

Movement of resistance genes in hospitals



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***Enterobacteriaceae* resistant to multiple antibiotics are an increasing global health problem that impacts treatment and survival of hospitalised patients. In these organisms much of the antibiotic resistance is due to a wide variety of 'mobile' resistance genes that have been captured from the chromosomes of different bacterial species and transferred to plasmids by the actions of various mobile genetic elements. These plasmids can then spread between bacterial cells, including different species. The association of resistance genes with mobile elements, these mobile elements with plasmids and plasmids with particular bacterial strains means that spread of resistance genes can occur at several different levels (Figure 1). Understanding more about the contributions of these different processes and how they interact may enable better prediction and control of the spread of resistance.**

Several different types of mobile elements are able to capture genes (which may confer antibiotic resistance) from various sources and transfer them to plasmids, enabling spread into other species including pathogenic bacteria. As gene capture events are rare, each particular resistance gene is usually associated with a particular mobile element; these elements have different characteristics but some features are common (Figure 2)¹. Insertion sequences (IS) consist of little more than a transposase (*tnpA*) gene flanked by inverted repeats (IR). These IR are recognised and processed by the encoded transposase protein resulting in copying or transfer of the IS to a new location (transposition). Some unusual IS (*ISEcp1*, *ISCR* elements) can capture and move adjacent DNA when present as a single copy, but for most IS two copies flanking a resistance gene are needed to form a composite transposon that moves as a single unit. Transposons (Tn) usually have an additional resolvase (*tnpR*) gene and can carry resistance genes internally. Tn and most IS create

direct repeats (DR) of characteristic length on insertion and these are useful signatures for understanding relationships between different resistance regions and plasmids. Integrons (In) capture resistance genes packaged as gene cassettes by site-specific recombination between the integron *attI* site and the cassette *attC* site, catalysed by an *IntI* integrase encoded in the integron. These mobile genetic elements often provide a promoter for expression of an associated resistance gene and can act as mobile regions of homology, allowing additional movement of resistance genes by recombination. The association of resistance genes with mobile elements provides the first level of movement of these genes, allowing transfer onto and between plasmids.

The 'backbones' of these plasmids carries genes for essential plasmid functions such as replication, partitioning and stability, some of which are involved in determining the 'host range' of the plasmid, that is, which species (and maybe which strains) it can transfer to and be maintained in. A mobile element/resistance gene combination inserted into this backbone in a location that does not disrupt plasmid integrity can act as a site for further insertions, so that resistance genes and associated mobile genetic elements tend to become clustered in complex multiresistance regions (Figure 2). Conjugative plasmids encode the machinery necessary for their own movement between cells and tend to be large (up to ~200 kb), while mobilisable plasmids, which may be much smaller, lack conjugation genes and can only move between bacterial cells if 'helped' by a conjugative plasmid². This transfer of plasmids

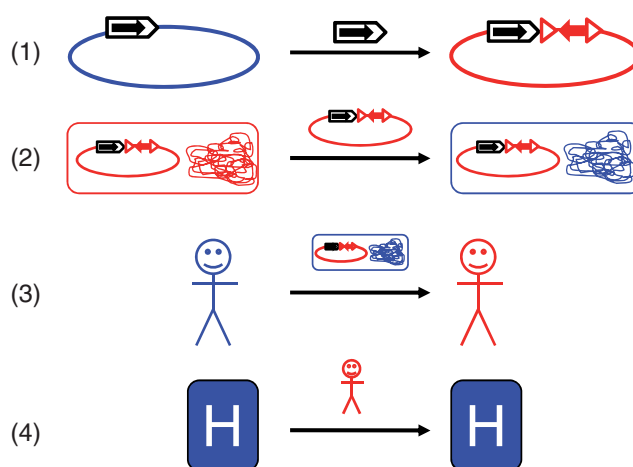


Figure 1. Different levels of movement of resistance genes. Mobile elements can move resistance genes between different plasmids in the same cell (1), plasmids can move resistance genes between bacterial cells (2), bacteria can move resistance genes between people (3) and people can move resistance genes between hospitals, locations, countries etc. (4).

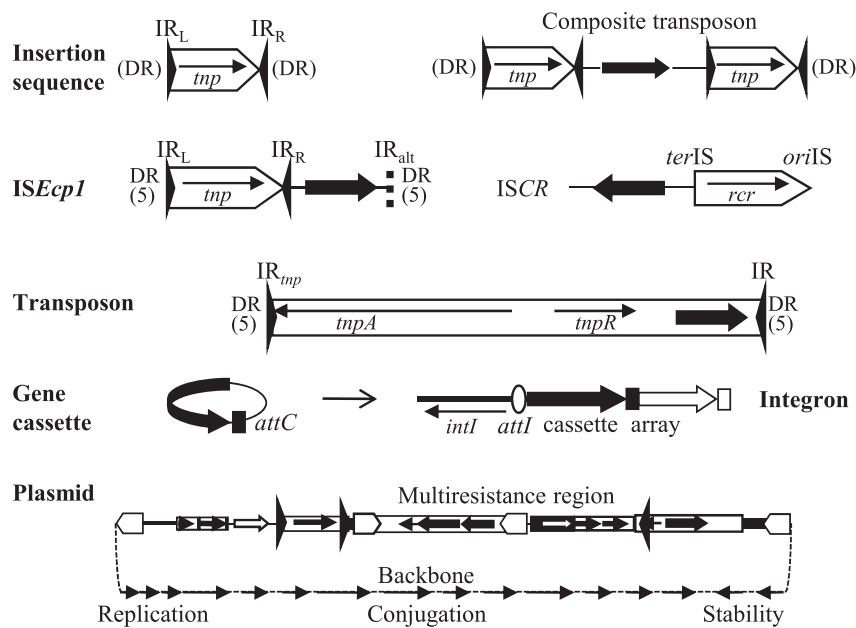


Figure 2. Characteristics of different mobile genetic elements. Resistance genes are shown as thick arrows and other genes as thin arrows. Inverted repeats (IR) are shown as triangles. Direct repeat (DR) lengths are shown in parentheses. ISCR elements appear to use a different transposition mechanism (rolling circle replication; *rcr*) from other elements, their ends are defined by origin (*ori*) and terminus (*ter*) regions rather than IR and they do not create DR.

carrying resistance genes between bacterial cells creates a second level of movement of resistance and multiresistance.

While the mechanisms by which different mobile elements move and transfer resistance genes between DNA molecules and by which plasmids move between cells have been well studied and the processes demonstrated experimentally, less is known about how these processes operate in the ‘real world’. A few studies illustrate movement of resistance genes between plasmids and plasmids between isolates in a clinical setting. For example, the *bla*_{KPC-2} (*Klebsiella pneumoniae* carbapenemase) gene was identified in two different plasmid types in the same isolate as part of the same transposon Tn4401³, implying movement of this transposon. Transfer of a plasmid carrying resistance genes between species in the same patient has also been documented, for example, a plasmid carrying the *bla*_{IMP-4} carbapenemase gene plus other resistance genes was identified first in a *Serratia* isolate and subsequently in an *Escherichia coli* isolate from the same patient⁴.

A third level of movement is transfer of bacteria between patients, which could occur via the hospital environment, medical instruments or by carers interacting with multiple patients. Recently, whole genome sequencing has been used to track the spread of bacterial isolates carrying important resistance genes during outbreaks. Single nucleotide polymorphisms (SNP) were used to follow the course of an outbreak of *K. pneumoniae* ST258 (CC292) isolates carrying the *bla*_{KPC-3} gene in the USA⁵. A similar approach was used in Australia to examine a neonatal outbreak of

E. coli, which was identified as ST131 carrying the *bla*_{CTX-M-15} gene that confers resistance to third generation cephalosporins⁶. Generating complete plasmid sequences from this type of data is more difficult than identifying resistance genes and SNPs, due to long repeats (often mobile elements) that complicate assembly, but would be useful in identifying which resistance genes are travelling together and which plasmid type carries each set of genes.

A fourth level of movement is transfer of patients carrying resistance genes between different healthcare facilities. A simulation using hospital admission data from England demonstrated that connections between hospitals due to patient transfers can have a profound effect on the epidemic behaviour of high-risk clones, with formation of specialist centres with very large catchment areas potentially greatly increasing the spread of resistance⁷. There are also many examples of the introduction of bacteria carrying different resistance genes by hospitalisation of patients who have been treated overseas⁸ and certain bacterial strains and/or plasmids appear to be very successful at spreading globally⁹. For example, *bla*_{KPC} genes are found in strains belonging to *K. pneumoniae* clonal complex (CC) 292 in many countries. Similarly, *E. coli* multilocus sequence type (ST) 131 is a successful clone often associated with the globally dominant *bla*_{CTX-M-15} gene that confers resistance to third-generation cephalosporins. Closely related plasmids have been found in isolates of the same ST from different locations¹⁰, suggesting that particular plasmid types may be linked to particular bacterial clones.

Tracking, understanding and trying to limit the spread of antibiotic resistance in hospitals is clearly a complex problem. Currently, identifying and isolating patients carrying problematic resistance genes and other interventions that prevent the spread of bacterial strains between patients seem most achievable. More extensive screening to detect particular combinations of resistance genes and selected plasmid and/or strain markers may allow identification of particularly troublesome plasmids and/or strains and indicate most important level(s) of movement for different resistance genes. This should inform isolation and infection control policies, as well as providing sets of samples that can be examined in more detail to try and understand how the genetic context of a resistance gene really influences its spread.

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Biography

Dr Sally Partridge is a Senior Research Fellow who has been working on the genetics of mobile antibiotic resistance in Gram-negative bacteria since 1997, first at CSIRO and Macquarie University and from 2005 at the Centre for Infectious Diseases and Microbiology, The University of Sydney, and the Westmead Millennium Institute, Westmead Hospital.



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