

## Review

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

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

## Introduction

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

Integrons are present in ~10% of the bacterial genomes sequenced, and contribute to genomic plasticity and environmental adaptation of bacteria (Boucher *et al.*, 2007). Integrons can be considered one of the major genetic carriers of and vectors for dissemination of antibiotic resistance determinants in bacteria (Cambray *et al.*, 2010). Integrons have been classified according to their genomic context as either mobile integrons, whenever they are associated with transposons, or chromosomal integrons, when located in the bacterial chromosome (Cambray *et al.*, 2010; Mazel, 2006). Mobile integrons are mainly found in Gram-negative bacteria, although a few studies have also reported their presence amongst Gram-positive species (Cambray

*et al.*, 2010; Domingues *et al.*, 2012a). The genetic relatedness of the integrase gene of the mobile integrons is used to group them into distinct classes (Boucher *et al.*, 2007; Stokes & Hall, 1989). Based on the nucleotide sequence of the integrase, five classes of mobile integrons have been described (Cambray *et al.*, 2010). Class 1 integrons were described in 1989 (Stokes & Hall, 1989), and are reported as the most common and widespread, especially in clinical settings. This class mainly carries antimicrobial resistance genes and it is highly disseminated due to the close association with transposons, often embedded in conjugative plasmids (Cambray *et al.*, 2010).

All integrons consist of three essential elements: the *intI* integrase gene, which encodes the IntI protein responsible for the site-specific recombination of gene cassettes, the adjacent recombination site *attI* and the gene cassette promoter  $P_C$  (previously called  $P_{ANT}$ ) (Hall & Collis, 1998), although the presence of the promoter has not been shown in all classes (Boucher *et al.*, 2007). An additional promoter,  $P_2$ , is present in some integrons (Collis & Hall, 1995).

The complete integron is not considered to be a mobile element itself as it lacks functions for self-mobility. However, the individual gene cassettes are considered mobile within integrons (Mazel, 2006). Furthermore, integrons are often

Abbreviations: CS, conserved segment; HGT, horizontal gene transfer; MGE, mobile genetic element

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

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

## Class 1 integrons

Class 1 integrons usually have three distinct genetic regions: two highly conserved regions: the 5'-conserved segment (5'-CS) and the 3'-CS, flanking the central but variable region where the gene cassettes are located (Stokes & Hall, 1989); these integrons have been designated classic class 1 integrons. The 5'-CS includes the *intI1* gene, the *attI1* site, and the promoters  $P_c$  and  $P_2$  when present. The 3'-CS consists of the *qacEΔ1* gene, which encodes an incomplete version of a protein that mediates resistance to certain detergents, the *sul1* gene, encoding resistance to sulphonamides, and an ORF, *orf5*, of unknown function (Fig. 1). The central variable region can have different numbers and types of gene cassettes resulting in integrons with diverse compositions of gene cassette arrays. The variable region of class 1 integrons is often targeted in PCR with a pair of primers called 5'-CS and 3'-CS, which bind in the conserved regions of this class (Lévesque

*et al.*, 1995). The size of the amplicon of each cassette array described in this review refers to the PCR product obtained with this primer pair. It is noted that several other primer pairs have been developed and the PCR amplicon produced by these can have different sizes, although they target the same arrays (Ajiboye *et al.*, 2009; Sandvang *et al.*, 1998; White *et al.*, 2000).

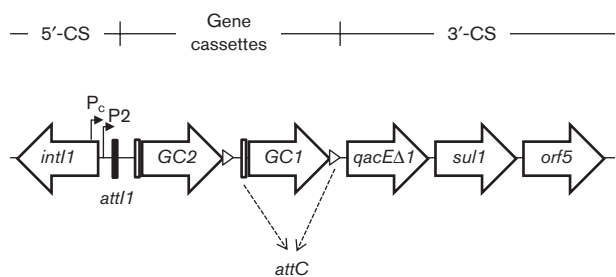
Although this is the most commonly described structure of class 1 integrons, other structures have been identified, such as the integrons without a 3'-CS (Dawes *et al.*, 2010; Pan *et al.*, 2006) and others with more complex structures. The term complex class 1 integrons has been used for those that include the insertion sequence common region *ISCR1*, partial duplications of the 3'-CS and an addition *ISCR1*-associated region that usually carries a non-cassette resistance gene (Bennett, 2008; Toleman *et al.*, 2006a, b).

## Gene cassettes

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

## Common gene cassette arrays

According to Partridge *et al.* (2009), the single gene cassettes *aadB*, *dfrA7*, *aadA1a*, *aadA2*, *blaP1* [now called



**Fig. 1.** Schematic structure of a classic class 1 integron. The 5'-CS includes the class 1 integrase gene *intI1*, the gene cassette promoters  $P_c$  and  $P_2$ , and the integron-associated recombination site *attI1*. The 3'-CS includes the truncated version of a quaternary ammonium resistance gene *qacEΔ1*, the sulphonamide resistance gene *sul1* and an ORF, *orf5*. The variable region contains the gene cassettes (GC) and the recombination site of the gene cassette, *attC*.

**Table 1.** Examples of alternative designations of gene cassettes

Gene cassette	Other designations*
<i>aadA1a</i>	<i>ant(3'')-1a</i> ; <i>aad(3'')(9)</i> ; <i>aadA1</i> ; <i>aadA</i>
<i>aadA5</i>	<i>ant(3'')-1e</i>
<i>aadB</i>	<i>ant(2'')-1a</i>
<i>bla<sub>CARB-2</sub></i>	<i>blaP1</i> ; <i>blaP1b</i> ; <i>bla<sub>PSE-1</sub></i>
<i>dfrA1</i>	<i>dfr1</i> ; <i>dhfrI</i> ; <i>dhfrIb</i>
<i>dfrA12</i>	<i>dfr12</i> ; <i>dhfrXII</i>
<i>dfrA17</i>	<i>dfr17</i> ; <i>dhfrXVII</i>
<i>dfrA7</i>	<i>dfrVII</i> ; <i>dhfrVII</i>
<i>gcuC</i>	<i>orf</i> ; <i>orf1</i> ; <i>orfC</i> ; <i>orfX</i>
<i>gcuF</i>	<i>orfF</i>

\*These are also valid names. A lack of standards for indicating variants of gene cassettes is noted.

*bla<sub>CARB-2</sub>* (www.lahey.org/Studies; accessed 17 November 2014)], and the arrays *dfrA1-gcuC*, *dfrA1-aadA1a*, *dfrA17-aadA5* and *dfrA12-gcuF-aadA2* were the most commonly reported in class 1 integrons surrounded by the 5'-CS and 3'-CS regions (see further description below).

There is no standard system available to indicate nucleotide variants of gene cassettes. For the purpose of this review, we assume, like Partridge *et al.* (2009), that the gene cassettes are only different (for the purpose of classification) if their nucleotide sequence differs by >2%. An exception was made for *bla<sub>CARB-2</sub>* cassettes for which a single nucleotide change, resulting in an amino acid change, led to classification as a different gene (www.lahey.org/Studies; accessed 7 April 2015). Below, we list key characteristics of commonly occurring gene cassette arrays identified by Partridge *et al.* (2009), before a closer examination of their species, geographical and environmental distribution.

Information on the distribution of each cassette array was collected from PubMed, GenBank and INTEGRALL databases using the designation of each gene cassette or cassette array as the search term. In PubMed, the term 'integron' was added to the search, together with each cassette/array. For each gene, additional searches with the alternative names given to the same cassette were performed. For example, for the cassette array '*dfrA17-aadA5*' the searches performed in PubMed were: '*dfrA17* AND integron', '*dfr17* AND integron', '*dhfrXVII* AND integron', '*aadA5* AND integron', '*ant(3'')-1e* AND integron', '*dfrA17-aadA5* AND integron', '*dfr17-aadA5* AND integron', '*dhfrXVII-aadA5* AND integron', '*dfrA17- ant(3'')-1e* AND integron', '*dfr17- ant(3'')-1e* AND integron' and '*dhfrXVII- ant(3'')-1e* AND integron'.

The references that are used as examples in this manuscript include studies that have determined the cassette array by nucleotide sequence, size of the PCR amplicon and restriction analysis, PCR amplification of the gene cassettes with specific primers, and/or Southern blot hybridization,

except for *bla<sub>CARB-2</sub>*, where only studies that performed nucleotide sequence are included.

### ***aadB***

The *aadB* gene encodes an aminoglycoside 2''-adenylyl-transferase conferring resistance to dibekacin, gentamicin, kanamycin, sisomicin and tobramycin (Shaw *et al.*, 1993). The *aadB* gene cassette is 591 bp (Recchia & Hall, 1995) and the PCR amplicon is 744 bp. This gene cassette was first identified in the variable region of a class 1 integron in an Australian clinical isolate of *Escherichia coli* (isolated in 1978) and first described in 1986 (Cameron *et al.*, 1986; Stokes & Hall, 1989). This was later shown to be embedded in the variable region of a complex class 1 integron, with duplication of the 3'-CS (Hall & Stokes, 1990).

### ***dfrA7***

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

### ***aadA1a***

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

### ***aadA2***

The *aadA2* gene encodes an aminoglycoside 3''-adenylyl-transferase that confers resistance to spectinomycin and streptomycin (Ramirez & Tolmasky, 2010). The *aadA2* gene cassette is 856 bp (Recchia & Hall, 1995) and the PCR amplicon is 1009 bp. The first report of a class 1 integron with this single cassette dates back to 1995 and refers to a clinical isolate of *Pseudomonas aeruginosa* isolated in Japan in 1965 (Kazama *et al.*, 1995). In addition to the classic class 1 integron, the widely disseminated *aadA2* gene cassette is also present in complex class 1 integrons, such

as in the *Salmonella* resistance island SGI1 and some of the variants (Boyd *et al.*, 2002, 2008).

### ***bla*<sub>CARB-2</sub>**

The  $\beta$ -lactamase encoded by the *bla*<sub>CARB-2</sub> gene confers resistance to penicillins including carbenicillin (Matthew & Sykes, 1977). The cassette is 1044 bp (Recchia & Hall, 1995) and the PCR amplicon is 1197 bp. The first report of the integron-borne *bla*<sub>CARB-2</sub> gene cassette was published in 1991 in a plasmid from a *P. aeruginosa* (Huovinen & Jacoby, 1991) isolate collected years before (Lévesque & Jacoby, 1988). The composition of this gene cassette is not always known in detail (Soufi *et al.*, 2012; Van *et al.*, 2007). The *bla*<sub>CARB-2</sub> cassette is often found adjacent to a 5'-CS fused to the *groEL* gene in the integron of the *Salmonella enterica* genomic islands SGI1, which can also include *ISCR1* (Boyd *et al.*, 2001; Doublet *et al.*, 2004). In addition, this cassette can also be part of complex class 1 integrons, such as that inserted in the *S. enterica* islands SGI1-A and SGI1-G (Doublet *et al.*, 2004).

### ***dfrA1-gcuC***

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

### ***dfrA1-aadA1a***

As mentioned previously, the *dfrA1* gene encodes a dihydrofolate reductase type I, conferring resistance to trimethoprim (Roberts *et al.*, 2012; van Hoek *et al.*, 2011), and the *aadA1a* gene encodes the enzyme aminoglycoside 3"-adenyltransferase associated with resistance to spectinomycin and streptomycin (Ramirez & Tolmasky, 2010). The individual sizes of the cassettes *dfrA1* and *aadA1a* are, as mentioned before, 577 and 856 bp, respectively (Recchia & Hall, 1995); the *dfrA1-aadA1a* array PCR amplicon is 1586 bp. The first report of this class 1 integron array dates from 1990, in the plasmid pLMO229 of an enterobacterium (Sundström & Sköld, 1990).

### ***dfrA17-aadA5***

The *dfrA17* gene encodes a dihydrofolate reductase type XVII, also conferring trimethoprim resistance (Roberts *et al.*, 2012; van Hoek *et al.*, 2011); an aminoglycoside 3"-

adenyltransferase, associated with spectinomycin and streptomycin resistance, is encoded by the *aadA5* gene (Ramirez & Tolmasky, 2010). The PCR product obtained from the amplification of a classic class 1 integron composed by the array *dfrA17-aadA5* is 1664 bp; the *dfrA17* and *aadA5* cassettes are 616 and 895 bp, respectively (Partridge *et al.*, 2009). This gene cassette array was reported for the first time in 2000, in the chromosome of a clinical *E. coli* isolate collected in Australia in 1998 (White *et al.*, 2000). It is noted that White *et al.* (2000) did not suggest the *aadA5* gene confers streptomycin resistance. However, reports studying the gene when present in other arrays suggest so (Sandvang, 1999).

### ***dfrA12-gcuF-aadA2***

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

## **Bacterial species distribution**

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

Some bacterial species seem more likely to carry integrons than others. For instance, more than six of the arrays have been found in bacteria belonging to the species *Acinetobacter baumannii*, *E. coli*, *Klebsiella pneumoniae*, *Proteus mirabilis* and *S. enterica*. In contrast, only one type of array has been described in the species *Citrobacter braakii*, *Pseudomonas putida*, *Serratia liquefaciens* and *Vibrio alginolyticus*. The species carrying the broader set of arrays are all known nosocomial pathogens, often exposed to diverse antibiotic classes, and they are present in the same environments. Thus, they are expected to have opportunities for physical contact and horizontal exchange as well as being under strong positive selection for the resistance traits encoded by the particular gene cassette compositions considered here.

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

Species	Gene cassette array										Total no. of arrays
	<i>aadB</i>	<i>dfrA7</i>	<i>aadA1a</i>	<i>aadA2</i>	<i>bla<sub>CARB-2</sub></i>	<i>dfrA1-gcuC</i>	<i>dfrA1-aadA1</i>	<i>dfrA17-aadA5</i>	<i>dfrA12-gcuF-aadA2</i>		
<i>Achromobacter xylosoxidans</i>							Traglia <i>et al.</i> (2012)				1
<i>Acidovorax defluvi</i>			Li <i>et al.</i> (2009)								1
<i>Acinetobacter baumannii</i>	Nemec <i>et al.</i> (2004)	Segal <i>et al.</i> (2003) Xu <i>et al.</i> (2008a)		Gu <i>et al.</i> (2007)	Koh <i>et al.</i> (2007) Valenzuela <i>et al.</i> (2007)	Kansakar <i>et al.</i> (2011)		Valenzuela <i>et al.</i> (2007) Valenzuela <i>et al.</i> (2007)	Gu <i>et al.</i> (2007)		7
<i>Acinetobacter nosocomialis</i>											3
<i>Aeromonas allosaccharophila</i>							Moura <i>et al.</i> (2012)				1
<i>Aeromonas bestiarum</i>											1
<i>Aeromonas caviae</i>			Barlow <i>et al.</i> (2008)	Carvalho <i>et al.</i> (2012)					Kadlec <i>et al.</i> (2011)		1
<i>Aeromonas eucrenophila</i>									Kadlec <i>et al.</i> (2011)		3
<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)		1
<i>Aeromonas media</i>			Moura <i>et al.</i> (2012)	Carvalho <i>et al.</i> (2012)					Carvalho <i>et al.</i> (2012)		4
<i>Aeromonas punctata</i>									Moura <i>et al.</i> (2012)		3
<i>Aeromonas salmonicida</i>			L'Abée-Lund & Sorum (2001)	L'Abée-Lund & Sorum (2001)					FM957886*		2
<i>Aeromonas sobria</i>									Xu <i>et al.</i> (2011a)		3
<i>Aeromonas</i> sp.									Kadlec <i>et al.</i> (2011)		1
<i>Aeromonas veronii</i>			Moura <i>et al.</i> (2012) Barlow <i>et al.</i> (2008)	Ndi & Barton (2011)					Tacão <i>et al.</i> (2014)		1
<i>Alcaligenes faecalis</i>									Carvalho <i>et al.</i> (2012)		4
<i>Arcanobacterium pyogenes</i>											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>											1

Table 2. cont.

Species	Gene cassette array										Total no. of arrays
	<i>aadB</i>	<i>dfrA7</i>	<i>aadA1a</i>	<i>aadA2</i>	<i>bla<sub>CARB-2</sub></i>	<i>dfrA1-gcuC</i>	<i>dfrA1-aadA1</i>	<i>dfrA17-aadA5</i>	<i>dfrA12-gcuF-aadA2</i>		
<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* Mokracka <i>et al.</i> (2012)	Mokracka <i>et al.</i> (2012)			6
<i>Citrobacter koseri</i>											1
<i>Citrobacter youngae</i>				Srinivasan <i>et al.</i> (2008)							1
<i>Corynebacterium glutamicum</i>				Nesvera <i>et al.</i> (1998)							1
<i>Enterobacter aerogenes</i>											2
<i>Enterobacter cloacae</i>		Frank <i>et al.</i> (2007)	Hussein <i>et al.</i> (2009)	Dahmen <i>et al.</i> (2010)							6
<i>Enterobacter hormaechei</i>			Mokracka <i>et al.</i> (2011)								3
<i>Enterobacter intermedium</i>			Bado <i>et al.</i> (2010)								3
<i>Enterobacter sakazakii</i>			Mokracka <i>et al.</i> (2012)								1
<i>Enterococcus faecalis</i>			Clark <i>et al.</i> (1999)								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)							8
<i>Klebsiella mobilis</i>			Koczura <i>et al.</i> (2011)								2
<i>Klebsiella ornithinolytica</i>			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)							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)							9
<i>Kluyvera georgiana</i>											1

Table 2. cont.

Species	Gene cassette array										Total no. of arrays
	<i>aadB</i>	<i>dfrA7</i>	<i>aadA1a</i>	<i>aadA2</i>	<i>bla<sub>CARB-2</sub></i>	<i>dfrA1-gcuC</i>	<i>dfrA1-aadA1</i>	<i>dfrA17-aadA5</i>	<i>dfrA12-gcuF-aadA2</i>		
<i>Kluyvera</i> sp.		Mokracka et al. (2012)	Mokracka et al. (2012)				Mokracka et al. (2012)				3
<i>Laribacter hongkongensis</i>						Feng et al. (2011)		Feng et al. (2011)			2
<i>Leclercia adecarboxylata</i>								Shin et al. (2012)			1
<i>Morganella morgani</i>	Mahrouki et al. (2012)		Hussein et al. (2009)	Barlow et al. (2008)		Kor et al. (2013)		Kor et al. (2013)		Kor et al. (2013)	6
<i>Ochrobactrum</i> sp.			Aibinu et al. (2012)	Barlow et al. (2008)				Li et al. (2010)			1
<i>Pantoea agglomerans</i>											2
<i>Pantoea</i> sp.		Mokracka et al. (2012)					Mokracka et al. (2012)				2
<i>Proteus mirabilis</i>	JX494728*	EU860402*	Gionechetti et al. (2008)	Falcone et al. (2010)	Boyd et al. (2008)		Gionechetti et al. (2008)	Wu et al. (2012)			7
<i>Proteus vulgaris</i>		Hussein et al. (2009)	Hussein et al. (2009)				Ozgumus et al. (2009)				3
<i>Providencia alcalifaciens</i>											1
<i>Pseudomonas aeruginosa</i>	Ruiz-Martínez et al. (2011)			Xu et al. (2011a) Gu et al. (2007)	HQ832476*			Xu et al. (2009)		Gu et al. (2007)	5
<i>Pseudomonas putida</i>											1
<i>Pseudomonas</i> sp.	Rosser & Young (1999)		Wu et al. (2012)								1
<i>Raouihella planticola</i>										Tseng et al. (2014)	1
<i>Riemerella anatipestifer</i>			Zheng et al. (2012)	Sun et al. (2012)							2
<i>Salmonella enterica</i>	Zhao et al. (2007)	Tamang et al. (2007)	Ranjbar et al. (2011)	Kim et al. (2011)	Havlickova et al. (2009)	Lee et al. (2009)	Pérez-Moreno et al. (2013)	Pérez-Moreno et al. (2013)	Pérez-Moreno et al. (2013)	Antunes et al. (2006)	9
<i>Serratia liquefaciens</i>			Mokracka et al. (2012)								1
<i>Serratia marcescens</i>	Peng et al. (2007)			Peng et al. (2007)						Peng et al. (2007)	5
<i>Serratia odorifera</i>			Mokracka et al. (2012)								2
<i>Serratia</i> sp.										Chakraborty et al. (2013)	1

Table 2. cont.

Species	Gene cassette array										Total no. of arrays
	<i>aadB</i>	<i>dfrA7</i>	<i>aadA1a</i>	<i>aadA2</i>	<i>bla<sub>CARB-2</sub></i>	<i>dfrA1-gcuC</i>	<i>dfrA1-aadA1</i>	<i>dfrA17-aadA5</i>	<i>dfrA12-gcuF-aadA2</i>		
<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>			Nógrády <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>Shingobacterium</i> sp.			KF687971*	Xu <i>et al.</i> (2007)			Xu <i>et al.</i> (2011b)		Li <i>et al.</i> (2010)		1
<i>Staphylococcus aureus</i>									Xu <i>et al.</i> (2011b)		4
<i>Staphylococcus CoN</i>									Shi <i>et al.</i> (2006a)		1
<i>Staphylococcus epidermidis</i>									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)		2
<i>Staphylococcus warneri</i>									Xu <i>et al.</i> (2008b)		1
<i>Stenotrophomonas maltophilia</i>	JX560784*										4
<i>Stenotrophomonas</i> sp.			Yang <i>et al.</i> (2010b)						Hu <i>et al.</i> (2011)		1
<i>Streptococcus</i> spp.									Xu <i>et al.</i> (2006a)		2
<i>Vibrio alginolyticus</i>									Shi <i>et al.</i> (2006a)		1
<i>Vibrio cholerae</i>											5
<i>Vibrio fluvialis</i>											2
<i>Xantomonas oryzae</i>											1
<b>Total no. of species</b>	11	15	39	31	6	12	22	26	37		

\*GenBank accession number.



Amongst the arrays reviewed, *aadA1a*, *aadA2* and *dfrA12-gcuF-aadA2* are present in a diverse range of bacterial species (>30), whilst *aadB* and *bla<sub>CARB-2</sub>* are restricted to a smaller number of species, and seem to have a preference for *Enterobacteriaceae* and *S. enterica*, respectively.

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

### Geographical dissemination

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

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

### Environmental distribution

As expected from the dissemination patterns of antimicrobial resistance in general, resistance-encoding gene cassette arrays are mostly reported in bacteria isolated from human clinical settings. Nonetheless, there are an increasing number of studies describing the presence of gene cassette arrays in other environments. Humans are in contact with animals, animal food products and other environmental sources of integrons, and can both be recipients and donors of integron-carrying bacteria or genetic material (Stokes & Gillings, 2011). The flow of integrons and gene cassettes between environments is spatially and temporally variable, and may be best explained as a multidimensional

process. The specific events of gene exchange and directions will depend on a multitude of factors, such as the encoded trait(s) and genetic composition of the integron, the mobility of the genetic region it is embedded in, randomness and chance dispersal, and the characteristics of the host and environmental conditions, including selection of the host bacterium for integron-encoded traits. Examples of the many clinical and environmental sources in which the arrays are found are given in Table 4.

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

### Observational bias and other limitations in studies

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

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

A limitation to the current study of class 1 integrons is that most studies are qualitative and descriptive in nature. The experimental study design is based on the need to better understand the genetic basis associated with the specific resistances observed in clinical isolates of bacterial pathogens. Such studies are often done with only limited consideration of the

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

Country	Gene cassette array								Total no. of arrays	
	<i>aadB</i>	<i>dfrA7</i>	<i>aadA1a</i>	<i>aadA2</i>	<i>bla<sub>CARR-2</sub></i>	<i>dfrA1-gcuC</i>	<i>dfrA1-aadA1</i>	<i>dfrA17-aadA5</i>		<i>dfrA12-gcuF-aadA2</i>
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)			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)		3
Brazil	DQ139277*		Peirano <i>et al.</i> (2006)	Sá <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)		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)		3
Chile			Lapierre <i>et al.</i> (2008)							2
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)	9
Colombia									GU304661*	1
Czech Republic			Dolejšká <i>et al.</i> (2008)		Havlicikova <i>et al.</i> (2009)			Dolejšká <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)	5
Ethiopia					Molla <i>et al.</i> (2007)				Molla <i>et al.</i> (2007)	4
Finland									Heikkilä <i>et al.</i> (1993)	1
France	Huys <i>et al.</i> (2005)		Vinué <i>et al.</i> (2011)	Casin <i>et al.</i> (1999)	Poirel <i>et al.</i> (1999)			Vinué <i>et al.</i> (2011)	Vinué <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)	8
Ghana			Labar <i>et al.</i> (2012)					Labar <i>et al.</i> (2012)		4

Table 3. cont.

Country	Gene cassette array										Total no. of arrays	
	<i>aadB</i>	<i>dfrA7</i>	<i>aadA1a</i>	<i>aadA2</i>	<i>bla<sub>CARB-2</sub></i>	<i>dfrA1-gcuC</i>	<i>dfrA1-aadA1</i>	<i>dfrA17-aadA5</i>	<i>dfrA12-gcuF-aadA2</i>			
Gibraltar			Ridley & Threlfall (1998)									1
Hungary	Libisch <i>et al.</i> (2009)		Nógrády <i>et al.</i> (2005)	Nógrády <i>et al.</i> (2005)	Nógrády <i>et al.</i> (2005)	Nógrády <i>et al.</i> (2005)		Nógrády <i>et al.</i> (2005)	Nógrády <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* (2011)	Pazhani <i>et al.</i> (2011)			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
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)			7
Italy	Huys <i>et al.</i> (2005)		Falbo <i>et al.</i> (1999)	Falcone <i>et al.</i> (2010)	GU987051*			Gionechetti <i>et al.</i> (2008)	Gionechetti <i>et al.</i> (2008)			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> (2007)	Ahmed <i>et al.</i> (2007)			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)			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)			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)			4
Madagascar			Rakotonirina <i>et al.</i> (2013)	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)			9
Mexico				Pérez-Valdespino <i>et al.</i> (2009)				Wiesner <i>et al.</i> (2009)	Wiesner <i>et al.</i> (2009)			3

Table 3. cont.

Country	Gene cassette array								Total no. of arrays	
	<i>aadB</i>	<i>dfra7</i>	<i>aadA1a</i>	<i>aadA2</i>	<i>bla<sub>CARB-2</sub></i>	<i>dfra1-gcuC</i>	<i>dfra1-aadA1</i>	<i>dfra17-aadA5</i>		<i>dfra12-gcuF-aadA2</i>
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)	Labar <i>et al.</i> (2012)	6
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)	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)	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)	Mokracka <i>et al.</i> (2012)	Mokracka <i>et al.</i> (2012)	5
Portugal		Ferreira da Silva <i>et al.</i> (2007)	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)	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)	Pérez-Moreno <i>et al.</i> (2013)	Rodríguez <i>et al.</i> (2006)	Pérez-Moreno <i>et al.</i> (2013)	Guerra <i>et al.</i> (2000)	Pérez-Moreno <i>et al.</i> (2013)	Pérez-Moreno <i>et al.</i> (2013)	Pérez-Moreno <i>et al.</i> (2013)	Pérez-Moreno <i>et al.</i> (2013)	8

Table 3. cont.

Country	Gene cassette array										Total no. of arrays	
	<i>aadB</i>	<i>dfrA7</i>	<i>aadA1a</i>	<i>aadA2</i>	<i>bla<sub>CARB-2</sub></i>	<i>dfrA1-gcuC</i>	<i>dfrA1-aadA1</i>	<i>dfrA17-aadA5</i>	<i>dfrA12-gcuF-aadA2</i>			
Sri Lanka		Sundström <i>et al.</i> (1987)										1
Sudan		Ibrahim <i>et al.</i> (2013)										4
Swaziland			Ceccarelli <i>et al.</i> (2006a)									1
Sweden		Tennhammar-Ekman & Sköld (1979)	Grape <i>et al.</i> (2005)	Grape <i>et al.</i> (2005)								6
Switzerland			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)								8
Thailand	Dalsgaard <i>et al.</i> (2000)		Lay <i>et al.</i> (2012)	Dalsgaard <i>et al.</i> (2000)								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)								8
Trinidad			Zandbergen <i>et al.</i> (2007)									1
			Ridley & Threlfall (1998)									
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)								9
Turkey			Sandalli <i>et al.</i> (2010)									6
Uganda			Guerra <i>et al.</i> (2006)									2
UK	Turton <i>et al.</i> (2006)	Rosser & Young (1999)	Rosser & Young (1999)	Corkill <i>et al.</i> (2005)								6
USA	Turton <i>et al.</i> (2006)	Ajiboye <i>et al.</i> (2009)	Li <i>et al.</i> (2006)	Zhao <i>et al.</i> (2007)								9
Uruguay			Bado <i>et al.</i> (2010)									8
Vietnam		Ploy <i>et al.</i> (2003)	Ploy <i>et al.</i> (2003)	Vo <i>et al.</i> (2010)								1
Zimbabwe			Ceccarelli <i>et al.</i> (2006a)									1
<b>Total no. of countries</b>	<b>24</b>	<b>37</b>	<b>54</b>	<b>38</b>	<b>27</b>	<b>11</b>	<b>44</b>	<b>38</b>	<b>42</b>	<b>38</b>	<b>42</b>	

\*GenBank accession number.

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

Source	Gene cassette array										Total no. of arrays	
	<i>aadB</i>	<i>dfpA7</i>	<i>aadA1a</i>	<i>aadA2</i>	<i>bla<sub>CARB-2</sub></i>	<i>dfpA1-gcuC</i>	<i>dfpA1-aadA1</i>	<i>dfpA17-aadA5</i>	<i>dfpA12-gcuF-aadA2</i>			
<b>Human</b>												
Clinical		Solberg <i>et al.</i> (2006)	Nógrády <i>et al.</i> (2005)	Kazama <i>et al.</i> (1995)	Kor <i>et al.</i> (2013)	Thungapathra <i>et al.</i> (2002)	Nógrády <i>et al.</i> (2005)	White <i>et al.</i> (2000)	Heikkilä <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
<b>Animal</b>												
Domestic	Vo <i>et al.</i> (2007)	Vo <i>et al.</i> (2007)	Kadlec & Schwarz (2008)	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)	Kikuví <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	Gionchetti <i>et al.</i> (2008)	Gionchetti <i>et al.</i> (2008)	Gionchetti (2008)	Ahmed <i>et al.</i> (2007)	Havlickova <i>et al.</i> (2009)		Gonçalves <i>et al.</i> (2013)	Dolejská <i>et al.</i> (2009)	Caljeja <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
<b>Water</b>												
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 Spring					Guerra <i>et al.</i> (2000)			Ozgumus <i>et al.</i> (2007)	Ozgumus <i>et al.</i> (2007)			1
Tap												1
Wastewater		Ferreira da Silva <i>et al.</i> (2007)	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
<b>Soil</b>												
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
<b>Other</b>												
Hospital inanimate surface	JX560784*			Xu <i>et al.</i> (2007)			GU731078*	Sidjabat <i>et al.</i> (2006)	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)	Pallecchi <i>et al.</i> (2007)			3
<b>Total no. of sources</b>	7	8	10	11	9	4	12	12	9			

\* GenBank accession number.

underlying population structure of the pathogen/species examined. These case- and isolate-focused studies therefore do not permit a quantitative analysis of integrons as present in a particular population of a bacterial species or community of several bacterial species. Quantitative analyses are, however, needed to enable monitoring of changes in actual prevalence of integrons over time, i.e. changes in the overall proportion of members of a particular bacterial population carrying a specific gene cassette array.

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

### General considerations

Our review highlights the broad diversity of bacterial species sharing the same gene cassette arrays. These species have been recovered from a wide range of environments (e.g. humans; domestic, food and wild animals; and various environmental sites) located in all regions of the world. This review substantiates further the observations of Partridge *et al.* (2009) on the broad distribution of these particular sequences in class 1 integrons.

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

### Emergence and persistence

Integrons have been found in a permafrost sample (Petrova *et al.*, 2011) and in bacteria isolated years before their characterization as MGEs involved in antibiotic resistance (Dalsgaard *et al.*, 2000; Hedges *et al.*, 1972; Huovinen & Jacoby, 1991; Kazama *et al.*, 1995; Stokes & Hall, 1989). These early observations support the view that integrons are not recent entities and that they have existed in bacterial populations for many decades (Rowe-Magnus *et al.*, 2002). The introduction of antibiotics in clinical, veterinary and agricultural settings has most likely contributed to the selective amplification of new resistance-encoding gene cassettes, and increased the distribution and prevalence of

integron-carrying bacteria with such cassettes. The majority of the gene cassettes reviewed here encode resistance to antibiotics that can also be produced naturally by environmental micro-organisms, suggesting that particular gene cassettes and integrons evolved before bacteria became exposed to pharmaceutically produced antibiotics. This view is also consistent with the recent finding of antibiotic resistance determinants in DNA millions of years old (D'Costa *et al.*, 2011). There is also evidence that class 1 integrons in bacteria exposed to antibiotics can capture gene cassettes from super-integrons – chromosomal integrons that contain long cassette arrays (>20), where the majority of the cassettes are not usually expressed due to the distance to the  $P_c$  promoter (Mazel, 2006; Rowe-Magnus *et al.*, 2001, 2002). Forsberg *et al.* (2012) recently also showed that soil bacteria and human pathogens share the same antibiotic resistance, and that horizontal transfer between both communities contributes to the resistance dissemination. The increased prevalence of integrons is likely the outcome of selection conferred by the exposure to pharmaceutically produced antimicrobials. Integrons have therefore, together with other resistance-conferring MGEs, been seen as xenogenetic pollutants (Gillings, 2013).

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

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

In bacterial species with an SOS response, the integrase gene is normally repressed, which allows the host bacterium to maintain the gene cassette arrays in a steady state. The SOS response is a global response to DNA damage, which controls DNA repair and mutagenesis. A stress-responsive regulation of integrase functions is expected to reduce the biological costs of such a genetic element (Guerin *et al.*, 2009). Triggering of the SOS system can

be observed after conjugation (Baharoglu *et al.*, 2010) and natural transformation (Baharoglu *et al.*, 2012), and by exposure to subinhibitory concentrations of antibiotics (Baharoglu & Mazel, 2011). The activation of the SOS response leads to increased transcription of the integrase gene and increased integrase activity, resulting in cassette rearrangements (Baharoglu *et al.*, 2010; Guerin *et al.*, 2009). A gene cassette rearrangement has also been recently observed *in vivo* after induction of the SOS system, leading to emergence of a resistant *P. aeruginosa* isolate that was then quickly spread amongst the hospital patients (Hocquet *et al.*, 2012).

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

### Clonal (vertical) dissemination versus HGT

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

On the one hand, clonal dissemination of integron-carrying bacteria can explain the occurrence of a particular integron in a specific bacterial species in different geographical regions. For instance, the high occurrence of the *aadA2* and *bla*<sub>CARB-2</sub> cassettes can be explained by their presence in the pathogenic *S. enterica* serovar Typhimurium DT104, which has been extensively sequenced (Antunes *et al.*, 2006; Casin *et al.*, 1999; Zhao *et al.*, 2007). Increased international travel in the last decades has increased the potential for dissemination of virulent clones carrying integrons. For instance, class 1 integrons were detected in 11 clinical isolates of *Shigella* spp. in Spain, which were associated with travel from other countries (Navia *et al.*, 2004). There are also examples of integron-containing *A. baumannii* clinical isolates found in the USA and the UK, which

were associated with patients travelling from Iraq (Turton *et al.*, 2006).

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

### Concluding remarks

A diverse set of bacterial species shares the same gene cassettes and arrays. These host species have been recovered from a wide range of environments located in all regions of the world. The current distribution pattern of commonly occurring gene cassette arrays suggests both (i) opportunities for rapid dissemination of successful clones at a global scale, and (ii) the existence of effective routes of HGT between geographical locations, environments and unrelated bacterial species. The current integron dispersal pattern has developed over the last three decades. Studies are now also emerging describing resistance-encoding gene cassettes in integrons in bacterial species rarely associated with clinical disease, suggesting ongoing HGT and dissemination processes in the broader environment. The evolutionary significance of resistance-carrying integrons from the pre-antibiotic era to current resistance patterns remains to be determined. Current data suggest multidirectional flow of bacteria and their integrons between humans, animals and other environments (Stokes & Gillings, 2011). Such flow has major and serious implications for human health and treatment of infections. We highlight the need for moving from a descriptive approach to integron dissemination to one that allows a more comprehensive understanding of the factors governing the prevalence, persistence and spread of integrons between and within bacterial populations.

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