integrons in such environments.

371 Large differences between countries in research focus and funding and in public health
372 monitoring and reporting systems will, moreover, necessarily lead to non-consistent
373 publication of data that are not representative for the dissemination of integrons at the
374 global scale. It is also recognized that the prevalence of particular cassette arrays are
375 expected to vary over time, so any overview of distribution patterns will be a snapshot
376 based on the available literature - with a time lag.

377 A limitation to the current study of class 1 integrons is that most studies are qualitative
378 and descriptive in nature. The experimental study design is based on the need to better
379 understand the genetic basis associated with the specific resistances observed in clinical
380 isolates of bacterial pathogens. Such studies are often done with only limited
381 consideration of the underlying population structure of the pathogen/species examined.
382 These case and isolate-focused studies do therefore not permit a quantitative analysis of
383 integrons as present in a particular population of a bacterial species or community of
384 several bacterial species. Quantitative analyses are, however, needed to enable
385 monitoring of changes in actual prevalence of integrons over time, i.e. changes in the
386 overall proportion of members of a particular bacterial population carrying a specific
387 gene cassette array.

388 Another limitation to the studies of the prevalence of integrons is the lack of sufficient
389 or complete information of the genetic composition of various bacterial communities.
390 Lack of information on the genetic composition of natural bacterial communities
391 precludes the opportunity to unambiguously track or assign directionality in the flow of
392 gene cassettes between anthropogenic and natural environments.

393

394 **General considerations**

395 Our review highlights the broad diversity of bacterial species sharing the same gene
396 cassette arrays. These species have been recovered from a wide range of environments
397 (e.g. humans; domestic, food and wild animals; and various environmental sites) located

398 in all regions of the world. This review substantiates further the observations of
399 Partridge and collaborators (Partridge *et al.*, 2009) on the broad distribution of these
400 particular sequences in class 1 integrons.

401 The current dissemination pattern of particular and sequence identical gene cassette
402 arrays suggests that opportunities exist for rapid clonal dissemination between
403 geographical locations and environments on a global scale, as well as the presence of
404 functional and effective mechanisms for horizontal gene transfer (HGT) between
405 unrelated bacterial species. It is also noteworthy that whereas the initial reports of
406 integrons focused mostly on their presence in bacteria from clinical specimens, several
407 recent studies now describe the dissemination of the same integrons in species rarely
408 associated with clinical disease. The impact of various sources of observational bias,
409 and limitations in sampling in the investigating and reporting the dissemination of
410 mobile integrons in species, environments and geographical areas remains unexplored,
411 but we consider it to be substantial.

412

413 Emergence and persistence

414 Integrons have been found in a permafrost sample (Petrova *et al.*, 2011) and in bacteria
415 isolated years before their characterization as mobile genetic elements involved in
416 antibiotic resistance (Dalsgaard *et al.*, 2000; Hedges *et al.*, 1972; Huovinen & Jacoby,
417 1991; Kazama *et al.*, 1995; Stokes & Hall, 1989). These early observations support the
418 view that integrons are not recent entities and that they have existed in bacterial
419 populations for many decades (Rowe-Magnus *et al.*, 2002). The introduction of
420 antibiotics in clinical, veterinary and agricultural settings have most likely contributed
421 to the selective amplification of new resistance-encoding gene cassettes and increased
422 the distribution and prevalence of integron-carrying bacteria with such cassettes. The
423 majority of the gene cassettes reviewed here encode resistance to antibiotics that can
424 also be produced naturally by environmental microorganisms, suggesting that particular
425 gene cassettes and integrons evolved before bacteria became exposed to
426 pharmaceutically produced antibiotics. This view is also consistent with the recent
427 finding of antibiotic resistance determinants in DNA millions of years old (D'Costa *et al.*
428 *et al.*, 2011). There is also evidence that class 1 integrons in bacteria exposed to antibiotics
429 can capture gene cassettes from superintegrons, chromosomal integrons that contain
430 long cassette arrays (>20), where the majority of the cassettes are not usually expressed
431 due to the distance to the P_c promoter (Mazel, 2006; Rowe-Magnus *et al.*, 2002; Rowe-

432 Magnus *et al.*, 2001). Forsberg and colleagues recently also showed that soil bacteria
433 and human pathogens share the same antibiotic resistome, and that horizontal transfer
434 between both communities contributes to the resistance dissemination (Forsberg *et al.*,
435 2012). The increased prevalence of integrons is likely the outcome of selection
436 conferred by the exposure to pharmaceutically produced antimicrobials. Integrons have
437 therefore, together with other resistance-conferring mobile genetic elements, been seen
438 as xenogenetic pollutants (Gillings, 2013).

439 Integrons, similar to those found in clinical settings, have also been detected in remote
440 communities with a history of minimal exposure to antibiotics (Pallecchi *et al.*, 2007).
441 This observation emphasizes that antibiotic usage levels are not the only factor
442 responsible for the existence of integrons in current bacterial populations. Several other
443 factors might contribute to the tempospatial distribution of cassette arrays, including the
444 activity of the integrase, the phenotypic traits provided to the host by each cassette, the
445 mobility of the element where the gene cassettes are inserted, positive selection of genes
446 and genetic elements linked to the integrons, and compensatory mutations that reduce
447 the cost of integron carriage (Partridge *et al.*, 2009; Starikova *et al.*, 2012).

448 Ten different variants of the class 1 integrase, resulting from 13 different variants of the
449 gene cassette promoter P_c , have been identified. The recombination activity of each
450 integrase is inversely related to the strength of the P_c promoter (Jove *et al.*, 2010), which
451 influences the stability of the gene cassette arrays. Thus, an unresolved question is if
452 particular arrays are more widely disseminated because of a low recombination activity
453 in the class 1 integrons carrying them? Determination of the nucleotide sequence of the
454 integrase could clarify the variant present in these class 1 integrons and allow prediction
455 of the recombination activity level.

456 In bacterial species with an SOS response, the integrase gene is normally repressed,
457 which allows the host bacterium to maintain the gene cassette arrays in a steady state.
458 The SOS response is a global response to DNA damage, which controls DNA repair and
459 mutagenesis. A stress responsive regulation of integrase functions is expected to reduce
460 the biological costs of such genetic element (Guerin *et al.*, 2009). Triggering of the SOS
461 system can be observed after conjugation (Baharoglu *et al.*, 2010), natural
462 transformation (Baharoglu *et al.*, 2012) and by exposure to subinhibitory concentrations
463 of antibiotics (Baharoglu & Mazel, 2011). The activation of the SOS response leads to
464 increased transcription of the integrase gene and increased integrase activity, resulting
465 in cassette rearrangements (Baharoglu *et al.*, 2010; Guerin *et al.*, 2009). A gene cassette

466 rearrangement has also been recently observed *in vivo* after induction of the SOS
467 system, leading to emergence of a resistant *P. aeruginosa* isolate that was then quickly
468 spread among the hospital patients (Hocquet *et al.*, 2012).

469 It was recently shown that the carriage of class 1 integrases can be costly to the host, but
470 that single point mutations can inactivate the integrase restoring bacterial fitness
471 (Starikova *et al.*, 2012). The inactivation of the integrase can be an alternative way of
472 controlling fitness-reducing effects of integrase expression in bacteria in the absence of
473 SOS system, which is not present in all bacterial species. The inactivation of the
474 integrase will contribute to a higher stability of the cassette arrays embedded in an
475 integron.

476

477 Clonal (vertical) dissemination versus horizontal gene transfer

478 A key question that emerges from the observation of a wide dissemination of class 1
479 integrons and associated cassette arrays is to what extent the current pattern is a result of
480 rapid clonal amplification and spread *or* highly efficient HGT mechanisms. The rapid
481 population expansion of particular bacterial clones carrying integrons can occur both as
482 a result of that the integrons enhance the fitness of their bacterial host through the traits
483 they encode, or that integrons can hitchhike with clones that are evolutionary successful
484 for other reasons. The dispersal pattern can also result from frequent intra and
485 interspecies HGT events. The mobility of class 1 integrons through various pathways of
486 HGT has been recently reviewed (Domingues *et al.*, 2012a; Domingues *et al.*, 2012b).
487 Often both clonal expansion and HGT events act together and contribute to the
488 dissemination of resistant bacteria, as observed by Krauland and colleagues (Krauland
489 *et al.*, 2009). Some studies suggest a larger role of clonal dissemination (Kouda *et al.*,
490 2009) and others horizontal transfer (Blahna *et al.*, 2006) in such propagation.

491 On one hand, clonal dissemination of integron-carrying bacteria can explain the
492 occurrence of a particular integron in a specific bacterial species in different
493 geographical regions. For instance, the high occurrence of the *aadA2* and *bla_{CARB-2}*
494 cassettes can be explained by their presence in the pathogenic *S. enterica* serovar
495 Typhimurium DT104, which has been extensively sequenced (Antunes *et al.*, 2006;
496 Casin *et al.*, 1999; Zhao *et al.*, 2007). Increased international travel in the last decades
497 has increased the potential for dissemination of virulent clones carrying integrons. For
498 instance, class 1 integrons were detected in 11 clinical isolates of *Shigella* spp. in Spain,
499 which were associated with travel from other countries (Navia *et al.*, 2004). There is

500 also the example of integron-containing *A. baumannii* clinical isolates found in the
501 United States and the United Kingdom, which were associated with patients travelling
502 from Iraq (Turton *et al.*, 2006).

503 On the other hand, the occurrence of integrons with the same nucleotide sequence in
504 genetically unrelated species clearly identify a HGT as a causal mechanism in the
505 dissemination of integrons. The observation of conserved gene cassette compositions in
506 a high variety of bacterial species emphasizes the unusual and broad potential for
507 horizontal dissemination of gene cassettes and integrons. The outcome of such HGT
508 processes has been the global dissemination of particular resistance traits and
509 combinations within a few decades. It is noted that horizontal exchange of genetic
510 material conferring antibiotic resistance can occur independent of the genetic
511 relatedness of the involved bacterial species by conjugation, transduction or
512 transformation (Domingues *et al.*, 2012a; Domingues *et al.*, 2012c). Historically, class 1
513 integrons have been associated with Tn402-like transposons and have later been
514 incorporated in transposons like Tn21 and Tn1696 due to shared recombination
515 mechanisms (Gillings *et al.*, 2008; Partridge *et al.*, 2001; Stokes *et al.*, 2006). However,
516 the population genetic processes that have produced the current dissemination patterns
517 of integrons remain to be fully understood.

518

519 **Concluding remarks**

520 A diverse set of bacterial species shares the same gene cassettes and arrays. These host
521 species have been recovered from a wide range of environments located in all regions of
522 the world. The current distribution pattern of commonly occurring gene cassette arrays
523 suggests both i) opportunities for rapid dissemination of successful clones at a global
524 scale and ii) the existence of effective routes of HGT between geographical locations,
525 environments and unrelated bacterial species. The current integron dispersal pattern has
526 developed over the last 3 decades. Studies now also emerge describing resistance
527 encoding gene cassettes in integrons in bacterial species rarely associated with clinical
528 disease, suggesting ongoing HGT and dissemination processes in the broader
529 environment. The evolutionary significance of resistance-carrying integrons from the
530 pre-antibiotic era to current resistance patterns remains to be determined. Current data
531 suggest multidirectional flow of bacteria and their integrons between humans, animals
532 and other environments (Stokes & Gillings, 2011). Such flow has major and serious
533 implications for human health and treatment of infections. We highlight the need of

534 moving from a descriptive approach to integron dissemination to one that allow a more
535 comprehensive understanding of the factors governing the prevalence, persistence and
536 spread of integrons between and within bacterial populations.

537

538

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541

542 References

543 **Adabi, M., Bakhshi, B., Goudarzi, H., Zahraei, S. M. & Pourshafie, M. R. (2009).** Distribution of
544 class I integron and sulfamethoxazole trimethoprim constin in *Vibrio cholerae* isolated
545 from patients in Iran. *Microb Drug Resist* **15**, 179-184.

546 **Ahmed, A. M. & Shimamoto, T. (2011).** Molecular characterization of antimicrobial resistance
547 in Gram-negative bacteria isolated from bovine mastitis in Egypt. *Microbiol Immunol*
548 **55**, 318-327.

549 **Ahmed, A. M., Nakano, H. & Shimamoto, T. (2005).** Molecular characterization of integrons in
550 non-typhoid *Salmonella* serovars isolated in Japan: description of an unusual class 2
551 integron. *J Antimicrob Chemother* **55**, 371-374.

552 **Ahmed, A. M., Shimabukuro, H. & Shimamoto, T. (2009a).** Isolation and molecular
553 characterization of multidrug-resistant strains of *Escherichia coli* and *Salmonella* from
554 retail chicken meat in Japan. *J Food Sci* **74**, M405-410.

555 **Ahmed, A. M., Younis, E. E., Osman, S. A., Ishida, Y., El-Khodery, S. A. & Shimamoto, T.**
556 **(2009b).** Genetic analysis of antimicrobial resistance in *Escherichia coli* isolated from
557 diarrheic neonatal calves. *Vet Microbiol* **136**, 397-402.

558 **Ahmed, A. M., Motoi, Y., Sato, M., Maruyama, A., Watanabe, H., Fukumoto, Y. &**
559 **Shimamoto, T. (2007).** Zoo animals as reservoirs of gram-negative bacteria harboring
560 integrons and antimicrobial resistance genes. *Appl Environ Microbiol* **73**, 6686-6690.

561 **Aibinu, I., Pfeifer, Y., Peters, F., Ogunisola, F., Adenipekun, E., Odugbemi, T. & Koenig, W.**
562 **(2012).** Emergence of *bla*(CTX-M-15), *qnrB1* and *aac(6')-Ib-cr* resistance genes in
563 *Pantoea agglomerans* and *Enterobacter cloacae* from Nigeria (sub-Saharan Africa). *J*
564 *Med Microbiol* **61**, 165-167.

565 **Ajiboye, R. M., Solberg, O. D., Lee, B. M., Raphael, E., Debroy, C. & Riley, L. W. (2009).** Global
566 spread of mobile antimicrobial drug resistance determinants in human and animal
567 *Escherichia coli* and *Salmonella* strains causing community-acquired infections. *Clin*
568 *Infect Dis* **49**, 365-371.

569 **Al-Sanouri, T. M., Paglietti, B., Haddadin, A., Murgia, M., Bacciu, D., Youssef, M. & Rubino, S.**
570 **(2008).** Emergence of plasmid-mediated multidrug resistance in epidemic and non-
571 epidemic strains of *Salmonella enterica* serotype Typhi from Jordan. *J Infect Dev Ctries*
572 **2**, 295-301.

573 **Allen, K. J. & Poppe, C. (2002).** Occurrence and characterization of resistance to extended-
574 spectrum cephalosporins mediated by β -lactamase CMY-2 in *Salmonella* isolated from
575 food-producing animals in Canada. *Can J Vet Res* **66**, 137-144.

576 **Aminov, R. I. (2011).** Horizontal gene exchange in environmental microbiota. *Front Microbiol*
577 **2**, 158.

578 **Antunes, P., Machado, J. & Peixe, L. (2006).** Characterization of antimicrobial resistance and
579 class 1 and 2 integrons in *Salmonella enterica* isolates from different sources in
580 Portugal. *J Antimicrob Chemother* **58**, 297-304.

- 581 **Bado, I., Cordeiro, N. F., Robino, L., Garcia-Fulgueiras, V., Seija, V., Bazet, C., Gutkind, G.,**
582 **Ayala, J. A. & Vignoli, R. (2010).** Detection of class 1 and 2 integrons, extended-
583 spectrum β -lactamases and *qnr* alleles in enterobacterial isolates from the digestive
584 tract of Intensive Care Unit inpatients. *Int J Antimicrob Agents* **36**, 453-458.
- 585 **Baharoglu, Z. & Mazel, D. (2011).** *Vibrio cholerae* triggers SOS and mutagenesis in response to
586 a wide range of antibiotics: a route towards multiresistance. *Antimicrob Agents*
587 *Chemother* **55**, 2438-2441.
- 588 **Baharoglu, Z., Bikard, D. & Mazel, D. (2010).** Conjugative DNA transfer induces the bacterial
589 SOS response and promotes antibiotic resistance development through integron
590 activation. *PLoS Genet* **6**, e1001165.
- 591 **Baharoglu, Z., Krin, E. & Mazel, D. (2012).** Connecting environment and genome plasticity in
592 the characterization of transformation-induced SOS regulation and carbon catabolite
593 control of the *Vibrio cholerae* integron integrase. *J Bacteriol* **194**, 1659-1667.
- 594 **Bailey, J. K., Pinyon, J. L., Anantham, S. & Hall, R. M. (2010).** Commensal *Escherichia coli* of
595 healthy humans: a reservoir for antibiotic-resistance determinants. *J Med Microbiol*
596 **59**, 1331-1339.
- 597 **Barlow, R. S., Fegan, N. & Gobius, K. S. (2008).** A comparison of antibiotic resistance integrons
598 in cattle from separate beef meat production systems at slaughter. *J Appl Microbiol*
599 **104**, 651-658.
- 600 **Ben Sallem, R., Ben Slama, K., Saenz, Y., Rojo-Bezares, B., Estepa, V., Jouini, A., Gharsa, H.,**
601 **Klibi, N., Boudabous, A. & other authors (2012).** Prevalence and characterization of
602 extended-spectrum β -lactamase (ESBL)- and CMY-2-producing *Escherichia coli* Isolates
603 from healthy food-producing animals in Tunisia. *Foodborne Pathog Dis* **9**, 1137-1142.
- 604 **Ben Slama, K., Ben Sallem, R., Jouini, A., Rachid, S., Moussa, L., Saenz, Y., Estepa, V., Somalo,**
605 **S., Boudabous, A. & other authors (2011).** Diversity of genetic lineages among CTX-M-
606 15 and CTX-M-14 producing *Escherichia coli* strains in a Tunisian hospital. *Curr*
607 *Microbiol* **62**, 1794-1801.
- 608 **Bennett, P. M. (2008).** Plasmid encoded antibiotic resistance: acquisition and transfer of
609 antibiotic resistance genes in bacteria. *Br J Pharmacol* **153 Suppl 1**, S347-357.
- 610 **Binh, C. T., Heuer, H., Kaupenjohann, M. & Smalla, K. (2009).** Diverse *aadA* gene cassettes on
611 class 1 integrons introduced into soil via spread manure. *Res Microbiol* **160**, 427-433.
- 612 **Blahna, M. T., Zalewski, C. A., Reuer, J., Kahlmeter, G., Foxman, B. & Marrs, C. F. (2006).** The
613 role of horizontal gene transfer in the spread of trimethoprim-sulfamethoxazole
614 resistance among uropathogenic *Escherichia coli* in Europe and Canada. *J Antimicrob*
615 *Chemother* **57**, 666-672.
- 616 **Boucher, Y., Labbate, M., Koenig, J. E. & Stokes, H. W. (2007).** Integrons: mobilizable
617 platforms that promote genetic diversity in bacteria. *Trends Microbiol* **15**, 301-309.
- 618 **Boyd, D., Cloeckert, A., Chaslus-Dancla, E. & Mulvey, M. R. (2002).** Characterization of
619 variant *Salmonella* genomic island 1 multidrug resistance regions from serovars
620 Typhimurium DT104 and Agona. *Antimicrob Agents Chemother* **46**, 1714-1722.
- 621 **Boyd, D., Peters, G. A., Cloeckert, A., Boumedine, K. S., Chaslus-Dancla, E., Imberechts, H. &**
622 **Mulvey, M. R. (2001).** Complete nucleotide sequence of a 43-kilobase genomic island
623 associated with the multidrug resistance region of *Salmonella enterica* serovar
624 Typhimurium DT104 and its identification in phage type DT120 and serovar Agona. *J*
625 *Bacteriol* **183**, 5725-5732.
- 626 **Boyd, D. A., Shi, X., Hu, Q. H., Ng, L. K., Doublet, B., Cloeckert, A. & Mulvey, M. R. (2008).**
627 *Salmonella* genomic island 1 (SGI1), variant SGI1-I, and new variant SGI1-O in *Proteus*
628 *mirabilis* clinical and food isolates from China. *Antimicrob Agents Chemother* **52**, 340-
629 344.
- 630 **Caleja, C., de Toro, M., Goncalves, A., Themudo, P., Vieira-Pinto, M., Monteiro, D.,**
631 **Rodrigues, J., Saenz, Y., Carvalho, C. & other authors (2011).** Antimicrobial resistance

- 632 and class I integrons in *Salmonella enterica* isolates from wild boars and Bisaro pigs. *Int*
633 *Microbiol* **14**, 19-24.
- 634 **Cambray, G., Guerout, A. M. & Mazel, D. (2010).** Integrons. *Annu Rev Genet* **44**, 141-166.
- 635 **Cameron, F. H., Groot Obbink, D. J., Ackerman, V. P. & Hall, R. M. (1986).** Nucleotide
636 sequence of the AAD(2'') aminoglycoside adenylyltransferase determinant *aadB*.
637 Evolutionary relationship of this region with those surrounding *aadA* in R538-1 and
638 *dhfrII* in R388. *Nucleic Acids Res* **14**, 8625-8635.
- 639 **Carvalho, M. J., Martinez-Murcia, A., Esteves, A. C., Correia, A. & Saavedra, M. J. (2012).**
640 Phylogenetic diversity, antibiotic resistance and virulence traits of *Aeromonas* spp.
641 from untreated waters for human consumption. *Int J Food Microbiol* **159**, 230-239.
- 642 **Casin, I., Breuil, J., Brisabois, A., Moury, F., Grimont, F. & Collatz, E. (1999).** Multidrug-
643 resistant human and animal *Salmonella* typhimurium isolates in France belong
644 predominantly to a DT104 clone with the chromosome- and integron-encoded β -
645 lactamase PSE-1. *J Infect Dis* **179**, 1173-1182.
- 646 **Ceccarelli, D., Bani, S., Cappuccinelli, P. & Colombo, M. M. (2006a).** Prevalence of *aadA1* and
647 *dfrA15* class 1 integron cassettes and SXT circulation in *Vibrio cholerae* O1 isolates
648 from Africa. *J Antimicrob Chemother* **58**, 1095-1097.
- 649 **Ceccarelli, D., Salvia, A. M., Sami, J., Cappuccinelli, P. & Colombo, M. M. (2006b).** New cluster
650 of plasmid-located class 1 integrons in *Vibrio cholerae* O1 and a *dfrA15* cassette-
651 containing integron in *Vibrio parahaemolyticus* isolated in Angola. *Antimicrob Agents*
652 *Chemother* **50**, 2493-2499.
- 653 **Chakraborty, R., Kumar, A., Bhowal, S. S., Mandal, A. K., Tiwary, B. K. & Mukherjee, S. (2013).**
654 Diverse gene cassettes in class 1 integrons of facultative oligotrophic bacteria of River
655 Mahananda, West Bengal, India. *PLoS One* **8**, e71753.
- 656 **Chang, C. Y., Chang, L. L., Chang, Y. H., Lee, T. M. & Chang, S. F. (2000).** Characterisation of
657 drug resistance gene cassettes associated with class 1 integrons in clinical isolates of
658 *Escherichia coli* from Taiwan, ROC. *J Med Microbiol* **49**, 1097-1102.
- 659 **Chen, H., Shu, W., Chang, X., Chen, J. A., Guo, Y. & Tan, Y. (2010).** The profile of antibiotics
660 resistance and integrons of extended-spectrum β -lactamase producing thermotolerant
661 coliforms isolated from the Yangtze River basin in Chongqing. *Environ Pollut* **158**, 2459-
662 2464.
- 663 **Clark, N. C., Olsvik, O., Swenson, J. M., Spiegel, C. A. & Tenover, F. C. (1999).** Detection of a
664 streptomycin/spectinomycin adenylyltransferase gene (*aadA*) in *Enterococcus faecalis*.
665 *Antimicrob Agents Chemother* **43**, 157-160.
- 666 **Cocchi, S., Grasselli, E., Gutacker, M., Benagli, C., Convert, M. & Piffaretti, J. C. (2007).**
667 Distribution and characterization of integrons in *Escherichia coli* strains of animal and
668 human origin. *FEMS Immunol Med Microbiol* **50**, 126-132.
- 669 **Collis, C. M. & Hall, R. M. (1995).** Expression of antibiotic resistance genes in the integrated
670 cassettes of integrons. *Antimicrob Agents Chemother* **39**, 155-162.
- 671 **Corkill, J. E., Anson, J. J. & Hart, C. A. (2005).** High prevalence of the plasmid-mediated
672 quinolone resistance determinant *qnrA* in multidrug-resistant Enterobacteriaceae from
673 blood cultures in Liverpool, UK. *J Antimicrob Chemother* **56**, 1115-1117.
- 674 **D'Costa, V. M., King, C. E., Kalan, L., Morar, M., Sung, W. W., Schwarz, C., Froese, D., Zazula,
675 G., Calmels, F. & other authors (2011).** Antibiotic resistance is ancient. *Nature* **477**,
676 457-461.
- 677 **Dahmen, S., Mansour, W., Boujaafar, N., Arlet, G. & Bouallegue, O. (2010).** Distribution of
678 cotrimoxazole resistance genes associated with class 1 integrons in clinical isolates of
679 *Enterobacteriaceae* in a university hospital in Tunisia. *Microb Drug Resist* **16**, 43-47.
- 680 **Dalsgaard, A., Forslund, A., Serichantalergs, O. & Sandvang, D. (2000).** Distribution and
681 content of class 1 integrons in different *Vibrio cholerae* O-serotype strains isolated in
682 Thailand. *Antimicrob Agents Chemother* **44**, 1315-1321.

- 683 **Dalsgaard, A., Forslund, A., Sandvang, D., Arntzen, L. & Keddy, K. (2001).** *Vibrio cholerae* O1
684 outbreak isolates in Mozambique and South Africa in 1998 are multiple-drug resistant,
685 contain the SXT element and the *aadA2* gene located on class 1 integrons. *J Antimicrob*
686 *Chemother* **48**, 827-838.
- 687 **Dawes, F. E., Kuzevski, A., Bettelheim, K. A., Hornitzky, M. A., Djordjevic, S. P. & Walker, M. J.**
688 **(2010).** Distribution of class 1 integrons with IS26-mediated deletions in their 3'-
689 conserved segments in *Escherichia coli* of human and animal origin. *PLoS One* **5**,
690 e12754.
- 691 **Di Conza, J., Ayala, J. A., Porto, A., Mollerach, M. & Gutkind, G. (2005).** Molecular
692 characterization of InJR06, a class 1 integron located in a conjugative plasmid of
693 *Salmonella enterica* ser. Typhimurium. *Int Microbiol* **8**, 287-290.
- 694 **Dolejska, M., Bierosova, B., Kohoutova, L., Literak, I. & Cizek, A. (2009).** Antibiotic-resistant
695 *Salmonella* and *Escherichia coli* isolates with integrons and extended-spectrum β -
696 lactamases in surface water and sympatric black-headed gulls. *J Appl Microbiol* **106**,
697 1941-1950.
- 698 **Dolejska, M., Senk, D., Cizek, A., Rybarikova, J., Sychra, O. & Literak, I. (2008).** Antimicrobial
699 resistant *Escherichia coli* isolates in cattle and house sparrows on two Czech dairy
700 farms. *Res Vet Sci* **85**, 491-494.
- 701 **Domingues, S., Da Silva, G. J. & Nielsen, K. M. (2012a).** Integrons: Vehicles and pathways for
702 horizontal dissemination in bacteria. *Mob Genet Elements* **2**, 211-223.
- 703 **Domingues, S., Nielsen, K. M. & Da Silva, G. J. (2012b).** Various pathways leading to the
704 acquisition of antibiotic resistance by natural transformation. *Mob Genet Elements* **2**,
705 257-260.
- 706 **Domingues, S., Harms, K., Fricke, W. F., Johnsen, P. J., da Silva, G. J. & Nielsen, K. M. (2012c).**
707 Natural transformation facilitates transfer of transposons, integrons and gene
708 cassettes between bacterial species. *PLoS Pathog* **8**, e1002837.
- 709 **Dotto, G., Giacomelli, M., Grilli, G., Ferrazzi, V., Carattoli, A., Fortini, D. & Piccirillo, A. (2014).**
710 High prevalence of *oqxAB* in *Escherichia coli* isolates from domestic and wild
711 lagomorphs in Italy. *Microb Drug Resist* **20**, 118-123.
- 712 **Doublet, B., Butaye, P., Imberechts, H., Boyd, D., Mulvey, M. R., Chaslus-Dancla, E. &**
713 **Cloeckaert, A. (2004).** *Salmonella* genomic island 1 multidrug resistance gene clusters
714 in *Salmonella enterica* serovar Agona isolated in Belgium in 1992 to 2002. *Antimicrob*
715 *Agents Chemother* **48**, 2510-2517.
- 716 **Du, X., Shen, Z., Wu, B., Xia, S. & Shen, J. (2005).** Characterization of class 1 integrons-
717 mediated antibiotic resistance among calf pathogenic *Escherichia coli*. *FEMS Microbiol*
718 *Lett* **245**, 295-298.
- 719 **Egorova, S., Kaftyreva, L., Grimont, P. A. & Weill, F. X. (2007).** Prevalence and characterization
720 of extended-spectrum cephalosporin-resistant nontyphoidal *Salmonella* isolates in
721 adults in Saint Petersburg, Russia (2002-2005). *Microb Drug Resist* **13**, 102-107.
- 722 **El-Najjar, N. G., Farah, M. J., Hashwa, F. A. & Tokajian, S. T. (2010).** Antibiotic resistance
723 patterns and sequencing of class I integron from uropathogenic *Escherichia coli* in
724 Lebanon. *Lett Appl Microbiol* **51**, 456-461.
- 725 **Falbo, V., Carattoli, A., Tosini, F., Pezzella, C., Dionisi, A. M. & Luzzi, I. (1999).** Antibiotic
726 resistance conferred by a conjugative plasmid and a class I integron in *Vibrio cholerae*
727 O1 El Tor strains isolated in Albania and Italy. *Antimicrob Agents Chemother* **43**, 693-
728 696.
- 729 **Falcone, M., Perilli, M., Mezzatesta, M. L., Mancini, C., Amicosante, G., Stefani, S. & Venditti,**
730 **M. (2010).** Prolonged bacteraemia caused by VIM-1 metallo- β -lactamase-producing
731 *Proteus mirabilis*: first report from Italy. *Clin Microbiol Infect* **16**, 179-181.
- 732 **Feng, J. L., Yan, H., Chowdhury, N., Neogi, S. B., Yamasaki, S., Shi, L., Hu, J. & Chen, Q. (2011).**
733 Identification and characterization of integron-associated antibiotic resistant

734 *Laribacter hongkongensis* isolated from aquatic products in China. *Int J Food Microbiol*
735 **144**, 337-341.

736 **Ferreira da Silva, M., Vaz-Moreira, I., Gonzalez-Pajuelo, M., Nunes, O. C. & Manaia, C. M.**
737 **(2007)**. Antimicrobial resistance patterns in *Enterobacteriaceae* isolated from an urban
738 wastewater treatment plant. *FEMS Microbiol Ecol* **60**, 166-176.

739 **Fluit, A. C. & Schmitz, F. J. (1999)**. Class 1 integrons, gene cassettes, mobility, and
740 epidemiology. *Eur J Clin Microbiol Infect Dis* **18**, 761-770.

741 **Forsberg, K. J., Reyes, A., Wang, B., Selleck, E. M., Sommer, M. O. & Dantas, G. (2012)**. The
742 shared antibiotic resistome of soil bacteria and human pathogens. *Science* **337**, 1107-
743 1111.

744 **Frank, T., Gautier, V., Talarmin, A., Bercion, R. & Arlet, G. (2007)**. Characterization of
745 sulphonamide resistance genes and class 1 integron gene cassettes in
746 *Enterobacteriaceae*, Central African Republic (CAR). *J Antimicrob Chemother* **59**, 742-
747 745.

748 **Gassama, A., Aidara-Kane, A., Chainier, D., Denis, F. & Ploy, M. C. (2004)**. Integron-associated
749 antibiotic resistance in enteroaggregative and enteroinvasive *Escherichia coli*. *Microb*
750 *Drug Resist* **10**, 27-30.

751 **Gillings, M., Boucher, Y., Labbate, M., Holmes, A., Krishnan, S., Holley, M. & Stokes, H. W.**
752 **(2008)**. The evolution of class 1 integrons and the rise of antibiotic resistance. *J*
753 *Bacteriol* **190**, 5095-5100.

754 **Gillings, M. R. (2013)**. Evolutionary consequences of antibiotic use for the resistome,
755 mobilome and microbial pangenome. *Front Microbiol* **4**, 4.

756 **Gionechetti, F., Zucca, P., Gombac, F., Monti-Bragadin, C., Lagatolla, C., Tonin, E., Edalucci, E.,**
757 **Vitali, L. A. & Dolzani, L. (2008)**. Characterization of antimicrobial resistance and class
758 1 integrons in *Enterobacteriaceae* isolated from Mediterranean herring gulls (*Larus*
759 *cachinnans*). *Microb Drug Resist* **14**, 93-99.

760 **Gombac, F., Riccio, M. L., Rossolini, G. M., Lagatolla, C., Tonin, E., Monti-Bragadin, C.,**
761 **Lavenia, A. & Dolzani, L. (2002)**. Molecular characterization of integrons in
762 epidemiologically unrelated clinical isolates of *Acinetobacter baumannii* from Italian
763 hospitals reveals a limited diversity of gene cassette arrays. *Antimicrob Agents*
764 *Chemother* **46**, 3665-3668.

765 **Goncalves, A., Igrejas, G., Radhouani, H., Santos, T., Monteiro, R., Pacheco, R., Alcaide, E.,**
766 **Zorrilla, I., Serra, R. & other authors (2013)**. Detection of antibiotic resistant
767 enterococci and *Escherichia coli* in free range Iberian Lynx (*Lynx pardinus*). *Sci Total*
768 *Environ* **456-457**, 115-119.

769 **Grape, M., Farra, A., Kronvall, G. & Sundstrom, L. (2005)**. Integrons and gene cassettes in
770 clinical isolates of co-trimoxazole-resistant Gram-negative bacteria. *Clin Microbiol*
771 *Infect* **11**, 185-192.

772 **Gruteke, P., Goessens, W., Van Gils, J., Peerbooms, P., Lemmens-Den Toom, N., Van Santen-**
773 **Verheuvell, M., Van Belkum, A. & Verbrugh, H. (2003)**. Patterns of resistance
774 associated with integrons, the extended-spectrum β -lactamase SHV-5 gene, and a
775 multidrug efflux pump of *Klebsiella pneumoniae* causing a nosocomial outbreak. *J Clin*
776 *Microbiol* **41**, 1161-1166.

777 **Gu, B., Tong, M., Zhao, W., Liu, G., Ning, M., Pan, S. & Zhao, W. (2007)**. Prevalence and
778 characterization of class I integrons among *Pseudomonas aeruginosa* and
779 *Acinetobacter baumannii* isolates from patients in Nanjing, China. *J Clin Microbiol* **45**,
780 241-243.

781 **Guerin, E., Cambray, G., Sanchez-Alberola, N., Campoy, S., Erill, I., Da Re, S., Gonzalez-Zorn,**
782 **B., Barbe, J., Ploy, M. C. & other authors (2009)**. The SOS response controls integron
783 recombination. *Science* **324**, 1034.

- 784 **Guerra, B., Soto, S., Cal, S. & Mendoza, M. C. (2000).** Antimicrobial resistance and spread of
785 class 1 integrons among *Salmonella* serotypes. *Antimicrob Agents Chemother* **44**, 2166-
786 2169.
- 787 **Guerra, B., Junker, E., Schroeter, A., Helmuth, R., Guth, B. E. & Beutin, L. (2006).** Phenotypic
788 and genotypic characterization of antimicrobial resistance in *Escherichia coli* O111
789 isolates. *J Antimicrob Chemother* **57**, 1210-1214.
- 790 **Hall, R. M. & Stokes, H. W. (1990).** The structure of a partial duplication in the integron of
791 plasmid pDGO100. *Plasmid* **23**, 76-79.
- 792 **Hall, R. M. & Collis, C. M. (1995).** Mobile gene cassettes and integrons: capture and spread of
793 genes by site-specific recombination. *Mol Microbiol* **15**, 593-600.
- 794 **Hall, R. M. & Collis, C. M. (1998).** Antibiotic resistance in gram-negative bacteria: the role of
795 gene cassettes and integrons. *Drug Resist Updat* **1**, 109-119.
- 796 **Han, N., Sheng, D. & Xu, H. (2012).** Role of *Escherichia coli* strain subgroups, integrons, and
797 integron-associated gene cassettes in dissemination of antimicrobial resistance in
798 aquatic environments of Jinan, China. *Water Sci Technol* **66**, 2385-2392.
- 799 **Harrison, E. M., Paterson, G. K., Holden, M. T., Larsen, J., Stegger, M., Larsen, A. R., Petersen,
800 A., Skov, R. L., Christensen, J. M. & other authors (2013).** Whole genome sequencing
801 identifies zoonotic transmission of MRSA isolates with the novel *mecA* homologue
802 *mecC*. *EMBO Mol Med* **5**, 509-515.
- 803 **Havlickova, H., Hradecka, H., Bernardyova, I. & Rychlik, I. (2009).** Distribution of integrons
804 and SGI1 among antibiotic-resistant *Salmonella enterica* isolates of animal origin. *Vet
805 Microbiol* **133**, 193-198.
- 806 **Hedges, R. W., Datta, N. & Fleming, M. P. (1972).** R factors conferring resistance to
807 trimethoprim but not sulphonamides. *J Gen Microbiol* **73**, 573-575.
- 808 **Heikkila, E., Skurnik, M., Sundstrom, L. & Huovinen, P. (1993).** A novel dihydrofolate
809 reductase cassette inserted in an integron borne on a Tn21-like element. *Antimicrob
810 Agents Chemother* **37**, 1297-1304.
- 811 **Heir, E., Lindstedt, B. A., Leegaard, T. M., Gjernes, E. & Kapperud, G. (2004).** Prevalence and
812 characterization of integrons in blood culture *Enterobacteriaceae* and gastrointestinal
813 *Escherichia coli* in Norway and reporting of a novel class 1 integron-located
814 lincosamide resistance gene. *Ann Clin Microbiol Antimicrob* **3**, 12.
- 815 **Heuer, H. & Smalla, K. (2007).** Manure and sulfadiazine synergistically increased bacterial
816 antibiotic resistance in soil over at least two months. *Environ Microbiol* **9**, 657-666.
- 817 **Heuer, H., Binh, C. T., Jechalke, S., Kopmann, C., Zimmerling, U., Krogerrecklenfort, E.,
818 Ledger, T., Gonzalez, B., Top, E. & other authors (2012).** IncP-1 ϵ plasmids are
819 important vectors of antibiotic resistance genes in agricultural systems: diversification
820 driven by class 1 integron gene cassettes. *Front Microbiol* **3**, 2.
- 821 **Hocquet, D., Llanes, C., Thouverez, M., Kulasekara, H. D., Bertrand, X., Plesiat, P., Mazel, D. &
822 Miller, S. I. (2012).** Evidence for induction of integron-based antibiotic resistance by
823 the SOS response in a clinical setting. *PLoS Pathog* **8**, e1002778.
- 824 **Holt, K. E., Thomson, N. R., Wain, J., Phan, M. D., Nair, S., Hasan, R., Bhutta, Z. A., Quail, M.
825 A., Norbertczak, H. & other authors (2007).** Multidrug-resistant *Salmonella enterica*
826 serovar Paratyphi A harbors IncHI1 plasmids similar to those found in serovar Typhi. *J
827 Bacteriol* **189**, 4257-4264.
- 828 **Hsu, S. C., Chiu, T. H., Pang, J. C., Hsuan-Yuan, C. H., Chang, G. N. & Tsen, H. Y. (2006).**
829 Characterisation of antimicrobial resistance patterns and class 1 integrons among
830 *Escherichia coli* and *Salmonella enterica* serovar Choleraesuis strains isolated from
831 humans and swine in Taiwan. *Int J Antimicrob Agents* **27**, 383-391.
- 832 **Hu, L. F., Chang, X., Ye, Y., Wang, Z. X., Shao, Y. B., Shi, W., Li, X. & Li, J. B. (2011).**
833 *Stenotrophomonas maltophilia* resistance to trimethoprim/sulfamethoxazole
834 mediated by acquisition of *sul* and *dfrA* genes in a plasmid-mediated class 1 integron.
835 *Int J Antimicrob Agents* **37**, 230-234.

836 **Huovinen, P. & Jacoby, G. A. (1991).** Sequence of the PSE-1 β -lactamase gene. *Antimicrob*
837 *Agents Chemother* **35**, 2428-2430.

838 **Hussein, A. I., Ahmed, A. M., Sato, M. & Shimamoto, T. (2009).** Characterization of integrons
839 and antimicrobial resistance genes in clinical isolates of Gram-negative bacteria from
840 Palestinian hospitals. *Microbiol Immunol* **53**, 595-602.

841 **Huys, G., Cnockaert, M., Nemec, A., Dijkshoorn, L., Brisse, S., Vaneechoutte, M. & Swings, J.**
842 **(2005).** Repetitive-DNA-element PCR fingerprinting and antibiotic resistance of pan-
843 European multi-resistant *Acinetobacter baumannii* clone III strains. *J Med Microbiol* **54**,
844 851-856.

845 **Ibrahim, M. E., Magzoub, M. A., Bilal, N. E. & Hamid, M. E. (2013).** Distribution of class I
846 integrons and their effect on the prevalence of multi-drug resistant *Escherichia coli*
847 clinical isolates from Sudan. *Saudi Med J* **34**, 240-247.

848 **Iversen, J., Sandvang, D., Srijan, A., Cam, P. D. & Dalsgaard, A. (2003).** Characterization of
849 antimicrobial resistance, plasmids, and gene cassettes in *Shigella* spp. from patients in
850 Vietnam. *Microb Drug Resist* **9 Suppl 1**, S17-24.

851 **Jones, L. A., McIver, C. J., Kim, M. J., Rawlinson, W. D. & White, P. A. (2005).** The *aadB* gene
852 cassette is associated with *bla_{SHV}* genes in *Klebsiella* species producing extended-
853 spectrum β -lactamases. *Antimicrob Agents Chemother* **49**, 794-797.

854 **Jove, T., Da Re, S., Denis, F., Mazel, D. & Ploy, M. C. (2010).** Inverse correlation between
855 promoter strength and excision activity in class 1 integrons. *PLoS Genet* **6**, e1000793.

856 **Kadlec, K. & Schwarz, S. (2008).** Analysis and distribution of class 1 and class 2 integrons and
857 associated gene cassettes among *Escherichia coli* isolates from swine, horses, cats and
858 dogs collected in the BfT-GermVet monitoring study. *J Antimicrob Chemother* **62**, 469-
859 473.

860 **Kadlec, K., von Czapiewski, E., Kaspar, H., Wallmann, J., Michael, G. B., Steinacker, U. &**
861 **Schwarz, S. (2011).** Molecular basis of sulfonamide and trimethoprim resistance in
862 fish-pathogenic *Aeromonas* isolates. *Appl Environ Microbiol* **77**, 7147-7150.

863 **Kang, H. Y., Jeong, Y. S., Oh, J. Y., Tae, S. H., Choi, C. H., Moon, D. C., Lee, W. K., Lee, Y. C.,**
864 **Seol, S. Y. & other authors (2005).** Characterization of antimicrobial resistance and
865 class 1 integrons found in *Escherichia coli* isolates from humans and animals in Korea. *J*
866 *Antimicrob Chemother* **55**, 639-644.

867 **Kang, M. S., Kim, A., Jung, B. Y., Her, M., Jeong, W., Cho, Y. M., Oh, J. Y., Lee, Y. J., Kwon, J. H.**
868 **& other authors (2010).** Characterization of antimicrobial resistance of recent
869 *Salmonella enterica* serovar Gallinarum isolates from chickens in South Korea. *Avian*
870 *Pathol* **39**, 201-205.

871 **Kansakar, P., Dorji, D., Chongtrakool, P., Mingmongkolchai, S., Mokmake, B. & Dubbs, P.**
872 **(2011).** Local dissemination of multidrug-resistant *Acinetobacter baumannii* clones in a
873 Thai hospital. *Microb Drug Resist* **17**, 109-119.

874 **Karczmarczyk, M., Abbott, Y., Walsh, C., Leonard, N. & Fanning, S. (2011).** Characterization of
875 multidrug-resistant *Escherichia coli* isolates from animals presenting at a university
876 veterinary hospital. *Appl Environ Microbiol* **77**, 7104-7112.

877 **Kazama, H., Kizu, K., Iwasaki, M., Hamashima, H., Sasatsu, M. & Arai, T. (1995).** Isolation and
878 structure of a new integron that includes a streptomycin resistance gene from the R
879 plasmid of *Pseudomonas aeruginosa*. *FEMS Microbiol Lett* **134**, 137-141.

880 **Khan, A. A., Cheng, C. M., Van, K. T., West, C. S., Nawaz, M. S. & Khan, S. A. (2006).**
881 Characterization of class 1 integron resistance gene cassettes in *Salmonella enterica*
882 serovars Oslo and Bareilly from imported seafood. *J Antimicrob Chemother* **58**, 1308-
883 1310.

884 **Khemtong, S. & Chuanchuen, R. (2008).** Class 1 integrons and *Salmonella* genomic island 1
885 among *Salmonella enterica* isolated from poultry and swine. *Microb Drug Resist* **14**, 65-
886 70.

- 887 **Kiiru, J., Butaye, P., Goddeeris, B. M. & Kariuki, S. (2013).** Analysis for prevalence and physical
888 linkages amongst integrons, *ISEcp1*, *ISCR1*, *Tn21* and *Tn7* encountered in *Escherichia*
889 *coli* strains from hospitalized and non-hospitalized patients in Kenya during a 19-year
890 period (1992-2011). *BMC Microbiol* **13**, 109.
- 891 **Kikuvi, G. M., Schwarz, S., Ombui, J. N., Mitema, E. S. & Kehrenberg, C. (2007).** Streptomycin
892 and chloramphenicol resistance genes in *Escherichia coli* isolates from cattle, pigs, and
893 chicken in Kenya. *Microb Drug Resist* **13**, 62-68.
- 894 **Kim, S., Kim, S. H., Kim, J., Shin, J. H., Lee, B. K. & Park, M. S. (2011).** Occurrence and
895 distribution of various genetic structures of class 1 and class 2 integrons in *Salmonella*
896 *enterica* isolates from foodborne disease patients in Korea for 16 years. *Foodborne*
897 *Pathog Dis* **8**, 319-324.
- 898 **Koczura, R., Mokracka, J., Krzyminska, S. & Kaznowski, A. (2011).** Virulence properties and
899 integron-associated antibiotic resistance of *Klebsiella mobilis* strains isolated from
900 clinical specimens. *J Med Microbiol* **60**, 281-288.
- 901 **Koh, T. H., Sng, L. H., Wang, G. C., Hsu, L. Y. & Zhao, Y. (2007).** IMP-4 and OXA β -lactamases in
902 *Acinetobacter baumannii* from Singapore. *J Antimicrob Chemother* **59**, 627-632.
- 903 **Kor, S. B., Choo, Q. C. & Chew, C. H. (2013).** New integron gene arrays from multiresistant
904 clinical isolates of members of the *Enterobacteriaceae* and *Pseudomonas aeruginosa*
905 from hospitals in Malaysia. *J Med Microbiol* **62**, 412-420.
- 906 **Kouda, S., Ohara, M., Onodera, M., Fujiue, Y., Sasaki, M., Kohara, T., Kashiya, S.,**
907 **Hayashida, S., Harino, T. & other authors (2009).** Increased prevalence and clonal
908 dissemination of multidrug-resistant *Pseudomonas aeruginosa* with the *bla*_{IMP-1} gene
909 cassette in Hiroshima. *J Antimicrob Chemother* **64**, 46-51.
- 910 **Krauland, M. G., Marsh, J. W., Paterson, D. L. & Harrison, L. H. (2009).** Integron-mediated
911 multidrug resistance in a global collection of nontyphoidal *Salmonella enterica* isolates.
912 *Emerg Infect Dis* **15**, 388-396.
- 913 **Kumai, Y., Suzuki, Y., Tanaka, Y., Shima, K., Bhadra, R. K., Yamasaki, S., Kuroda, K. & Endo, G.**
914 **(2005).** Characterization of multidrug-resistance phenotypes and genotypes of
915 *Escherichia coli* strains isolated from swine from an abattoir in Osaka, Japan. *Epidemiol*
916 *Infect* **133**, 59-70.
- 917 **L'Abée-Lund, T. M. & Sorum, H. (2001).** Class 1 integrons mediate antibiotic resistance in the
918 fish pathogen *Aeromonas salmonicida* worldwide. *Microb Drug Resist* **7**, 263-272.
- 919 **Labar, A. S., Millman, J. S., Ruebush, E., Opintan, J. A., Bishar, R. A., Aboderin, A. O.,**
920 **Newman, M. J., Lamikanra, A. & Okeke, I. N. (2012).** Regional dissemination of a
921 trimethoprim-resistance gene cassette via a successful transposable element. *PLoS*
922 *One* **7**, e38142.
- 923 **Lapierre, L., Cornejo, J., Borie, C., Toro, C. & San Martin, B. (2008).** Genetic characterization of
924 antibiotic resistance genes linked to class 1 and class 2 integrons in commensal strains
925 of *Escherichia coli* isolated from poultry and swine. *Microb Drug Resist* **14**, 265-272.
- 926 **Lay, K. K., Koowattananukul, C., Chansong, N. & Chuanchuen, R. (2012).** Antimicrobial
927 resistance, virulence, and phylogenetic characteristics of *Escherichia coli* isolates from
928 clinically healthy swine. *Foodborne Pathog Dis* **9**, 992-1001.
- 929 **Lee, K., Yong, D., Yum, J. H., Lim, Y. S., Kim, H. S., Lee, B. K. & Chong, Y. (2004).** Emergence of
930 multidrug-resistant *Salmonella enterica* serovar Typhi in Korea. *Antimicrob Agents*
931 *Chemother* **48**, 4130-4135.
- 932 **Lee, K. E. & Lee, Y. (2007).** Isolation of multidrug-resistant *Salmonella typhimurium* DT104
933 from swine in Korea. *J Microbiol* **45**, 590-592.
- 934 **Lee, M. F., Chen, Y. H. & Peng, C. F. (2009).** Molecular characterisation of class 1 integrons in
935 *Salmonella enterica* serovar Choleraesuis isolates from southern Taiwan. *Int J*
936 *Antimicrob Agents* **33**, 216-222.

- 937 **Lee, M. F., Peng, C. F., Lin, Y. H., Lin, S. R. & Chen, Y. H. (2008).** Molecular diversity of class 1
938 integrons in human isolates of *Aeromonas* spp. from southern Taiwan. *Jpn J Infect Dis*
939 **61**, 343-349.
- 940 **Levesque, C., Piche, L., Larose, C. & Roy, P. H. (1995).** PCR mapping of integrons reveals
941 several novel combinations of resistance genes. *Antimicrob Agents Chemother* **39**, 185-
942 191.
- 943 **Levesque, R. C. & Jacoby, G. A. (1988).** Molecular structure and interrelationships of
944 multiresistance β -lactamase transposons. *Plasmid* **19**, 21-29.
- 945 **Li, D., Yu, T., Zhang, Y., Yang, M., Li, Z., Liu, M. & Qi, R. (2010).** Antibiotic resistance
946 characteristics of environmental bacteria from an oxytetracycline production
947 wastewater treatment plant and the receiving river. *Appl Environ Microbiol* **76**, 3444-
948 3451.
- 949 **Li, D., Yang, M., Hu, J., Zhang, J., Liu, R., Gu, X., Zhang, Y. & Wang, Z. (2009).** Antibiotic-
950 resistance profile in environmental bacteria isolated from penicillin production
951 wastewater treatment plant and the receiving river. *Environ Microbiol* **11**, 1506-1517.
- 952 **Li, Q., Skyberg, J. A., Fakhr, M. K., Sherwood, J. S., Nolan, L. K. & Logue, C. M. (2006).**
953 Antimicrobial susceptibility and characterization of *Salmonella* isolates from processed
954 bison carcasses. *Appl Environ Microbiol* **72**, 3046-3049.
- 955 **Libisch, B., Balogh, B. & Fuzi, M. (2009).** Identification of two multidrug-resistant
956 *Pseudomonas aeruginosa* clonal lineages with a countrywide distribution in Hungary.
957 *Curr Microbiol* **58**, 111-116.
- 958 **Liebert, C. A., Hall, R. M. & Summers, A. O. (1999).** Transposon Tn21, flagship of the floating
959 genome. *Microbiol Mol Biol Rev* **63**, 507-522.
- 960 **Lindstedt, B. A., Heir, E., Nygard, I. & Kapperud, G. (2003).** Characterization of class I integrons
961 in clinical strains of *Salmonella enterica* subsp. *enterica* serovars Typhimurium and
962 Enteritidis from Norwegian hospitals. *J Med Microbiol* **52**, 141-149.
- 963 **Lu, L., Dai, L., Wang, Y., Wu, C., Chen, X., Li, L., Qi, Y., Xia, L. & Shen, J. (2010).**
964 Characterization of antimicrobial resistance and integrons among *Escherichia coli*
965 isolated from animal farms in Eastern China. *Acta Trop* **113**, 20-25.
- 966 **Lukkana, M., Wongtavatchai, J. & Chuanchuen, R. (2012).** Class 1 integrons in *Aeromonas*
967 *hydrophila* isolates from farmed Nile tilapia (*Oreochromis nilotica*). *J Vet Med Sci* **74**,
968 435-440.
- 969 **Machado, E., Coque, T. M., Cantón, R., Sousa, J. C. & Peixe, L. (2008).** Antibiotic resistance
970 integrons and extended-spectrum β -lactamases among Enterobacteriaceae isolates
971 recovered from chickens and swine in Portugal. *J Antimicrob Chemother* **62**, 296-302.
- 972 **Mahrouki, S., Belhadj, O., Chihi, H., Mohamed, B. M., Celenza, G., Amicosante, G. & Perilli,
973 M. (2012).** Chromosomal bla_{CTX-M-15} associated with ISEcp1 in *Proteus mirabilis* and
974 *Morganella morganii* isolated at the Military Hospital of Tunis, Tunisia. *J Med Microbiol*
975 **61**, 1286-1289.
- 976 **Majtan, T., Majtanova, L., Timko, J. & Majtan, V. (2007).** Oligonucleotide microarray for
977 molecular characterization and genotyping of *Salmonella* spp. strains. *J Antimicrob*
978 *Chemother* **60**, 937-946.
- 979 **Matthew, M. & Sykes, R. B. (1977).** Properties of the β -lactamase specified by the
980 *Pseudomonas* plasmid RPL11. *J Bacteriol* **132**, 341-345.
- 981 **Mazel, D. (2006).** Integrons: agents of bacterial evolution. *Nat Rev Microbiol* **4**, 608-620.
- 982 **Mokracka, J., Koczura, R. & Kaznowski, A. (2012).** Multiresistant *Enterobacteriaceae* with class
983 1 and class 2 integrons in a municipal wastewater treatment plant. *Water Res* **46**,
984 3353-3363.
- 985 **Mokracka, J., Koczura, R., Pawlowski, K. & Kaznowski, A. (2011).** Resistance patterns and
986 integron cassette arrays of *Enterobacter cloacae* complex strains of human origin. *J*
987 *Med Microbiol* **60**, 737-743.

- 988 **Molla, B., Miko, A., Pries, K., Hildebrandt, G., Kleer, J., Schroeter, A. & Helmuth, R. (2007).**
989 Class 1 integrons and resistance gene cassettes among multidrug resistant *Salmonella*
990 serovars isolated from slaughter animals and foods of animal origin in Ethiopia. *Acta*
991 *Trop* **103**, 142-149.
- 992 **Morabito, S., Tozzoli, R., Caprioli, A., Karch, H. & Carattoli, A. (2002).** Detection and
993 characterization of class 1 integrons in enterohemorrhagic *Escherichia coli*. *Microb*
994 *Drug Resist* **8**, 85-91.
- 995 **Moura, A., Henriques, I., Ribeiro, R. & Correia, A. (2007).** Prevalence and characterization of
996 integrons from bacteria isolated from a slaughterhouse wastewater treatment plant. *J*
997 *Antimicrob Chemother* **60**, 1243-1250.
- 998 **Moura, A., Pereira, C., Henriques, I. & Correia, A. (2012).** Novel gene cassettes and integrons
999 in antibiotic-resistant bacteria isolated from urban wastewaters. *Res Microbiol* **163**,
1000 92-100.
- 1001 **Moura, A., Soares, M., Pereira, C., Leitao, N., Henriques, I. & Correia, A. (2009).** INTEGRALL: a
1002 database and search engine for integrons, integrases and gene cassettes.
1003 *Bioinformatics* **25**, 1096-1098.
- 1004 **Mukherjee, S. & Chakraborty, R. (2006).** Incidence of class 1 integrons in multiple antibiotic-
1005 resistant Gram-negative copiotrophic bacteria from the River Torsa in India. *Res*
1006 *Microbiol* **157**, 220-226.
- 1007 **Murphy, B. P., O'Mahony, R., Buckley, J. F., Shine, P., Boyd, E. F., Gilroy, D. & Fanning, S.**
1008 **(2007).** Investigation of a global collection of nontyphoidal *Salmonella* of various
1009 serotypes cultured between 1953 and 2004 for the presence of class 1 integrons. *FEMS*
1010 *Microbiol Lett* **266**, 170-176.
- 1011 **Najibi, S., Bakhshi, B., Fallahzad, S., Pourshafie, M. R., Katouli, M., Sattari, M., Alebouyeh, M.**
1012 **& Tajbakhsh, M. (2012).** Distribution of class 1 integrons among enteropathogenic
1013 *Escherichia coli*. *Can J Microbiol* **58**, 637-643.
- 1014 **Nakaya, R., Nakamura, A. & Murata, Y. (1960).** Resistance transfer agents in *Shigella*. *Biochem*
1015 *Biophys Res Commun* **3**, 654-659.
- 1016 **Nardelli, M., Scalzo, P. M., Ramirez, M. S., Quiroga, M. P., Cassini, M. H. & Centron, D. (2012).**
1017 Class 1 integrons in environments with different degrees of urbanization. *PLoS One* **7**,
1018 e39223.
- 1019 **Navia, M. M., Ruiz, J. & Vila, J. (2004).** Molecular characterization of the integrons in *Shigella*
1020 strains isolated from patients with traveler's diarrhea. *Diagn Microbiol Infect Dis* **48**,
1021 175-179.
- 1022 **Ndi, O. L. & Barton, M. D. (2011).** Incidence of class 1 integron and other antibiotic resistance
1023 determinants in *Aeromonas* spp. from rainbow trout farms in Australia. *J Fish Dis* **34**,
1024 589-599.
- 1025 **Nemec, A., Dolzani, L., Brisse, S., van den Broek, P. & Dijkshoorn, L. (2004).** Diversity of
1026 aminoglycoside-resistance genes and their association with class 1 integrons among
1027 strains of pan-European *Acinetobacter baumannii* clones. *J Med Microbiol* **53**, 1233-
1028 1240.
- 1029 **Nesvera, J., Hochmannova, J. & Patek, M. (1998).** An integron of class 1 is present on the
1030 plasmid pCG4 from gram-positive bacterium *Corynebacterium glutamicum*. *FEMS*
1031 *Microbiol Lett* **169**, 391-395.
- 1032 **Ng, L. K., Mulvey, M. R., Martin, I., Peters, G. A. & Johnson, W. (1999).** Genetic
1033 characterization of antimicrobial resistance in Canadian isolates of *Salmonella* serovar
1034 Typhimurium DT104. *Antimicrob Agents Chemother* **43**, 3018-3021.
- 1035 **Nogrady, N., Gado, I., Toth, A. & Paszti, J. (2005).** Antibiotic resistance and class 1 integron
1036 patterns of non-typhoidal human *Salmonella* serotypes isolated in Hungary in 2002
1037 and 2003. *Int J Antimicrob Agents* **26**, 126-132.

- 1038 **Nogrady, N., Kiraly, M., Borbas, K., Toth, A., Paszti, J. & Toth, I. (2013).** Antimicrobial
1039 resistance and genetic characteristics of integron-carrier *Shigellae* isolated in Hungary;
1040 1998-2008. *J Med Microbiol*.
- 1041 **O'Halloran, F., Lucey, B., Cryan, B., Buckley, T. & Fanning, S. (2004).** Molecular
1042 characterization of class 1 integrons from Irish thermophilic *Campylobacter* spp. *J*
1043 *Antimicrob Chemother* **53**, 952-957.
- 1044 **Ozgumus, O. B., Celik-Sevim, E., Alpay-Karaoglu, S., Sandalli, C. & Sevim, A. (2007).** Molecular
1045 characterization of antibiotic resistant *Escherichia coli* strains isolated from tap and
1046 spring waters in a coastal region in Turkey. *J Microbiol* **45**, 379-387.
- 1047 **Ozgumus, O. B., Sandalli, C., Sevim, A., Celik-Sevim, E. & Sivri, N. (2009).** Class 1 and class 2
1048 integrons and plasmid-mediated antibiotic resistance in coliforms isolated from ten
1049 rivers in northern Turkey. *J Microbiol* **47**, 19-27.
- 1050 **Pallecchi, L., Lucchetti, C., Bartoloni, A., Bartalesi, F., Mantella, A., Gamboa, H., Carattoli, A.,
1051 Paradisi, F. & Rossolini, G. M. (2007).** Population structure and resistance genes in
1052 antibiotic-resistant bacteria from a remote community with minimal antibiotic
1053 exposure. *Antimicrob Agents Chemother* **51**, 1179-1184.
- 1054 **Pan, J. C., Ye, R., Meng, D. M., Zhang, W., Wang, H. Q. & Liu, K. Z. (2006).** Molecular
1055 characteristics of class 1 and class 2 integrons and their relationships to antibiotic
1056 resistance in clinical isolates of *Shigella sonnei* and *Shigella flexneri*. *J Antimicrob*
1057 *Chemother* **58**, 288-296.
- 1058 **Partridge, S. R. & Hall, R. M. (2005).** Correctly identifying the streptothricin resistance gene
1059 cassette. *J Clin Microbiol* **43**, 4298-4300.
- 1060 **Partridge, S. R., Brown, H. J. & Hall, R. M. (2002).** Characterization and movement of the class
1061 1 integron known as Tn2521 and Tn1405. *Antimicrob Agents Chemother* **46**, 1288-
1062 1294.
- 1063 **Partridge, S. R., Brown, H. J., Stokes, H. W. & Hall, R. M. (2001).** Transposons Tn1696 and
1064 Tn21 and their integrons In4 and In2 have independent origins. *Antimicrob Agents*
1065 *Chemother* **45**, 1263-1270.
- 1066 **Partridge, S. R., Tsafnat, G., Coiera, E. & Iredell, J. R. (2009).** Gene cassettes and cassette
1067 arrays in mobile resistance integrons. *FEMS Microbiol Rev* **33**, 757-784.
- 1068 **Pazhani, G. P., Chakraborty, S., Fujihara, K., Yamasaki, S., Ghosh, A., Nair, G. B. &
1069 Ramamurthy, T. (2011).** QRDR mutations, efflux system & antimicrobial resistance
1070 genes in enterotoxigenic *Escherichia coli* isolated from an outbreak of diarrhoea in
1071 Ahmedabad, India. *Indian J Med Res* **134**, 214-223.
- 1072 **Peirano, G., Agero, Y., Aarestrup, F. M., dos Reis, E. M. & dos Prazeres Rodrigues, D. (2006).**
1073 Occurrence of integrons and antimicrobial resistance genes among *Salmonella enterica*
1074 from Brazil. *J Antimicrob Chemother* **58**, 305-309.
- 1075 **Pellegrini, C., Mercuri, P. S., Celenza, G., Galleni, M., Segatore, B., Sacchetti, E., Volpe, R.,
1076 Amicosante, G. & Perilli, M. (2009).** Identification of *bla*(IMP-22) in *Pseudomonas* spp.
1077 in urban wastewater and nosocomial environments: biochemical characterization of a
1078 new IMP metallo-enzyme variant and its genetic location. *J Antimicrob Chemother* **63**,
1079 901-908.
- 1080 **Peng, C. F., Lee, M. F., Fu, H. T., Chen, Y. J. & Hsu, H. J. (2007).** Characterization of class 1
1081 integrons and antimicrobial resistance in CTX-M-3-producing *Serratia marcescens*
1082 isolates from southern Taiwan. *Jpn J Infect Dis* **60**, 250-256.
- 1083 **Pepperell, C., Kus, J. V., Gardam, M. A., Humar, A. & Burrows, L. L. (2002).** Low-virulence
1084 *Citrobacter* species encode resistance to multiple antimicrobials. *Antimicrob Agents*
1085 *Chemother* **46**, 3555-3560.
- 1086 **Perez-Moreno, M. O., Pico-Plana, E., de Toro, M., Grande-Armas, J., Quiles-Fortuny, V., Pons,
1087 M. J., Gomes, C., Saenz, Y., Torres, C. & other authors (2013).** β -Lactamases,
1088 transferable quinolone resistance determinants, and class 1 integron-mediated

- 1089 antimicrobial resistance in human clinical *Salmonella enterica* isolates of non-
1090 Typhimurium serotypes. *Int J Med Microbiol* **303**, 25-31.
- 1091 **Perez-Valdespino, A., Fernandez-Rendon, E. & Curiel-Quesada, E. (2009).** Detection and
1092 characterization of class 1 integrons in *Aeromonas* spp. isolated from human diarrheic
1093 stool in Mexico. *J Basic Microbiol* **49**, 572-578.
- 1094 **Peters, E. D., Leverstein-van Hall, M. A., Box, A. T., Verhoef, J. & Fluit, A. C. (2001).** Novel
1095 gene cassettes and integrons. *Antimicrob Agents Chemother* **45**, 2961-2964.
- 1096 **Petrova, M., Gorlenko, Z. & Mindlin, S. (2011).** Tn5045, a novel integron-containing antibiotic
1097 and chromate resistance transposon isolated from a permafrost bacterium. *Res*
1098 *Microbiol* **162**, 337-345.
- 1099 **Plante, I., Centron, D. & Roy, P. H. (2003).** Direct sequencing and PCR mapping of integrons
1100 reveals multiple class 1 integrons in the multiresistant strain *Enterobacter cloacae*
1101 SCH88040794. *FEMS Microbiol Lett* **221**, 59-62.
- 1102 **Ploy, M. C., Chainier, D., Tran Thi, N. H., Poilane, I., Cruaud, P., Denis, F., Collignon, A. &**
1103 **Lambert, T. (2003).** Integron-associated antibiotic resistance in *Salmonella enterica*
1104 serovar Typhi from Asia. *Antimicrob Agents Chemother* **47**, 1427-1429.
- 1105 **Poirel, L., Guibert, M., Bellais, S., Naas, T. & Nordmann, P. (1999).** Integron- and
1106 carbenicillinase-mediated reduced susceptibility to amoxicillin-clavulanic acid in
1107 isolates of multidrug-resistant *Salmonella enterica* serotype typhimurium DT104 from
1108 French patients. *Antimicrob Agents Chemother* **43**, 1098-1104.
- 1109 **Povilonis, J., Seputiene, V., Ruzauskas, M., Siugzdiniene, R., Virgailis, M., Pavilonis, A. &**
1110 **Suziedeliene, E. (2010).** Transferable class 1 and 2 integrons in *Escherichia coli* and
1111 *Salmonella enterica* isolates of human and animal origin in Lithuania. *Foodborne*
1112 *Pathog Dis* **7**, 1185-1192.
- 1113 **Power, M. L., Emery, S. & Gillings, M. R. (2013).** Into the wild: dissemination of antibiotic
1114 resistance determinants via a species recovery program. *PLoS One* **8**, e63017.
- 1115 **Rajpara, N., Patel, A., Tiwari, N., Bahuguna, J., Antony, A., Choudhury, I., Ghosh, A., Jain, R. &**
1116 **Bhardwaj, A. K. (2009).** Mechanism of drug resistance in a clinical isolate of *Vibrio*
1117 *fluvialis*: involvement of multiple plasmids and integrons. *Int J Antimicrob Agents* **34**,
1118 220-225.
- 1119 **Rakotonirina, H. C., Garin, B., Randrianirina, F., Richard, V., Talarmin, A. & Arlet, G. (2013).**
1120 Molecular characterization of multidrug-resistant extended-spectrum β -lactamase-
1121 producing *Enterobacteriaceae* isolated in Antananarivo, Madagascar. *BMC Microbiol*
1122 **13**, 85.
- 1123 **Ramirez, M. S. & Tolmasky, M. E. (2010).** Aminoglycoside modifying enzymes. *Drug Resist*
1124 *Updat* **13**, 151-171.
- 1125 **Ranjbar, R., Giammanco, G. M., Farshad, S., Owlia, P., Aleo, A. & Mamma, C. (2011).**
1126 Serotypes, antibiotic resistance, and class 1 integrons in *Salmonella* isolates from
1127 pediatric cases of enteritis in Tehran, Iran. *Foodborne Pathog Dis* **8**, 547-553.
- 1128 **Recchia, G. D. & Hall, R. M. (1995).** Gene cassettes: a new class of mobile element.
1129 *Microbiology* **141**, 3015-3027.
- 1130 **Ridley, A. & Threlfall, E. J. (1998).** Molecular epidemiology of antibiotic resistance genes in
1131 multiresistant epidemic *Salmonella* typhimurium DT 104. *Microb Drug Resist* **4**, 113-
1132 118.
- 1133 **Roberts, M. C., Schwarz, S. & Aarts, H. J. (2012).** Erratum: Acquired antibiotic resistance
1134 genes: an overview. *Front Microbiol* **3**, 384.
- 1135 **Rodriguez, I., Martin, M. C., Mendoza, M. C. & Rodicio, M. R. (2006).** Class 1 and class 2
1136 integrons in non-prevalent serovars of *Salmonella enterica*: structure and association
1137 with transposons and plasmids. *J Antimicrob Chemother* **58**, 1124-1132.
- 1138 **Rodriguez, I., Barownick, W., Helmuth, R., Mendoza, M. C., Rodicio, M. R., Schroeter, A. &**
1139 **Guerra, B. (2009).** Extended-spectrum β -lactamases and AmpC β -lactamases in

1140 ceftiofur-resistant *Salmonella enterica* isolates from food and livestock obtained in
1141 Germany during 2003-07. *J Antimicrob Chemother* **64**, 301-309.

1142 **Rodriguez, M. M., Power, P., Sader, H., Galleni, M. & Gutkind, G. (2010).** Novel chromosome-
1143 encoded CTX-M-78 β -lactamase from a *Kluyvera georgiana* clinical isolate as a putative
1144 origin of CTX-M-25 subgroup. *Antimicrob Agents Chemother* **54**, 3070-3071.

1145 **Rosser, S. J. & Young, H. K. (1999).** Identification and characterization of class 1 integrons in
1146 bacteria from an aquatic environment. *J Antimicrob Chemother* **44**, 11-18.

1147 **Rowe-Magnus, D. A., Guerout, A. M. & Mazel, D. (2002).** Bacterial resistance evolution by
1148 recruitment of super-integron gene cassettes. *Mol Microbiol* **43**, 1657-1669.

1149 **Rowe-Magnus, D. A., Guerout, A. M., Ploncard, P., Dychinco, B., Davies, J. & Mazel, D. (2001).**
1150 The evolutionary history of chromosomal super-integrons provides an ancestry for
1151 multiresistant integrons. *Proc Natl Acad Sci U S A* **98**, 652-657.

1152 **Ruiz-Martinez, L., Lopez-Jimenez, L., Fuste, E., Vinuesa, T., Martinez, J. P. & Vinas, M. (2011).**
1153 Class 1 integrons in environmental and clinical isolates of *Pseudomonas aeruginosa*. *Int*
1154 *J Antimicrob Agents* **38**, 398-402.

1155 **Sa, L. L., Fonseca, E. L., Pellegrini, M., Freitas, F., Loureiro, E. C. & Vicente, A. C. (2010).**
1156 Occurrence and composition of class 1 and class 2 integrons in clinical and
1157 environmental O1 and non-O1/non-O139 *Vibrio cholerae* strains from the Brazilian
1158 Amazon. *Mem Inst Oswaldo Cruz* **105**, 229-232.

1159 **Sandalli, C., Buruk, C. K., Sancaktar, M. & Ozgumus, O. B. (2010).** Prevalence of integrons and
1160 a new *dfrA17* variant in Gram-negative bacilli which cause community-acquired
1161 infections. *Microbiol Immunol* **54**, 164-169.

1162 **Sandvang, D. (1999).** Novel streptomycin and spectinomycin resistance gene as a gene
1163 cassette within a class 1 integron isolated from *Escherichia coli*. *Antimicrob Agents*
1164 *Chemother* **43**, 3036-3038.

1165 **Sandvang, D. & Aarestrup, F. M. (2000).** Characterization of aminoglycoside resistance genes
1166 and class 1 integrons in porcine and bovine gentamicin-resistant *Escherichia coli*.
1167 *Microb Drug Resist* **6**, 19-27.

1168 **Sandvang, D., Aarestrup, F. M. & Jensen, L. B. (1998).** Characterisation of integrons and
1169 antibiotic resistance genes in Danish multiresistant *Salmonella enterica* Typhimurium
1170 DT104. *FEMS Microbiol Lett* **160**, 37-41.

1171 **Segal, H., Thomas, R. & Gay Elisha, B. (2003).** Characterization of class 1 integron resistance
1172 gene cassettes and the identification of a novel IS-like element in *Acinetobacter*
1173 *baumannii*. *Plasmid* **49**, 169-178.

1174 **Shahcheraghi, F., Badmasti, F. & Feizabadi, M. M. (2010).** Molecular characterization of class
1175 1 integrons in MDR *Pseudomonas aeruginosa* isolated from clinical settings in Iran,
1176 Tehran. *FEMS Immunol Med Microbiol* **58**, 421-425.

1177 **Shaw, K. J., Rather, P. N., Hare, R. S. & Miller, G. H. (1993).** Molecular genetics of
1178 aminoglycoside resistance genes and familial relationships of the aminoglycoside-
1179 modifying enzymes. *Microbiol Rev* **57**, 138-163.

1180 **Shi, L., Zheng, M., Xiao, Z., Asakura, M., Su, J., Li, L. & Yamasaki, S. (2006a).** Unnoticed spread
1181 of class 1 integrons in gram-positive clinical strains isolated in Guangzhou, China.
1182 *Microbiol Immunol* **50**, 463-467.

1183 **Shi, L., Fujihara, K., Sato, T., Ito, H., Garg, P., Chakrabarty, R., Ramamurthy, T., Nair, G. B.,
1184 Takeda, Y. & other authors (2006b).** Distribution and characterization of integrons in
1185 various serogroups of *Vibrio cholerae* strains isolated from diarrhoeal patients
1186 between 1992 and 2000 in Kolkata, India. *J Med Microbiol* **55**, 575-583.

1187 **Shin, G. W., You, M. J., Lee, H. S. & Lee, C. S. (2012).** Catheter-related bacteremia caused by
1188 multidrug-resistant *Leclercia adecarboxylata* in a patient with breast cancer. *J Clin*
1189 *Microbiol* **50**, 3129-3132.

1190 **Sidjabat, H. E., Townsend, K. M., Lorentzen, M., Gobius, K. S., Fegan, N., Chin, J. J.,
1191 Bettelheim, K. A., Hanson, N. D., Bensink, J. C. & other authors (2006).** Emergence

1192 and spread of two distinct clonal groups of multidrug-resistant *Escherichia coli* in a
1193 veterinary teaching hospital in Australia. *J Med Microbiol* **55**, 1125-1134.

1194 **Sivri, N., Sandalli, C., Ozgumus, O. B., Colakoglu, F. & Dogan, D. (2012).** Antibiotic Resistance
1195 Profiles of Enteric Bacteria Isolated from Kucukcekmece Lagoon (Istanbul–Turkey) *Turk*
1196 *J Fish Aquat Sci* **12**, 699-707.

1197 **Solberg, O. D., Ajiboye, R. M. & Riley, L. W. (2006).** Origin of class 1 and 2 integrons and gene
1198 cassettes in a population-based sample of uropathogenic *Escherichia coli*. *J Clin*
1199 *Microbiol* **44**, 1347-1351.

1200 **Soufi, L., Saenz, Y., de Toro, M., Abbassi, M. S., Rojo-Bezares, B., Vinue, L., Bouchami, O.,
1201 Touati, A., Ben Hassen, A. & other authors (2012).** Phenotypic and genotypic
1202 characterization of *Salmonella enterica* recovered from poultry meat in Tunisia and
1203 identification of new genetic traits. *Vector Borne Zoonotic Dis* **12**, 10-16.

1204 **Sow, A. G., Wane, A. A., Diallo, M. H., Boye, C. S. & Aidara-Kane, A. (2007).** Genotypic
1205 characterization of antibiotic-resistant *Salmonella enteritidis* isolates in Dakar, Senegal.
1206 *J Infect Dev Ctries* **1**, 284-288.

1207 **Srinivasan, V., Nam, H. M., Sawant, A. A., Headrick, S. I., Nguyen, L. T. & Oliver, S. P. (2008).**
1208 Distribution of tetracycline and streptomycin resistance genes and class 1 integrons in
1209 Enterobacteriaceae isolated from dairy and nondairy farm soils. *Microb Ecol* **55**, 184-
1210 193.

1211 **Srinivasan, V. B., Virk, R. K., Kaundal, A., Chakraborty, R., Datta, B., Ramamurthy, T.,
1212 Mukhopadhyay, A. K. & Ghosh, A. (2006).** Mechanism of drug resistance in clonally
1213 related clinical isolates of *Vibrio fluvialis* isolated in Kolkata, India. *Antimicrob Agents*
1214 *Chemother* **50**, 2428-2432.

1215 **Stalder, T., Barraud, O., Jove, T., Casellas, M., Gaschet, M., Dagot, C. & Ploy, M. C. (2014).**
1216 Quantitative and qualitative impact of hospital effluent on dissemination of the
1217 integron pool. *ISME J* **8**, 768-777.

1218 **Starikova, I., Harms, K., Haugen, P., Lunde, T. T. M., Primicerio, R., Samuelsen, O., Nielsen, K.
1219 M. & Johnsen, P. J. (2012).** A trade-off between the fitness cost of functional
1220 integrases and long-term stability of integrons. *PLoS Pathog* **8**, e1003043.

1221 **Stokes, H. W. & Hall, R. M. (1989).** A novel family of potentially mobile DNA elements
1222 encoding site-specific gene-integration functions: integrons. *Mol Microbiol* **3**, 1669-
1223 1683.

1224 **Stokes, H. W. & Gillings, M. R. (2011).** Gene flow, mobile genetic elements and the
1225 recruitment of antibiotic resistance genes into Gram-negative pathogens. *FEMS*
1226 *Microbiol Rev* **35**, 790-819.

1227 **Stokes, H. W., Nesbo, C. L., Holley, M., Bahl, M. I., Gillings, M. R. & Boucher, Y. (2006).** Class 1
1228 integrons potentially predating the association with Tn402-like transposition genes are
1229 present in a sediment microbial community. *J Bacteriol* **188**, 5722-5730.

1230 **Su, H. C., Ying, G. G., Tao, R., Zhang, R. Q., Fogarty, L. R. & Kolpin, D. W. (2011).** Occurrence of
1231 antibiotic resistance and characterization of resistance genes and integrons in
1232 Enterobacteriaceae isolated from integrated fish farms in South China. *J Environ Monit*
1233 **13**, 3229-3236.

1234 **Su, H. C., Ying, G. G., Tao, R., Zhang, R. Q., Zhao, J. L. & Liu, Y. S. (2012).** Class 1 and 2
1235 integrons, sul resistance genes and antibiotic resistance in *Escherichia coli* isolated
1236 from Dongjiang River, South China. *Environ Pollut* **169**, 42-49.

1237 **Sun, N., Liu, J. H., Yang, F., Lin, D. C., Li, G. H., Chen, Z. L. & Zeng, Z. L. (2012).** Molecular
1238 characterization of the antimicrobial resistance of *Riemerella anatipestifer* isolated
1239 from ducks. *Vet Microbiol* **158**, 376-383.

1240 **Sunde, M. (2005).** Prevalence and characterization of class 1 and class 2 integrons in
1241 *Escherichia coli* isolated from meat and meat products of Norwegian origin. *J*
1242 *Antimicrob Chemother* **56**, 1019-1024.

- 1243 **Sundstrom, L. & Skold, O. (1990).** The *dhfrI* trimethoprim resistance gene of Tn7 can be found
1244 at specific sites in other genetic surroundings. *Antimicrob Agents Chemother* **34**, 642-
1245 650.
- 1246 **Sundstrom, L., Vinayagamoorthy, T. & Skold, O. (1987).** Novel type of plasmid-borne
1247 resistance to trimethoprim. *Antimicrob Agents Chemother* **31**, 60-66.
- 1248 **Sundstrom, L., Swedberg, G. & Skold, O. (1993).** Characterization of transposon Tn5086,
1249 carrying the site-specifically inserted gene *dhfrVII* mediating trimethoprim resistance. *J*
1250 *Bacteriol* **175**, 1796-1805.
- 1251 **Tacao, M., Moura, A., Correia, A. & Henriques, I. (2014).** Co-resistance to different classes of
1252 antibiotics among ESBL-producers from aquatic systems. *Water Res* **48**, 100-107.
- 1253 **Tamang, M. D., Oh, J. Y., Seol, S. Y., Kang, H. Y., Lee, J. C., Lee, Y. C., Cho, D. T. & Kim, J.**
1254 **(2007).** Emergence of multidrug-resistant *Salmonella enterica* serovar Typhi associated
1255 with a class 1 integron carrying the *dfrA7* gene cassette in Nepal. *Int J Antimicrob*
1256 *Agents* **30**, 330-335.
- 1257 **Taviani, E., Ceccarelli, D., Lazaro, N., Bani, S., Cappuccinelli, P., Colwell, R. R. & Colombo, M.**
1258 **M. (2008).** Environmental *Vibrio* spp., isolated in Mozambique, contain a polymorphic
1259 group of integrative conjugative elements and class 1 integrons. *FEMS Microbiol Ecol*
1260 **64**, 45-54.
- 1261 **Tennhammar-Ekman, B. & Skold, O. (1979).** Trimethoprim resistance plasmids of different
1262 origin encode different drug-resistant dihydrofolate reductases. *Plasmid* **2**, 334-346.
- 1263 **Tennstedt, T., Szczepanowski, R., Braun, S., Puhler, A. & Schluter, A. (2003).** Occurrence of
1264 integron-associated resistance gene cassettes located on antibiotic resistance plasmids
1265 isolated from a wastewater treatment plant. *FEMS Microbiol Ecol* **45**, 239-252.
- 1266 **Thungapathra, M., Amita, Sinha, K. K., Chaudhuri, S. R., Garg, P., Ramamurthy, T., Nair, G. B.**
1267 **& Ghosh, A. (2002).** Occurrence of antibiotic resistance gene cassettes *aac(6')-Ib*,
1268 *dfrA5*, *dfrA12*, and *ereA2* in class I integrons in non-O1, non-O139 *Vibrio cholerae*
1269 strains in India. *Antimicrob Agents Chemother* **46**, 2948-2955.
- 1270 **Toleman, M. A., Bennett, P. M. & Walsh, T. R. (2006a).** ISCR elements: novel gene-capturing
1271 systems of the 21st century? *Microbiol Mol Biol Rev* **70**, 296-316.
- 1272 **Toleman, M. A., Bennett, P. M. & Walsh, T. R. (2006b).** Common regions e.g. *orf513* and
1273 antibiotic resistance: IS91-like elements evolving complex class 1 integrons. *J*
1274 *Antimicrob Chemother* **58**, 1-6.
- 1275 **Traglia, G. M., Almuzara, M., Merzier, A. K., Adams, C., Galanternik, L., Vay, C., Centron, D. &**
1276 **Ramirez, M. S. (2012).** *Achromobacter xylosoxidans*: an emerging pathogen carrying
1277 different elements involved in horizontal genetic transfer. *Curr Microbiol* **65**, 673-678.
- 1278 **Tseng, S. P., Wang, J. T., Liang, C. Y., Lee, P. S., Chen, Y. C. & Lu, P. L. (2014).** First Report of
1279 *bla_{IMP-8}* in *Raoultella planticola*. *Antimicrob Agents Chemother* **58**, 593-595.
- 1280 **Turton, J. F., Kaufmann, M. E., Gill, M. J., Pike, R., Scott, P. T., Fishbain, J., Craft, D., Deye, G.,**
1281 **Riddell, S. & other authors (2006).** Comparison of *Acinetobacter baumannii* isolates
1282 from the United Kingdom and the United States that were associated with repatriated
1283 casualties of the Iraq conflict. *J Clin Microbiol* **44**, 2630-2634.
- 1284 **Valenzuela, J. K., Thomas, L., Partridge, S. R., van der Reijden, T., Dijkshoorn, L. & Iredell, J.**
1285 **(2007).** Horizontal gene transfer in a polyclonal outbreak of carbapenem-resistant
1286 *Acinetobacter baumannii*. *J Clin Microbiol* **45**, 453-460.
- 1287 **van Essen-Zandbergen, A., Smith, H., Veldman, K. & Mevius, D. (2007).** Occurrence and
1288 characteristics of class 1, 2 and 3 integrons in *Escherichia coli*, *Salmonella* and
1289 *Campylobacter* spp. in the Netherlands. *J Antimicrob Chemother* **59**, 746-750.
- 1290 **van Hoek, A. H., Mevius, D., Guerra, B., Mullany, P., Roberts, A. P. & Aarts, H. J. (2011).**
1291 Acquired antibiotic resistance genes: an overview. *Front Microbiol* **2**, 203.
- 1292 **Van, T. T., Moutafis, G., Tran, L. T. & Coloe, P. J. (2007).** Antibiotic resistance in food-borne
1293 bacterial contaminants in Vietnam. *Appl Environ Microbiol* **73**, 7906-7911.

- 1294 **Vinue, L., Jove, T., Torres, C. & Ploy, M. C. (2011).** Diversity of class 1 integron gene cassette
1295 Pc promoter variants in clinical *Escherichia coli* strains and description of a new P2
1296 promoter variant. *Int J Antimicrob Agents* **38**, 526-529.
- 1297 **Vo, A. T., van Duijkeren, E., Fluit, A. C. & Gaastra, W. (2007).** A novel *Salmonella* genomic
1298 island 1 and rare integron types in *Salmonella* Typhimurium isolates from horses in The
1299 Netherlands. *J Antimicrob Chemother* **59**, 594-599.
- 1300 **Vo, A. T., van Duijkeren, E., Gaastra, W. & Fluit, A. C. (2010).** Antimicrobial resistance, class 1
1301 integrons, and genomic island 1 in *Salmonella* isolates from Vietnam. *PLoS One* **5**,
1302 e9440.
- 1303 **Waturangi, D. E., Suwanto, A., Schwarz, S. & Erdelen, W. (2003).** Identification of class 1
1304 integrons-associated gene cassettes in *Escherichia coli* isolated from *Varanus* spp. in
1305 Indonesia. *J Antimicrob Chemother* **51**, 175-177.
- 1306 **White, P. A., McIver, C. J., Deng, Y. & Rawlinson, W. D. (2000).** Characterisation of two new
1307 gene cassettes, *aadA5* and *dfrA17*. *FEMS Microbiol Lett* **182**, 265-269.
- 1308 **Wiesner, M., Zaidi, M. B., Calva, E., Fernandez-Mora, M., Calva, J. J. & Silva, C. (2009).**
1309 Association of virulence plasmid and antibiotic resistance determinants with
1310 chromosomal multilocus genotypes in Mexican *Salmonella enterica* serovar
1311 Typhimurium strains. *BMC Microbiol* **9**, 131.
- 1312 **Wright, M. S., Baker-Austin, C., Lindell, A. H., Stepanauskas, R., Stokes, H. W. & McArthur, J.
1313 V. (2008).** Influence of industrial contamination on mobile genetic elements: class 1
1314 integron abundance and gene cassette structure in aquatic bacterial communities.
1315 *ISME Journal* **2**, 417-428.
- 1316 **Wu, K., Wang, F., Sun, J., Wang, Q., Chen, Q., Yu, S. & Rui, Y. (2012).** Class 1 integron gene
1317 cassettes in multidrug-resistant Gram-negative bacteria in southern China. *Int J*
1318 *Antimicrob Agents* **40**, 264-267.
- 1319 **Wu, R. B., Alexander, T. W., Li, J. Q., Munns, K., Sharma, R. & McAllister, T. A. (2011).**
1320 Prevalence and diversity of class 1 integrons and resistance genes in antimicrobial-
1321 resistant *Escherichia coli* originating from beef cattle administered subtherapeutic
1322 antimicrobials. *J Appl Microbiol* **111**, 511-523.
- 1323 **Xu, H., Broersma, K., Miao, V. & Davies, J. (2011a).** Class 1 and class 2 integrons in multidrug-
1324 resistant gram-negative bacteria isolated from the Salmon River, British Columbia. *Can*
1325 *J Microbiol* **57**, 460-467.
- 1326 **Xu, H., Su, Z., Wang, S., Dai, X., Chen, J., Kong, F., Li, Y., Peng, S., Shao, Q. & other authors
1327 (2009).** Four novel resistance integron gene-cassette occurrences in bacterial isolates
1328 from Zhenjiang, China. *Curr Microbiol* **59**, 113-117.
- 1329 **Xu, X., Kong, F., Cheng, X., Yan, B., Du, X., Gai, J., Ai, H., Shi, L. & Iredell, J. (2008a).** Integron
1330 gene cassettes in *Acinetobacter* spp. strains from South China. *Int J Antimicrob Agents*
1331 **32**, 441-445.
- 1332 **Xu, Z., Shi, L., Alam, M. J., Li, L. & Yamasaki, S. (2008b).** Integron-bearing methicillin-resistant
1333 coagulase-negative staphylococci in South China, 2001-2004. *FEMS Microbiol Lett* **278**,
1334 223-230.
- 1335 **Xu, Z., Shi, L., Zhang, C., Zhang, L., Li, X., Cao, Y., Li, L. & Yamasaki, S. (2007).** Nosocomial
1336 infection caused by class 1 integron-carrying *Staphylococcus aureus* in a hospital in
1337 South China. *Clin Microbiol Infect* **13**, 980-984.
- 1338 **Xu, Z., Li, L., Shirliff, M. E., Peters, B. M., Li, B., Peng, Y., Alam, M. J., Yamasaki, S. & Shi, L.
1339 (2011b).** Resistance class 1 integron in clinical methicillin-resistant *Staphylococcus*
1340 *aureus* strains in southern China, 2001-2006. *Clin Microbiol Infect* **17**, 714-718.
- 1341 **Yang, B., Qu, D., Zhang, X., Shen, J., Cui, S., Shi, Y., Xi, M., Sheng, M., Zhi, S. & other authors
1342 (2010a).** Prevalence and characterization of *Salmonella* serovars in retail meats of
1343 marketplace in Shaanxi, China. *Int J Food Microbiol* **141**, 63-72.

1344 **Yang, C. M., Lin, M. F., Lin, C. H., Huang, Y. T., Hsu, C. T. & Liou, M. L. (2009).** Characterization
1345 of antimicrobial resistance patterns and integrons in human fecal *Escherichia coli* in
1346 Taiwan. *Jpn J Infect Dis* **62**, 177-181.

1347 **Yang, H., Byelashov, O. A., Geornaras, I., Goodridge, L. D., Nightingale, K. K., Belk, K. E.,**
1348 **Smith, G. C. & Sofos, J. N. (2010b).** Characterization and transferability of class 1
1349 integrons in commensal bacteria isolated from farm and nonfarm environments.
1350 *Foodborne Pathog Dis* **7**, 1441-1451.

1351 **Yokoyama, E., Maruyama, S., Kabeya, H., Hara, S., Sata, S., Kuroki, T. & Yamamoto, T. (2007).**
1352 Prevalence and genetic properties of *Salmonella enterica* serovar Typhimurium
1353 definitive phage type 104 isolated from *Rattus norvegicus* and *Rattus rattus* house rats
1354 in Yokohama City, Japan. *Appl Environ Microbiol* **73**, 2624-2630.

1355 **Yu, H. S., Lee, J. C., Kang, H. Y., Ro, D. W., Chung, J. Y., Jeong, Y. S., Tae, S. H., Choi, C. H., Lee,**
1356 **E. Y. & other authors (2003).** Changes in gene cassettes of class 1 integrons among
1357 *Escherichia coli* isolates from urine specimens collected in Korea during the last two
1358 decades. *J Clin Microbiol* **41**, 5429-5433.

1359 **Zhao, K. L., Liu, Y., Zhang, X. Y., Palahati, P., Wang, H. N. & Yue, B. S. (2011).** Detection and
1360 characterization of antibiotic-resistance genes in *Arcanobacterium pyogenes* strains
1361 from abscesses of forest musk deer. *J Med Microbiol* **60**, 1820-1826.

1362 **Zhao, S., Datta, A. R., Ayers, S., Friedman, S., Walker, R. D. & White, D. G. (2003).**
1363 Antimicrobial-resistant *Salmonella* serovars isolated from imported foods. *Int J Food*
1364 *Microbiol* **84**, 87-92.

1365 **Zhao, S., Fedorka-Cray, P. J., Friedman, S., McDermott, P. F., Walker, R. D., Qaiyumi, S., Foley,**
1366 **S. L., Hubert, S. K., Ayers, S. & other authors (2005).** Characterization of *Salmonella*
1367 Typhimurium of animal origin obtained from the National Antimicrobial Resistance
1368 Monitoring System. *Foodborne Pathog Dis* **2**, 169-181.

1369 **Zhao, S., McDermott, P. F., White, D. G., Qaiyumi, S., Friedman, S. L., Abbott, J. W., Glenn, A.,**
1370 **Ayers, S. L., Post, K. W. & other authors (2007).** Characterization of multidrug
1371 resistant *Salmonella* recovered from diseased animals. *Vet Microbiol* **123**, 122-132.

1372 **Zheng, F., Lin, G., Zhou, J., Cao, X., Gong, X., Wang, G. & Qiu, C. (2012).** Discovery and
1373 characterization of gene cassettes-containing integrons in clinical strains of *Riemerella*
1374 *anatipestifer*. *Vet Microbiol* **156**, 434-438.

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1401 Table 1 – Examples of alternative designations of gene cassettes^a.

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| Gene cassette | Other designations used ^a | |
|-----------------------------|--|------|
| <i>aadA1a</i> | <i>ant(3'')-1a; aad(3'')(9); aadA1; aadA</i> | 1403 |
| <i>aadA5</i> | <i>ant(3'')-1e</i> | 1404 |
| <i>aadB</i> | <i>ant(2'')-1a</i> | 1405 |
| <i>bla_{CARB-2}</i> | <i>blaP1; blaP1b; bla_{PSE-1}</i> | 1406 |
| <i>dfrA1</i> | <i>dfr1; dhfrI; dhfrIb</i> | 1407 |
| <i>dfrA12</i> | <i>dfr12; dhfrXII</i> | 1408 |
| <i>dfrA17</i> | <i>dfr17; dhfrXVII</i> | 1409 |
| <i>dfrA7</i> | <i>dfrVII; dhfrVII</i> | 1410 |
| <i>gcuC</i> | <i>orf; orf1; orfC; orfX</i> | 1411 |
| <i>gcuF</i> | <i>orfF</i> | 1412 |
| | | 1413 |
| | | 1414 |
| | | 1415 |

1416 ^aThese are also valid names. A lack of standards for indicating variants of gene cassettes is noted.

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1420 Table 2 – Examples of the occurrence of common gene cassette arrays in class 1 integrons in diverse bacterial species

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| Gene cassette array | <i>aadB</i> | <i>dfrA7</i> | <i>aadA1a</i> | <i>aadA2</i> | <i>bla_{CARB-2}</i> | <i>dfrA1-gcuC</i> | <i>dfrA1-aadA1a</i> | <i>dfrA17-aadA5</i> | <i>dfrA12-gcuF-aadA2</i> | Total nr arrays |
|------------------------------------|----------------------------|----------------------------|-----------------------------|-------------------------------|---------------------------------|-------------------------------|---------------------|---------------------------------|-------------------------------|------------------------|
| <i>Achromobacter xylooxidans</i> | | | | | | | | Traglia <i>et al.</i> , 2012 | | 1 |
| <i>Acidovorax defluvii</i> | | | Li <i>et al.</i> , 2009 | | | | | | | 1 |
| <i>Acinetobacter baumannii</i> | Nemec <i>et al.</i> , 2004 | Segal <i>et al.</i> , 2003 | | Gu <i>et al.</i> , 2007 | Koh <i>et al.</i> , 2007 | Kansakar <i>et al.</i> , 2011 | | Valenzuela <i>et al.</i> , 2007 | Gu <i>et al.</i> , 2007 | 7 |
| <i>Acinetobacter nosocomialis</i> | | Xu <i>et al.</i> , 2008a | | | Valenzuela <i>et al.</i> , 2007 | | | Valenzuela <i>et al.</i> , 2007 | | 3 |
| <i>Aeromonas allosaccharophila</i> | | | | | | | | Moura <i>et al.</i> , 2012 | | 1 |
| <i>Aeromonas bestiarum</i> | | | | | | | | | Kadlec <i>et al.</i> , 2011 | 1 |
| <i>Aeromonas caviae</i> | | | Barlow <i>et al.</i> , 2008 | Carvalho <i>et al.</i> , 2012 | | | | | Kadlec <i>et al.</i> , 2011 | 3 |
| <i>Aeromonas eucrenophila</i> | | | | | | | | | Carvalho <i>et al.</i> , 2012 | 1 |
| <i>Aeromonas hydrophila</i> | | | Lee <i>et al.</i> , 2008 | Lukkana <i>et al.</i> , 2012 | | Lukkana <i>et al.</i> , 2012 | | | Carvalho <i>et al.</i> , 2012 | 4 |
| <i>Aeromonas media</i> | | | Moura <i>et al.</i> , 2012 | Carvalho <i>et al.</i> , 2012 | | | | | Moura <i>et al.</i> , 2012 | 3 |
| <i>Aeromonas punctata</i> | | | | | | Xu <i>et al.</i> , 2011a | | | FM957886 ^a | 2 |
| <i>Aeromonas</i> | | | L'Abée-Lund & | L'Abée-Lund & | | | | | Kadlec <i>et al.</i> , | 3 |

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|-------------------------------------|-------------------------------|-----------------------------------|-------------------------------------|-----------------------------------|-----------------------------------|----------------------------------|---|
| <i>salmonicida</i> | | Sorum, 2001 | Sorum, 2001 | 2011 | | | |
| <i>Aeromonas sobria</i> | | | | Kadlec <i>et al.</i> , 2011 | | | 1 |
| <i>Aeromonas</i> sp. | | | | | Tacao <i>et al.</i> , 2014 | | 1 |
| <i>Aeromonas veronii</i> | | Moura <i>et al.</i> , 2012 | Ndi & Barton, 2011 | Kadlec <i>et al.</i> , 2011 | | Carvalho <i>et al.</i> , 2012 | 4 |
| <i>Alcaligines faecalis</i> | | Barlow <i>et al.</i> , 2008 | | | | | 1 |
| <i>Arcanobacterium pyogenes</i> | | | Zhao <i>et al.</i> , 2011 | | | | 1 |
| <i>Bacillus endophyticus</i> | | Li <i>et al.</i> , 2009 | | | | | 1 |
| <i>Brevundimonas</i> sp. | | Yang <i>et al.</i> , 2010b | | | | | 1 |
| <i>Buttiauxella agrestis</i> | | | | | Chen <i>et al.</i> , 2010 | | 1 |
| <i>Campylobacter coli</i> | | | O'Halloran <i>et al.</i> , 2004 | | | | 1 |
| <i>Campylobacter jejuni</i> | | | O'Halloran <i>et al.</i> , 2004 | | | | 1 |
| <i>Citrobacter amalonaticus</i> | | Pepperell <i>et al.</i> , 2002 | | | | | 1 |
| <i>Citrobacter braakii</i> | | Mokracka <i>et al.</i> , 2012 | | | | | 1 |
| <i>Citrobacter freundii</i> | Frank <i>et al.</i> , 2007 | Mokracka <i>et al.</i> , 2012 | Pepperell <i>et al.</i> , 2002 | Mokracka <i>et al.</i> , 2012 | JN645876 ^a | Mokracka <i>et al.</i> , 2012 | 6 |
| <i>Citrobacter koseri</i> | | | | | Mokracka <i>et al.</i> , 2012 | | 1 |
| <i>Citrobacter youngae</i> | | | Srinivasan <i>et al.</i> , 2008 | | | | 1 |

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|-----------------------------------|------------------------------|-------------------------------|-------------------------------|------------------------------|--------------------------|-------------------------|-------------------------------|---------------------------------|-------------------------------|---|
| <i>Corynebacterium glutamicum</i> | | | | Nesvera <i>et al.</i> , 1998 | | | | | | 1 |
| <i>Enterobacter aerogenes</i> | | | | | | | | Su <i>et al.</i> , 2011 | Kor <i>et al.</i> , 2013 | 2 |
| <i>Enterobacter cloacae</i> | Frank <i>et al.</i> , 2007 | Hussein <i>et al.</i> , 2009 | Dahmen <i>et al.</i> , 2010 | | | | Mokracka <i>et al.</i> , 2012 | Mokracka <i>et al.</i> , 2012 | Mokracka <i>et al.</i> , 2012 | 6 |
| <i>Enterobacter hormaechei</i> | | Mokracka <i>et al.</i> , 2011 | | | | | Mokracka <i>et al.</i> , 2011 | | Mokracka <i>et al.</i> , 2011 | 3 |
| <i>Enterobacter intermedius</i> | | Bado <i>et al.</i> , 2010 | | | | | Mokracka <i>et al.</i> , 2012 | Pellegrini <i>et al.</i> , 2009 | | 3 |
| <i>Enterobacter sakazakii</i> | | Mokracka <i>et al.</i> , 2012 | | | | | | | | 1 |
| <i>Enterococcus faecalis</i> | | Clark <i>et al.</i> , 1999 | | | | | | | Shi <i>et al.</i> , 2006a | 2 |
| <i>Escherichia coli</i> | Cameron <i>et al.</i> , 1986 | Frank <i>et al.</i> , 2007 | Lay <i>et al.</i> , 2012 | Su <i>et al.</i> , 2012 | | Wu <i>et al.</i> , 2012 | Vinue <i>et al.</i> , 2011 | Wu <i>et al.</i> , 2012 | Hsu <i>et al.</i> , 2006 | 8 |
| <i>Klebsiella mobilis</i> | | | Koczura <i>et al.</i> , 2011 | | | | Mokracka <i>et al.</i> , 2012 | | | 2 |
| <i>Klebsiella ornithinolytica</i> | | | Mokracka <i>et al.</i> , 2012 | | | | | Mokracka <i>et al.</i> , 2012 | Mokracka <i>et al.</i> , 2012 | 3 |
| <i>Klebsiella oxytoca</i> | Kor <i>et al.</i> , 2013 | | Mokracka <i>et al.</i> , 2012 | Peters <i>et al.</i> , 2001 | | | Ahmed & Shimamoto, 2011 | Mokracka <i>et al.</i> , 2012 | JX560787 ^a | 6 |
| <i>Klebsiella pneumoniae</i> | Gruteke <i>et al.</i> , 2003 | Frank <i>et al.</i> , 2007 | Mokracka <i>et al.</i> , 2012 | Gruteke <i>et al.</i> , 2003 | Kor <i>et al.</i> , 2013 | Wu <i>et al.</i> , 2012 | Frank <i>et al.</i> , 2007 | Wu <i>et al.</i> , 2012 | Wu <i>et al.</i> , 2012 | 9 |
| <i>Kluyvera georgiana</i> | | | | | | | | Rodriguez <i>et al.</i> , 2010 | | 1 |
| <i>Kluyvera</i> sp. | | Mokracka <i>et al.</i> , 2012 | Mokracka <i>et al.</i> , 2012 | | | | Mokracka <i>et al.</i> , 2012 | | | 3 |

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| <i>Laribacter hongkongensis</i> | | | | | | Feng <i>et al.</i> , 2011 | | Feng <i>et al.</i> , 2011 | | 2 |
| <i>Leclercia adecarboxylata</i> | | | | | | | | | Shin <i>et al.</i> , 2012 | 1 |
| <i>Morganella morganii</i> | Mahrouki <i>et al.</i> , 2012 | | Hussein <i>et al.</i> , 2009 | Barlow <i>et al.</i> , 2008 | | Kor <i>et al.</i> , 2013 | | Kor <i>et al.</i> , 2013 | Kor <i>et al.</i> , 2013 | 6 |
| <i>Ochrobactrum</i> sp. | | | | | | | | | Li <i>et al.</i> , 2010 | 1 |
| <i>Pantoea agglomerans</i> | | | Aibinu <i>et al.</i> , 2012 | Barlow <i>et al.</i> , 2008 | | | | | | 2 |
| <i>Pantoea</i> sp. | | Mokracka <i>et al.</i> , 2012 | | | | | | Mokracka <i>et al.</i> , 2012 | | 2 |
| <i>Proteus mirabilis</i> | JX494728* | EU860402* | Gionechetti <i>et al.</i> , 2008 | Falcone <i>et al.</i> , 2010 | | Boyd <i>et al.</i> , 2008 | Gionechetti <i>et al.</i> , 2008 | | Wu <i>et al.</i> , 2012 | 7 |
| <i>Proteus vulgaris</i> | | Hussein <i>et al.</i> , 2009 | Hussein <i>et al.</i> , 2009 | | | | Ozgumus <i>et al.</i> , 2009 | | | 3 |
| <i>Providencia alcalifaciens</i> | | | | Xu <i>et al.</i> , 2011a | | | | | | 1 |
| <i>Pseudomonas aeruginosa</i> | Ruiz-Martinez <i>et al.</i> , 2011 | | | | Gu <i>et al.</i> , 2007 | HQ832476* | | Xu <i>et al.</i> , 2009 | Gu <i>et al.</i> , 2007 | 5 |
| <i>Pseudomonas putida</i> | | | Wu <i>et al.</i> , 2012 | | | | | | | 1 |
| <i>Pseudomonas</i> sp. | | Rosser & Young, 1999 | | | | | | | | 1 |
| <i>Raoultella planticola</i> | | | | | | | | | Tseng <i>et al.</i> , 2014 | 1 |
| <i>Riemerella anatipestifer</i> | | | Zheng <i>et al.</i> , 2012 | Sun <i>et al.</i> , 2012 | | | | | | 2 |
| <i>Salmonella enterica</i> | Zhao <i>et al.</i> , 2007 | Tamang <i>et al.</i> , 2007 | Ranjbar <i>et al.</i> , 2011 | Kim <i>et al.</i> , 2011 | Havlickova <i>et al.</i> , 2009 | Lee <i>et al.</i> , 2009 | Perez-Moreno <i>et al.</i> , 2013 | Perez-Moreno <i>et al.</i> , 2013 | Antunes <i>et al.</i> , 2006 | 9 |

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| <i>Serratia liquefaciens</i> | | Mokracka <i>et al.</i> , 2012 | | | | | | 1 |
| <i>Serratia marcescens</i> | Peng <i>et al.</i> , 2007 | | Peng <i>et al.</i> , 2007 | Peng <i>et al.</i> , 2007 | Mokracka <i>et al.</i> , 2012 | | Peng <i>et al.</i> , 2007 | 5 |
| <i>Serratia odorifera</i> | | Mokracka <i>et al.</i> , 2012 | | | Mokracka <i>et al.</i> , 2012 | | | 2 |
| <i>Serratia</i> sp. | | | | | | Chakraborty <i>et al.</i> , 2013 | | 1 |
| <i>Shigella boydii</i> | Frank <i>et al.</i> , 2007 | | | | | | | 1 |
| <i>Shigella dysenteriae</i> | Frank <i>et al.</i> , 2007 | | | | | | Iversen <i>et al.</i> , 2003 | 2 |
| <i>Shigella flexneri</i> | Frank <i>et al.</i> , 2007 | Navia <i>et al.</i> , 2004 | Iversen <i>et al.</i> , 2003 | | Navia <i>et al.</i> , 2004 | Pan <i>et al.</i> , 2006 | Iversen <i>et al.</i> , 2003 | 6 |
| <i>Shigella sonnei</i> | | Nogrady <i>et al.</i> , 2013 | Pan <i>et al.</i> , 2006 | | Navia <i>et al.</i> , 2004 | Pan <i>et al.</i> , 2006 | Iversen <i>et al.</i> , 2003 | 5 |
| <i>Sphingobacterium</i> sp. | | | | | | | Li <i>et al.</i> , 2010 | 1 |
| <i>Staphylococcus aureus</i> | | KF687971* | Xu <i>et al.</i> , 2007 | | | Xu <i>et al.</i> , 2011b | Xu <i>et al.</i> , 2011b | 4 |
| <i>Staphylococcus</i> CoN | | | | | | | Shi <i>et al.</i> , 2006a | 1 |
| <i>Staphylococcus epidermidis</i> | | | Xu <i>et al.</i> , 2008b | | | Xu <i>et al.</i> , 2008b | Xu <i>et al.</i> , 2008b | 3 |
| <i>Staphylococcus haemolyticus</i> | | | | | | | Xu <i>et al.</i> , 2008b | 1 |
| <i>Staphylococcus hominis</i> | | | | | | Xu <i>et al.</i> , 2008b | Xu <i>et al.</i> , 2008b | 2 |
| <i>Staphylococcus warneri</i> | | | | | | | Xu <i>et al.</i> , 2008b | 1 |

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| <i>Stenotrophomonas maltophilia</i> | JX560784* | | | | | | | Xu <i>et al.</i> , 2011a | Hu <i>et al.</i> , 2011 | Hu <i>et al.</i> , 2011 | 4 |
| <i>Stenotrophomonas</i> sp. | | | Yang <i>et al.</i> , 2010b | | | | | | | | 1 |
| <i>Streptococcus</i> spp. | | | | Shi <i>et al.</i> , 2006a | | | | | | Shi <i>et al.</i> , 2006a | 2 |
| <i>Vibrio alginolyticus</i> | | | | Taviani <i>et al.</i> , 2008 | | | | | | | 1 |
| <i>Vibrio cholerae</i> | Dalsgaard <i>et al.</i> , 2000 | | Ceccarelli <i>et al.</i> , 2006a | Dalsgaard <i>et al.</i> , 2000 | Dalsgaard <i>et al.</i> , 2000 | Thungapathra <i>et al.</i> , 2002 | | | | | 5 |
| <i>Vibrio fluvialis</i> | | | Rajpara <i>et al.</i> , 2009 | | | Srinivasan <i>et al.</i> , 2006 | | | | | 2 |
| <i>Xantomonas oryzae</i> | | | FJ501978* | | | | | | | | 1 |
| Total nr species | 11 | 15 | 39 | 31 | 6 | 12 | 22 | 26 | 37 | | |

* GenBank accession number

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1431 Table 3 – Examples of the geographical distribution of some of the most common gene cassette arrays embedded in class 1 integrons

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| Gene cassette array | <i>aadB</i> | <i>dfrA7</i> | <i>aadA1a</i> | <i>aadA2</i> | <i>bla_{CARB-2}</i> | <i>dfrA1-gcuC</i> | <i>dfrA1-aadA1 a</i> | <i>dfrA17-aadA5</i> | <i>dfrA12-gcuF-aadA2</i> | Total n^{ef} arrays |
|----------------------------|----------------------------|--------------------------------|--------------------------------|--------------------------------|---------------------------------|----------------------------------|--------------------------------|--------------------------------|------------------------------|------------------------------------|
| Country | | | | | | | | | | |
| Albania | | | Falbo <i>et al.</i> , 1999 | | | | | | | 1 |
| Angola | | | | | | Ceccarelli <i>et al.</i> , 2006b | | | | 1 |
| Argentina | | | Di Conza <i>et al.</i> , 2005 | | | | Traglia <i>et al.</i> , 2012 | | | 2 |
| Australia | Jones <i>et al.</i> , 2005 | Bailey <i>et al.</i> , 2010 | Barlow <i>et al.</i> , 2008 | Bailey <i>et al.</i> , 2010 | Valenzuela <i>et al.</i> , 2007 | | Bailey <i>et al.</i> , 2010 | Sidjabat <i>et al.</i> , 2006 | Power <i>et al.</i> , 2013 | 8 |
| Austria | | | Morabito <i>et al.</i> , 2002 | | | | | | | 1 |
| Belgium | Huys <i>et al.</i> , 2005 | | | | | | Plante <i>et al.</i> , 2003 | | | 2 |
| Bolivia | | Pallecchi <i>et al.</i> , 2007 | | | | | Pallecchi <i>et al.</i> , 2007 | Pallecchi <i>et al.</i> , 2007 | | 3 |
| Brazil | DQ139277* | | Peirano <i>et al.</i> , 2006 | Sa <i>et al.</i> , 2010 | | | | | Peirano <i>et al.</i> , 2006 | 4 |
| Canada | Allen & Poppe, 2002 | | Pepperell <i>et al.</i> , 2002 | Pepperell <i>et al.</i> , 2002 | Ng <i>et al.</i> , 1999 | Xu <i>et al.</i> , 2011a | Xu <i>et al.</i> , 2011a | Wu <i>et al.</i> , 2011 | Wu <i>et al.</i> , 2011 | 8 |
| Central African Republic | | Frank <i>et al.</i> , 2007 | | | | | Frank <i>et al.</i> , 2007 | Frank <i>et al.</i> , 2007 | | 3 |
| Chile | | | Lapierre <i>et al.</i> , 2008 | | | | Lapierre <i>et al.</i> , 2008 | | | 2 |

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|----------------|-----------------------------------|-------------------------------|-----------------------------------|-------------------------------|---------------------------------|---------------------------------|--------------------------------|-------------------------------|-------------------------------|---|
| China | Xu <i>et al.</i> , 2009 | Su <i>et al.</i> , 2012 | Lu <i>et al.</i> , 2010 | Su <i>et al.</i> , 2012 | Yang <i>et al.</i> , 2010a | Feng <i>et al.</i> , 2011 | Su <i>et al.</i> , 2012 | Su <i>et al.</i> , 2012 | Su <i>et al.</i> , 2012 | 9 |
| Colombia | | | | | | | | | GU304661* | 1 |
| Czech Republic | | | Dolejska <i>et al.</i> , 2008 | | Havlickova <i>et al.</i> , 2009 | | Dolejska <i>et al.</i> , 2008 | Dolejska <i>et al.</i> , 2009 | | 4 |
| Denmark | Sandvang & Aarestrup, 2000 | Krauland <i>et al.</i> , 2009 | Sandvang & Aarestrup, 2000 | Sandvang <i>et al.</i> , 1998 | Sandvang <i>et al.</i> , 1998 | | | | Krauland <i>et al.</i> , 2009 | 6 |
| Egypt | | | Ahmed <i>et al.</i> , 2009b | Ahmed & Shimamoto, 2011 | | | Ahmed <i>et al.</i> , 2009b | Ahmed <i>et al.</i> , 2009b | Ahmed <i>et al.</i> , 2009b | 5 |
| Ethiopia | | | | Molla <i>et al.</i> , 2007 | Molla <i>et al.</i> , 2007 | | Molla <i>et al.</i> , 2007 | | Molla <i>et al.</i> , 2007 | 4 |
| Finland | | | | | | | | | Heikkila <i>et al.</i> , 1993 | 1 |
| France | Huys <i>et al.</i> , 2005 | | Vinue <i>et al.</i> , 2011 | Casin <i>et al.</i> , 1999 | Poirel <i>et al.</i> , 1999 | | Vinue <i>et al.</i> , 2011 | Vinue <i>et al.</i> , 2011 | Vinue <i>et al.</i> , 2011 | 7 |
| Germany | Rodriguez <i>et al.</i> , 2009 | Blahna <i>et al.</i> , 2006 | Kadlec & Schwarz, 2008 | Heuer & Smalla, 2007 | Rodriguez <i>et al.</i> , 2009 | | Kadlec & Schwarz, 2008 | Kadlec & Schwarz, 2008 | Kadlec & Schwarz, 2008 | 8 |
| Ghana | | Labar <i>et al.</i> , 2012 | Labar <i>et al.</i> , 2012 | | | | Labar <i>et al.</i> , 2012 | Labar <i>et al.</i> , 2012 | | 4 |
| Gibraltar | | | Ridley & Threlfall, 1998 | | | | | | | 1 |
| Hungary | Libisch <i>et al.</i> , 2009 | | Nogrady <i>et al.</i> , 2005 | Nogrady <i>et al.</i> , 2005 | Nogrady <i>et al.</i> , 2005 | | Nogrady <i>et al.</i> , 2005 | Nogrady <i>et al.</i> , 2005 | | 6 |
| India | | Ploy <i>et al.</i> , 2003 | Thungapathra <i>et al.</i> , 2002 | Shi <i>et al.</i> , 2006b | Shi <i>et al.</i> , 2006b | | HE653235* | Pazhani <i>et al.</i> , 2011 | FM179328* | 7 |
| Indonesia | | | | | | | Waturangi <i>et al.</i> , 2003 | | | 2 |
| Iran | Shahcheraghi <i>et al.</i> , 2010 | Najibi <i>et al.</i> , 2012 | Ranjbar <i>et al.</i> , 2011 | Adabi <i>et al.</i> , 2009 | HQ132377* | Srinivasan <i>et al.</i> , 2006 | Ranjbar <i>et al.</i> , 2011 | | Najibi <i>et al.</i> , 2012 | 8 |

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|------------|---------------------------|--------------------------------------|--------------------------------------|--|---------------------------------|-------------------------------|--------------------------------------|--------------------------------------|--------------------------------------|---|
| Ireland | | Karczmarczyk <i>et al.</i> , 2011 | Karczmarczyk <i>et al.</i> , 2011 | O'Halloran <i>et al.</i> , 2004 | Murphy <i>et al.</i> , 2007 | | Karczmarczyk <i>et al.</i> , 2011 | Karczmarczyk <i>et al.</i> , 2011 | Karczmarczyk <i>et al.</i> , 2011 | 7 |
| Italy | Huys <i>et al.</i> , 2005 | | Falbo <i>et al.</i> , 1999 | Falcone <i>et al.</i> , 2010 | GU987051 ^a | | Gionechetti <i>et al.</i> , 2008 | Gionechetti <i>et al.</i> , 2008 | Morabito <i>et al.</i> , 2002 | 7 |
| Japan | | Ahmed <i>et al.</i> , 2009a | Ahmed <i>et al.</i> , 2009a | Yokoyama <i>et al.</i> , 2007 | Ahmed <i>et al.</i> , 2005 | Ahmed <i>et al.</i> , 2005 | Ahmed <i>et al.</i> , 2007 | Ahmed <i>et al.</i> , 2007 | Kumai <i>et al.</i> , 2005 | 8 |
| Jordan | | Al-Sanouri <i>et al.</i> , 2008 | | | | | | | | 1 |
| Kenya | | Kikui <i>et al.</i> , 2007 | Kiiru <i>et al.</i> , 2013 | | | | Kikui <i>et al.</i> , 2007 | Kiiru <i>et al.</i> , 2013 | Kiiru <i>et al.</i> , 2013 | 5 |
| Korea | Kang <i>et al.</i> , 2010 | Lee <i>et al.</i> , 2004 | Kang <i>et al.</i> , 2005 | Yu <i>et al.</i> , 2003 | Lee & Lee, 2007 | | Kim <i>et al.</i> , 2011 | Kang <i>et al.</i> , 2005 | Kang <i>et al.</i> , 2005 | 8 |
| Lebanon | | El-Najjar <i>et al.</i> , 2010 | | | | | El-Najjar <i>et al.</i> , 2010 | El-Najjar <i>et al.</i> , 2010 | | 3 |
| Lithuania | JF412714* | | Povilonis <i>et al.</i> , 2010 | | | | Povilonis <i>et al.</i> , 2010 | Povilonis <i>et al.</i> , 2010 | Povilonis <i>et al.</i> , 2010 | 4 |
| Madagascar | | | Rakotonirina <i>et al.</i> , 2013 | Rakotonirina <i>et al.</i> , 2013 | | | | Rakotonirina <i>et al.</i> , 2013 | | 3 |
| Malaysia | Kor <i>et al.</i> , 2013 | Kor <i>et al.</i> , 2013 | Kor <i>et al.</i> , 2013 | Mukherjee & Chakraborty, 2006 | Kor <i>et al.</i> , 2013 | Kor <i>et al.</i> , 2013 | Kor <i>et al.</i> , 2013 | Kor <i>et al.</i> , 2013 | Kor <i>et al.</i> , 2013 | 9 |
| Mexico | | | | Perez- Valdespino <i>et al.</i> , 2009 | | | | Wiesner <i>et al.</i> , 2009 | Wiesner <i>et al.</i> , 2009 | 3 |
| Mozambique | | | Ceccarelli <i>et al.</i> , 2006a | Taviani <i>et al.</i> , 2008 | Taviani <i>et al.</i> , 2008 | | | | | 3 |
| Nepal | | Tamang <i>et al.</i> , 2007 | | | | | | | | 1 |
| Nigeria | | Labar <i>et al.</i> , 2012 | Labar <i>et al.</i> , 2012 | Labar <i>et al.</i> , 2012 | | | Labar <i>et al.</i> , 2012 | Labar <i>et al.</i> , 2012 | Labar <i>et al.</i> , 2012 | 6 |

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|---------------------|--|-----------------------------------|----------------------------------|-----------------------------------|------------------------------|-----------------------------------|-----------------------------------|-----------------------------------|---|
| Norway | | Heir <i>et al.</i> , 2004 | Sunde, 2005 | Lindstedt <i>et al.</i> , 2003 | | Sunde, 2005 | Lindstedt <i>et al.</i> , 2003 | Lindstedt <i>et al.</i> , 2003 | 6 |
| Pakistan | | Holt <i>et al.</i> , 2007 | | | | | | | 1 |
| Palestine territory | Hussein <i>et al.</i> , 2009 | Hussein <i>et al.</i> , 2009 | Hussein <i>et al.</i> , 2009 | Hussein <i>et al.</i> , 2009 | | | Hussein <i>et al.</i> , 2009 | Hussein <i>et al.</i> , 2009 | 6 |
| Philippines | | | | | | | | Krauland <i>et al.</i> , 2009 | 1 |
| Poland | | Mokracka <i>et al.</i> , 2012 | Mokracka <i>et al.</i> , 2012 | | | Mokracka <i>et al.</i> , 2012 | Mokracka <i>et al.</i> , 2012 | Mokracka <i>et al.</i> , 2012 | 5 |
| Portugal | Ferreira da Silva <i>et al.</i> , 2007 | EU860402* | Antunes <i>et al.</i> , 2006 | Moura <i>et al.</i> , 2007 | Antunes <i>et al.</i> , 2006 | Moura <i>et al.</i> , 2007 | Antunes <i>et al.</i> , 2006 | Carvalho <i>et al.</i> , 2012 | 8 |
| Russia | GQ924772* | | GQ924774* | Petrova <i>et al.</i> , 2011 | HQ832476* | GQ924770* | GQ896490* | Egorova <i>et al.</i> , 2007 | 7 |
| Rwanda | | | Ceccarelli <i>et al.</i> , 2006a | | | | | | 1 |
| Scotland | | | | L'Abée-Lund & Sorum, 2001 | | | | | 1 |
| Senegal | | Gassama <i>et al.</i> , 2004 | Gassama <i>et al.</i> , 2004 | | | Sow <i>et al.</i> , 2007 | | | 3 |
| Singapore | | | | | Koh <i>et al.</i> , 2007 | | | FM957886* | 2 |
| Slovakia | | | Majtan <i>et al.</i> , 2007 | Majtan <i>et al.</i> , 2007 | Majtan <i>et al.</i> , 2007 | Majtan <i>et al.</i> , 2007 | | Majtan <i>et al.</i> , 2007 | 5 |
| Slovenia | | | Ridley & Threlfall, 1998 | | | | | | 1 |
| Somalia | | | Ceccarelli <i>et al.</i> , 2006a | | | | | | 1 |
| South Africa | | Krauland <i>et al.</i> , 2009 | Ridley & Threlfall, 1998 | Dalsgaard <i>et al.</i> , 2001 | | | | Krauland <i>et al.</i> , 2009 | 4 |
| Spain | Huys <i>et al.</i> , 2005 | Perez-Moreno <i>et al.</i> , 2013 | Rodriguez <i>et al.</i> , 2006 | Perez-Moreno <i>et al.</i> , 2013 | Guerra <i>et al.</i> , 2000 | Perez-Moreno <i>et al.</i> , 2013 | Perez-Moreno <i>et al.</i> , 2013 | Perez-Moreno <i>et al.</i> , 2013 | 8 |

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|-----------------|--------------------------------|--------------------------------|---|----------------------------------|--------------------------------|---|------------------------------|------------------------------|---|---|---|
| Sri Lanka | | Sundstrom <i>et al.</i> , 1987 | | | | | | | | 1 | |
| Sudan | | Ibrahim <i>et al.</i> , 2013 | | | | | | Ibrahim <i>et al.</i> , 2013 | Ibrahim <i>et al.</i> , 2013 | Ibrahim <i>et al.</i> , 2013 | 4 |
| Swaziland | | | | Ceccarelli <i>et al.</i> , 2006a | | | | | | | 1 |
| Sweden | | Tennhammar-Ekman & Skold, 1979 | Grape <i>et al.</i> , 2005 | Grape <i>et al.</i> , 2005 | | | | Grape <i>et al.</i> , 2005 | Grape <i>et al.</i> , 2005 | Grape <i>et al.</i> , 2005 | 6 |
| Switzerland | | | | Cocchi <i>et al.</i> , 2007 | | | | Cocchi <i>et al.</i> , 2007 | Cocchi <i>et al.</i> , 2007 | | 2 |
| Taiwan | Peng <i>et al.</i> , 2007 | Yang <i>et al.</i> , 2009 | Hsu <i>et al.</i> , 2006 | Hsu <i>et al.</i> , 2006 | | Lee <i>et al.</i> , 2009 | Chang <i>et al.</i> , 2000 | Hsu <i>et al.</i> , 2006 | Hsu <i>et al.</i> , 2006 | | 8 |
| Thailand | Dalsgaard <i>et al.</i> , 2000 | | Lay <i>et al.</i> , 2012 | Dalsgaard <i>et al.</i> , 2000 | Dalsgaard <i>et al.</i> , 2000 | | | | | Lukkana <i>et al.</i> , 2012 | 6 |
| The Netherlands | Huys <i>et al.</i> , 2005 | Vo <i>et al.</i> , 2007 | van Essen-Zandbergen <i>et al.</i> , 2007 | Gruteke <i>et al.</i> , 2003 | | van Essen-Zandbergen <i>et al.</i> , 2007 | | Vo <i>et al.</i> , 2007 | van Essen-Zandbergen <i>et al.</i> , 2007 | van Essen-Zandbergen <i>et al.</i> , 2007 | 8 |
| Trinidad | | | Ridley & Threlfall, 1998 | | | | | | | | 1 |
| Tunisia | Mahrouki <i>et al.</i> , 2012 | Dahmen <i>et al.</i> , 2010 | Ben Sallem <i>et al.</i> , 2012 | Dahmen <i>et al.</i> , 2010 | Soufi <i>et al.</i> , 2012 | Mahrouki <i>et al.</i> , 2012 | Dahmen <i>et al.</i> , 2010 | Dahmen <i>et al.</i> , 2010 | | Ben Slama <i>et al.</i> , 2011 | 9 |
| Turkey | | Ozgumus <i>et al.</i> , 2009 | Sandalli <i>et al.</i> , 2010 | Sandalli <i>et al.</i> , 2010 | | | | Ozgumus <i>et al.</i> , 2009 | Sandalli <i>et al.</i> , 2010 | Sivri <i>et al.</i> , 2012 | 6 |
| Uganda | | Krauland <i>et al.</i> , 2009 | Guerra <i>et al.</i> , 2006 | | | | | | | | 2 |
| United Kingdom | Turton <i>et al.</i> , 2006 | Rosser & Young, 1999 | Rosser & Young, 1999 | Corkill <i>et al.</i> , 2005 | | | | Rosser & Young, 1999 | | Rosser & Young, 1999 | 6 |
| United States | Turton <i>et al.</i> , 2006 | Ajiboye <i>et al.</i> , 2009 | Li <i>et al.</i> , 2006 | Zhao <i>et al.</i> , 2007 | Zhao <i>et al.</i> , 2003 | Khan <i>et al.</i> , 2006 | Ajiboye <i>et al.</i> , 2009 | Solberg <i>et al.</i> , 2006 | Solberg <i>et al.</i> , 2006 | | 9 |

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|---------------------------------------|----|------------------------------|----------------------------------|-------------------------|-----------------------------|-----------------------|---------------------------|--------------------------|--------------------------|---|
| Uruguay | | | Bado <i>et al.</i> , 2010 | | | | Bado <i>et al.</i> , 2010 | | | |
| Vietnam | | Ploy <i>et al.</i> , 2003 | Ploy <i>et al.</i> , 2003 | Vo <i>et al.</i> , 2010 | Van <i>et al.</i> , 2007 | DQ238103 ^a | Van <i>et al.</i> , 2007 | Van <i>et al.</i> , 2007 | Van <i>et al.</i> , 2007 | 8 |
| Zimbabwe | | | Ceccarelli <i>et al.</i> , 2006a | | | | | | | 1 |
| Total n^{er} countries | 24 | 37 | 54 | 38 | 27 | 11 | 44 | 38 | 42 | |

* GenBank accession number

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1439 Table 4 – Examples of the source of bacteria containing common gene cassette arrays embedded in class 1 integrons

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| Gene cassette array | <i>aadB</i> | <i>dfrA7</i> | <i>aadA1a</i> | <i>aadA2</i> | <i>bla_{CARB-2}</i> | <i>dfrA1-gcuC</i> | <i>dfrA1-aadA1a</i> | <i>dfrA17-aadA5</i> | <i>dfrA12-gcuF-aadA2</i> | Total n ^{er} arrays |
|---------------------|----------------------------------|------------------------------|----------------------------------|---------------------------------|---------------------------------|-----------------------------------|--------------------------------|-------------------------------|-------------------------------|------------------------------|
| Source | | | | | | | | | | |
| Human | | | | | | | | | | |
| Clinical | | Solberg <i>et al.</i> , 2006 | Nogrady <i>et al.</i> , 2005 | Kazama <i>et al.</i> , 1995 | Kor <i>et al.</i> , 2013 | Thungapathra <i>et al.</i> , 2002 | Nogrady <i>et al.</i> , 2005 | White <i>et al.</i> , 2000 | Heikkila <i>et al.</i> , 1993 | 8 |
| Healthy | | Kang <i>et al.</i> , 2005 | Labar <i>et al.</i> , 2012 | Labar <i>et al.</i> , 2012 | Molla <i>et al.</i> , 2007 | | Labar <i>et al.</i> , 2012 | Kang <i>et al.</i> , 2005 | Kang <i>et al.</i> , 2005 | 7 |
| Animal | | | | | | | | | | |
| Domestic | Vo <i>et al.</i> , 2007 | Vo <i>et al.</i> , 2007 | Kadlec & Schwarz, 2008 | | Rodriguez <i>et al.</i> , 2009 | | Kadlec <i>et al.</i> , 2011 | Cocchi <i>et al.</i> , 2007 | Kadlec & Schwarz, 2008 | 7 |
| Food-producing | Zhao <i>et al.</i> , 2005 | Kikivi <i>et al.</i> , 2007 | Zhao <i>et al.</i> , 2005 | O'Halloran <i>et al.</i> , 2004 | Khemtong & Chuanchuen, 2008 | Du <i>et al.</i> , 2005 | Kadlec <i>et al.</i> , 2011 | Dotto <i>et al.</i> , 2014 | Ahmed <i>et al.</i> , 2009b | 9 |
| Food product | | Ahmed <i>et al.</i> , 2009a | Sunde, 2005 | Dalsgaard <i>et al.</i> , 2000 | Zhao <i>et al.</i> , 2003 | Khan <i>et al.</i> , 2006 | Antunes <i>et al.</i> , 2006 | Machado <i>et al.</i> , 2008 | Antunes <i>et al.</i> , 2006 | 8 |
| Wild | Gionechetti <i>et al.</i> , 2008 | | Gionechetti <i>et al.</i> , 2008 | | Havlickova <i>et al.</i> , 2009 | | Goncalves <i>et al.</i> , 2013 | Dolejska <i>et al.</i> , 2009 | Caleja <i>et al.</i> , 2011 | 6 |
| Zoo | | | | Ahmed <i>et al.</i> , 2007 | | | Ahmed <i>et al.</i> , 2007 | Ahmed <i>et al.</i> , 2007 | | 3 |
| Water | | | | | | | | | | |
| Lake | | | Yang <i>et al.</i> , 2010b | | | | | | | 1 |

| | | | | | | | | | | |
|-------------------------------------|--|-----------------------------------|-------------------------------|---------------------------------|-------------------------------------|-------------------------------|-----------------------------------|-----------------------------------|----------------------------------|---|
| River | | Su <i>et al.</i> , 2012 | Xu <i>et al.</i> , 2011a | Su <i>et al.</i> , 2012 | Ceccarelli <i>et al.</i> , 2006b | Ahmed <i>et al.</i> , 2005 | Su <i>et al.</i> , 2012 | Su <i>et al.</i> , 2012 | Su <i>et al.</i> , 2012 | 8 |
| Sewage | | | | | | | | | Guerra <i>et al.</i> , 2000 | 1 |
| Spring | | | | | | | | | Ozgumus <i>et al.</i> , 2007 | 1 |
| Tap | | | | | | | | | Ozgumus <i>et al.</i> , 2007 | 1 |
| Wastewater | Ferreira da Silva <i>et al.</i> , 2007 | Tennstedt <i>et al.</i> , 2003 | Moura <i>et al.</i> , 2012 | Taviani <i>et al.</i> , 2008 | Taviani <i>et al.</i> , 2008 | | Han <i>et al.</i> , 2012 | Moura <i>et al.</i> , 2012 | Mokracka <i>et al.</i> , 2012 | 8 |
| Soil | | | | | | | | | | |
| Dairy farm | | | | | Srinivasan <i>et al.</i> , 2008 | | | | Srinivasan <i>et al.</i> , 2008 | 2 |
| Manure | Heuer <i>et al.</i> , 2012 | | Binh <i>et al.</i> , 2009 | Heuer & Smalla, 2007 | | | | | | 3 |
| Other | | | | | | | | | | |
| Hospital inanimate surface | JX560784* | | | | Xu <i>et al.</i> , 2007 | | GU731078* | | Sidjabat <i>et al.</i> , 2006 | 4 |
| Permafrost | | | | | Petrova <i>et al.</i> , 2011 | | | | | 1 |
| Remote community | | Pallecchi <i>et al.</i> , 2007 | | | | | Pallecchi <i>et al.</i> , 2007 | Pallecchi <i>et al.</i> , 2007 | | 3 |
| Total n^{er} sources | 7 | 8 | 10 | 11 | 9 | 4 | 12 | 12 | 9 | |

* GenBank accession number

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1443 **Figure 1.** Schematic structure of a classic class 1 integron. 5'-CS is the 5' conserved segment of the integron and 3'-CS the 3' conserved segment
1444 of the integron. The 5'-CS includes the class 1 integrase gene, *intI1*; the gene cassettes promoters, P_c and P₂; and the integron-associated
1445 recombination site, *attI1*. The 3'-CS includes the truncated version of a quaternary ammonium resistance gene, *qacEΔ1*; the sulphonamide
1446 resistance gene, *sul1*; and an open reading frame, *orf5*. The variable region contains the gene cassettes, GC; and the recombination site of the
1447 gene cassette, *attC*.
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1449