

Bottlenecks in the transferability of antibiotic resistance from natural ecosystems...

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Introduction

Bacterial pathogens can develop antibiotic resistance either by mutations, or by the acquisition of antibiotic resistance genes from other microorganisms through horizontal gene transfer (HGT). Since bacterial pathogens were (presumably) susceptible to antibiotics at the time of the development of these compounds, it is reasonable to think that resistance genes have been acquired from non-pathogenic microorganisms. Indeed, the analysis of *Escherichia coli* plasmids from bacterial strains isolated before and after the use of antibiotics for therapy demonstrated that the plasmid families were similar, but incorporated resistance genes after the antibiotic era ([Datta and Hughes, 1983](#)).

Since the resistance genes did not originate in bacterial pathogens, the sources for these genes would be environmental microorganisms ([Martinez et al., 2009a](#) ; [Davies and Davies, 2010](#)). Indeed, the fact that most antibiotics currently used in clinics originated in environmental microorganisms ([Waksman and Woodruff, 1940](#)) led to the proposal that the origin of resistance genes are the antibiotic-producing organisms, where resistance genes may play an auto-protective role ([Benveniste and Davies, 1973](#) ; [Davies, 1997](#)). Recent work indicates that indeed antibiotic-producing environmental microorganisms harbor a large number of resistance genes that could be potentially transferred to human pathogens ([D'Costa et al., 2006](#)). Nevertheless, the presence of resistance genes in the environment is not confined to antibiotic producers ([Aminov, 2009](#)). For instance, the quinolone resistance gene *qnrA* originated in the water-borne bacteria

Shewanella algae, which is not known to produce an antibiotic ([Poirel et al., 2005](#)). Given that quinolones are synthetic drugs, the existence of these determinants indicate the antibiotic resistance genes can have disparate functions in their original hosts, in such a way that the universe of potential resistance genes that can be incorporated into mobile genetic elements is even larger than predicted from the analysis of antibiotic producers. Support for this statement is the finding of genes that contribute to intrinsic resistance in different bacterial species ([Fajardo et al., 2008](#) ; [Tamae et al., 2008](#) ; [Girgis et al., 2009](#) ; [Alvarez-Ortega et al., 2010](#) ; [Liu et al., 2010](#)) and functional metagenomic analyses indicating that the wide dissemination of a large number of resistance genes ([D'Costa et al., 2006](#) ; [Sommer et al., 2009](#)) in all analyzed ecosystems (including the human gut) whether or not contaminated by human activities.

It would be expected that this diversity of resistance genes in microorganisms, that can confer an antibiotic resistant phenotype on their transfer to a new host might be mirrored by a large variability of resistance genes, acquired by HGT, in human pathogens. However, the number of different resistance determinants found among human bacterial pathogens is low in comparison to those present in the different metagenomes. This indicates that the transfer of a resistance gene from its original host to a human pathogen might be constrained by different bottlenecks, as discussed in this review.

The Two Faces of Antibiotic Resistance Determinants: Housekeeping Genes and Human-Driven Contaminants

The existence of resistance genes in natural ecosystems, even those without any record of pollution by antibiotics was reported more than four decades ago ([Gardner et al., 1969](#)). However, detailed studies on this topic are more recent. In the last years an increasing number of studies of the presence of resistance genes in non-clinical ecosystems have been published. Several are based on non-culture methods for detecting resistance. Briefly, two different methodologies are applied; one is the search for any potential gene that confers resistance on expression in a heterologous host by using functional genomic techniques ([D'Costa et al., 2006](#) , [2011](#) ; [Sommer et al., 2009](#)). The other is the search for resistance genes already present in human pathogens, usually by PCR, in metagenomic DNA ([Koike et al., 2007](#)). Whereas, in the first analysis the purpose is to characterize any gene that can cause resistance if transferred and hence study the potential natural resistome of the studied ecosystem, the second type of study analyses contamination by resistance genes already acquired by human pathogen.

These studies thus provide different information. Functional metagenomics serves to define novel mechanisms of resistance (potentiality, see [Martinez et al., 2007](#)), but predicting whether such mechanisms will be transferred to human pathogens is not obvious (see below). Indeed, the fact that the origin of the antibiotic resistance genes currently present in human pathogens is known in only a few cases indicates that defining the environmental resistome is a needed but not sufficient condition for predicting the emergence of resistance. It is important to note however that the finding of

novel mechanisms of resistance can be a valuable tool for the design of antibiotic modifications before resistance arises ([Wright, 2007](#) ; [Martinez et al., 2011](#)).

The analysis of the presence in different ecosystems (contaminated and pristine) of genes that have been already acquired by human pathogens would provide information on the stability of these elements, the reservoirs and the factors that enrich their presence in nature. These studies can be used to evaluate the risks for human health from pollution of natural ecosystems by antibiotic resistance determinants, together with antibiotics that serve as selectors of resistance themselves ([Martinez, 2008](#) , [2009](#)).

This knowledge might serve for the identification of intervention strategies to reduce the impact of anthropogenic activities on the enrichment of resistance elements, already present in mobile genetic elements (MGEs), in natural (non-clinical) ecosystems ([Baquero et al., 2008](#)). The relevance that farming and transport of food-borne animals or pets ([Guardabassi et al., 2004](#) ; [Aarestrup, 2005](#) ; [Moreno et al., 2008](#)), as well as the transport of goods ([Ruiz et al., 2000](#)), or human migration ([Kumarasamy et al., 2010](#)) may have for the dissemination or resistance is well known. For these processes, procedures for tracking the presence and dissemination of resistance genes might be implemented. More difficult will be the implementation of such studies for analyzing the role of wild animals in the spread of resistance ([Gilliver et al., 1999](#) ; [Livermore et al., 2001](#) ; [Allen et al., 2010](#)). Important in this respect is the finding of resistance in migratory birds that can disseminate both antibiotic resistance determinants and

infective resistant bacteria all over the world ([Middleton and Ambrose, 2005](#) ; [Steele et al., 2005](#) ; [Simoes et al., 2010](#)).

Between these types of studies are functional analyses on the resistance mobilome, those resistance genes that are already present on mobile elements, irrespective of whether or not they have been acquired by human pathogens. The transfer of a potential resistance gene from the chromosome of an environmental bacterium to a human pathogen requires it to be mobilizable after its capture by a translocative element and its integration in an MGE. This means that once the resistance element has been incorporated in a mobile element, the possibility of its acquisition by a human pathogen can be high, especially if this element is present in the human bacterial population. Unfortunately, studies on the environmental resistance mobilome are difficult and still rare ([Szczepanowski et al., 2008](#) , [2009](#) ; [Moura et al., 2010](#) ; [Parsley et al., 2010](#)).

Ecological Connectivity

The first requirement for the transfer of a resistance gene is that both the donor and the receptor share the same habitat. In the case of pathogenic bacteria, the pathogens need not co-exist with the donor, because a chain of microorganisms may link the donor and the recipient. However, since acquiring resistance genes might confer a fitness cost (see below), the establishment of a successful gene-transfer chain is possible only with positive selection for the resistance determinant. In other words, unless resistance is selected (mainly by antibiotics), it is unlikely that MGEs containing resistance genes will be fixed in the populations of environmental

microorganisms en route to human pathogens. Since the natural concentrations of antibiotics in non-clinical ecosystems are much lower than at hospitals ([Davies, 2006](#)), only in the case of pollution by antibiotics (aquaculture, waste disposal from cities, farms, or industries) a positive selection for MGEs containing resistance genes can be envisaged. Following this reasoning, it has been proposed that the possibility of a given resistance gene being transferred to a human pathogen will largely depend on whether the habitat where the donor micro-organism is present close to human-linked ecosystems ([Baquero et al., 2009](#)). For instance, it would be rare for resistance genes found in deep soil allocations ([Brown and Balkwill, 2009](#)) or at a glacial ice core ([Miteva et al., 2004](#)) would be transferred to human pathogens. In contrast, it has been suggested that ecosystems such as waste-water treatment plants or farms, where human pathogens and environmental bacteria co-exist in the presence of contaminating antibiotic residues, might be hot-spots for the acquisition of resistance genes by bacterial pathogens ([Baquero et al., 2008](#) ; [Aminov, 2011](#)).

Ecological connectivity is not restricted to the spatial distribution of microorganisms. For those microorganisms sharing the same ecosystem, some of them are more prone to exchange genetic material than others. The organisms that can share genes, have been named as genetic exchange communities ([Jain et al., 2003](#)). As stated in ([Skippington and Ragan, 2011](#)), “ gene exchange communities can vary widely in spatial extent, taxonomic diversity, density of internal connectivity, and involvement of vector types.” These communities usually share some plasmid (or transposon) types and do not possess strong restriction/modification systems that would impede the

interchange of DNA. As a consequence, the entrance of a resistance gene, located in a proficient MGE into a well established gene exchange community might allow its spread among different organisms and consequently fixation in populations of bacterial pathogens. This spread will be modulated by specific fitness costs that preclude the stability of the gene in some bacterial species.

Founder Effect

By founder effect, we refer to the situation in which the first gene to arrive is the one to win ([Baquero et al., 2009](#)). When there are several resistance determinants with a similar substrate profile, usually one prevails once transferred to human bacterial pathogens. As we will discuss later, this situation can be the consequence of differential fitness costs, nevertheless, a certain degree of serendipity might be the basis of the successful transfer, spread and fixation of a given resistance determinant. One example of this situation is the TEM-1 beta-lactamase, which, followed by SHV-1 and OXA enzymes, has been the predominant plasmid-encoded beta-lactamase in *Enterobacteriaceae* for many years ([Simpson et al., 1980](#) ; [Medeiros, 1997](#)).

The TEM-1 beta-lactamase was acquired soon after the introduction of the first generation of beta-lactams for therapy, and plasmids coding this beta-lactamase spread rapidly among bacterial pathogens. The study of several different ecosystems has shown that there exist a large number of beta-lactamases nearly everywhere, which can confer resistance to the same antibiotics as TEM-1. Why then, has TEM-1 prevailed in these pathogen populations? Antibiotic resistance genes are acquired and maintained because of the strong selective pressure of antibiotics. Once bacteria have

acquired a determinant that allow them to resist antibiotics, there is not a selection pressure for replacement of the determinant already present in bacterial populations. This situation can change if the selective pressure is altered, for example when new antibiotics are launched into clinical use ([Livermore, 2009](#) ; [Salverda et al., 2010](#)). Indeed, the introduction of beta-lactamase inhibitors and novel beta-lactams for which TEM-1 presented low activity generated two different processes: (i) evolution of the TEM-enzyme that most likely occurred in clinical settings when bacterial pathogens were exposed to the novel selective pressure (ii) acquisition of novel beta-lactamase coding genes by human pathogens with novel substrate profiles.

Fitness Costs

It is generally assumed that the acquisition of an antibiotic resistance determinant confers a fitness cost ([Andersson and Levin, 1999](#)), meaning that in the absence of selection, resistant bacteria will be outcompeted by the susceptible ones. In the case of genes acquired by HGT, these costs might be the consequence of the metabolic load imposed by the replication, transcription, and translation of the novel genetic elements. If this was the unique cause of fitness costs, the disadvantage of carrying one or another resistance gene will be similar and the fitness cost would not constitute a relevant bottleneck in selecting one resistance determinant over another. However, different studies have shown that, at least on occasion, the introduction of a given resistance gene does not impose a non-specific metabolic burden but leads to specific changes in bacterial physiology. This may be the case for AmpC beta-lactamase genes, which are infrequently found on *Salmonella* plasmids unless the plasmid also harbors the repressor

of their expression ([Verdet et al., 2000](#)) or elements that compensate the biological costs associated to AmpC expression ([Hossain et al., 2004](#)). It has been found that AmpC alters the physiology of *Salmonella* , decreasing its virulence and hence a differential fitness cost that decreases the probability of dissemination of specific gene among *Salmonella* strains ([Morosini et al., 2000](#)). This example indicates that the fitness costs can be gene-specific and do not necessarily derive from a general metabolic burden. In this context, those resistance determinants conferring high fitness costs are unlikely to be fixed in bacterial populations because they would be outcompeted by other resistance determinants which lower fitness costs ([Martinez et al., 2011](#)).

This reasoning must be however modified by the chances of acquiring compensatory mutations ([Andersson and Hughes, 2011](#) ; [Martinez et al., 2011](#)). If a resistance determinant confers high fitness costs, but compensatory mutations are easily selected, the probability of being maintained in bacterial pathogens is high. In such cases, the location of the mutations is a relevant issue. If the compensatory mutations occur in the chromosome, not in the MGE, the acquisition of the resistance gene by a new host implies a new fitness cost, and as a consequence the spread of the resistance determinant will be compromised. However, if the mutation occurs in the MGE, the chances for spread will be enhanced.

Second-Order Selection and Maintenance of Resistance Genes in the Absence of Selection

If the acquisition of resistance confers fitness costs it is logical to suppose that resistant organisms will be outcompeted by their susceptible, fitter

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counterparts in the absence of selection. However, some resistant strains present no-cost ([Rozen et al., 2007](#) ; [Balsalobre and De La Campa, 2008](#)) and even some resistance determinants can be beneficial under certain conditions ([Alonso et al., 2004](#) ; [Maughan et al., 2004](#) ; [Luo et al., 2005](#) ; [Perkins and Nicholson, 2008](#) ; [Michon et al., 2011](#)). Finally, some fitness costs can be compensated by mutations that do not impede to keep resistance ([Bjorkman et al., 1998](#) ; [Maisnier-Patin et al., 2002](#) ; [Paulander et al., 2007](#) ; [Lind et al., 2010](#) ; [Shcherbakov et al., 2010](#)). This indicates that reversing resistance once established can be a difficult task ([Andersson and Hughes, 2010](#)).

Maintenance of resistance genes in habitats without a strong antibiotic pressure is favored as well by second-order selection processes. Antibiotic resistance genes on MGEs are usually in association to other resistance determinants. This means that the selection for one antibiotic will select for the whole array of resistance genes present in this specific MGE.

Furthermore, MGEs besides resistance genes may carry other elements such as heavy-metal resistance determinants ([Baker-Austin et al., 2006](#)), or genes coding for production of siderophores, toxins, or bacteriocins ([De Lorenzo and Martinez, 1988](#) ; [Clewell, 1990](#) ; [Herrero et al., 2008](#)); these can confer an ecological advantage in some ecosystems and thus co-select resistance in the absence of antibiotics. Cross-selection might also be a relevant second-order process that allows maintenance of resistance in the absence of selection. Certain resistance determinants, such as multidrug (MDR) efflux pumps confer resistance to different compounds (antibiotics, biocides, or heavy metals; [Martinez et al., 2009b](#)). This means that selection

with the biocide or the heavy metal might result in cross-resistance to the antibiotic ([Hernandez et al., 1998](#) ; [Sanchez et al., 2005](#)).

A final mechanism for the maintenance of resistance is based on the inherent systems for plasmid stability. Plasmids frequently encode toxin/antitoxin systems, which provoke death of bacteria that lose the plasmid ([Hayes, 2003](#) ; [Hayes and Van Melderren, 2011](#)). If one such plasmid incorporates an antibiotic resistance determinant, the probabilities for its maintenance will be high.

Taking these considerations into account, resistance genes might evade elimination ([Andersson and Hughes, 2011](#)) in the absence of antibiotics; indeed, resistance determinants present in human pathogens have been found on identical MGEs, in antibiotic-pristine habitats ([Pallecchi et al., 2008](#)) such as wild animals ([Gilliver et al., 1999](#) ; [Livermore et al., 2001](#)) and primitive human populations without any known exposure to antibiotics ([Grenet et al., 2004](#) ; [Bartoloni et al., 2009](#)). These observations indicate that anthropogenic activity has enriched for a small number of resistance genes in natural ecosystems and that this type of pollution will be difficult to eradicate ([Salyers and Amabile-Cuevas, 1997](#) ; [Martinez, 2009](#)). Supporting this notion, analyses of soils sampled in The Netherlands from 1940 to 2008, reveal that the abundance of different antibiotic resistance genes increased during this period. This, in spite of the fact that restrictions on non-therapeutic use of antibiotics in agriculture and in waste management procedures have been strongly enforced ([Knapp et al., 2010](#)).

Conclusion

Research on antibiotic resistance has been mainly focused on bacterial pathogens isolated from infections or in clinical settings. However, the fact that HGT-acquired genes originated in natural, non-clinically relevant microorganisms and that the first step in the transfer of resistance likely occurs in natural ecosystems emphasizes the need to analyze resistance in non-clinical ecosystems. Furthermore, the constant release of antibiotic resistance determinants already present in MGEs located in human pathogens, and in some circumstances associated with selective concentrations of antibiotics, may disrupt natural microbiota, which then serve as reservoirs for resistance genes. Non-culture based methods have demonstrated their value for the analysis of resistance in natural ecosystems. Among them, functional metagenomics provides the means to identify novel mechanisms of resistance independently of whether they will be acquired by bacterial pathogens. On the other hand, PCR analyses for specific genes serve to define reservoirs and to study elements like pollution in the dissemination and maintenance of resistance. Functional metagenomic studies indicate that very few among the resistance genes present in nature have been transferred to human pathogens. Whereas the founder effect can provide stochasticity to these acquisitions, other factors such as fitness costs, ecological connectivity, which includes the formation of gene exchange communities, are relevant bottlenecks that serve to modulate the acquisition of resistance genes by animal or human pathogens.

Conflict of Interest Statement

The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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