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REVIEW

Can the legacy of industrial pollution influence antimicrobial resistance in estuarine sediments?

Kiri Rodgers[1] · Iain McLellan[1] · Tatyana Peshkur[2] · Roderick Williams[1] · Rebecca Tonner[2] · Andrew S. Hursthouse[1] · Charles W. Knapp[2] · Fiona L. Henriquez[1]

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Abstract
Antimicrobial resistance (AMR) represents a major global health threat, as well as a major hazard to sustainable economic development and national security. It remains, therefore, vital that current research aligns to policy development and implementation to alleviate a potential crisis. One must consider, for example, whether drivers of antibiotic resistance can be controlled in the future, or have they already accumulated in the past, whether from antibiotics and/or other pollutants? Unfortunately, industrial heritage and its pollution impact on the prevalence of environmental AMR have largely been ignored. Focussing on industrialised estuaries, we demonstrate that anthropogenic pollution inputs in addition to the natural diurnal environmental conditions can sufficiently create stressful conditions to the microbiome and thus promote selective pressures to shift the resistome (i.e., collection of resistance traits in the microbiological community). Unfortunately, the bacteria's survival mechanisms, via co-selective pressures, can affect their susceptibility to antibiotics. This review highlights the complexity of estuarine environments, using two key contaminant groups (metals/toxic elements and polyaromatic hydrocarbons), through which a variety of possible chemical and biological pollutant stressors can promote the emergence and dissemination of antimicrobial resistance. We find compelling divers to call on more focused research on historically disrupted ecosystems, in propagating AMR in the real world.

Keywords Antimicrobial resistance · Metals · Polyaromatic hydrocarbons · Environment · Microbiome · Pollution

Introduction

The development of bacterial antimicrobial resistance (AMR) represents a central contributor to ecosystem-mediate health impacts (Munita and Arias 2016). However, these "superbugs" not only develop from exposure to antibiotics, but also, among other factors, exposure to natural and anthropogenic conditions in their environment. As a survival strategy, some bacteria can acquire genes as an attempt to resist the stressors—e.g., SOS response (Beaber et al. 2004). Any acquired, or developed, resistance traits proven beneficially effective to their survival becomes retained in future generations and increases the prevalence of resistance genes within a single population. However, there are cases where resistance genes can become horizontally transferred on genetic elements to other bacteria; the unfortunate consequence is that recipient bacteria could be pathogenic. This, in summary, highlights the possibility that stressed bacteria could trigger genetic exchanges, which may ultimately lead to increased antibiotic resistance.

Antibiotics are pharmaceutical products used to fight bacterial infections and are considered a type of antimicrobial; sub-inhibitory exposures to antibiotics can result in bacteria developing a resistance as a natural adaptive reaction (European Centre for Disease Prevention and Control 2014; Lemire et al. 2013; Bernier and Surette 2013). Furthermore, this can be applicable to other micro-organisms such as fungi, viruses and some parasites, which collectively would be referred to as resistant organisms (World Health Organization 2018). These are known to be the cause of antimicrobial resistance.

✉ Kiri Rodgers
kiri.rodgers@uws.ac.uk

[1] School of Science and Sport, University of the West of Scotland, Paisley, UK

[2] Centre for Water, Environment, Sustainability & Public Health, Department of Civil and Environmental Engineering, University of Strathclyde, Glasgow, UK

Furthermore, there has been an increase in pharmaceutical products within effluent introduced into water bodies (Larsson 2014); industrial effluent and pollution can be considered a major contributor to ARG presence which is discussed below.

Here, we focus on the conditions within estuaries and how they may stress the bacteria. The determination of AMR development (or retention) in estuarine systems is critical as they often represent highly impacted sensitive ecosystems: (1) they have historically been chosen for industrial and shipping activities; (2) they represent a major receptors and conveyors of pollutants that could, either currently or in future, threaten public or aqua-cultural health; (3) the confluence of marine and fresh waters continuously change in water properties, which can ecologically impact the microbiomes (communities of micro-organisms) with a range of sedimentary and geochemical conditions; and (4) the intertidal zones are globally the most densely populated regions (Martinez 2008).

In many developed nations, contemporary regulations help limit discharges into major estuaries, and many systems have (at least) begun the process towards ecological recovery. However, issues of legacy pollutants, which have been deposited and accumulated from past anthropogenic activities, often remain. People tend to investigate, remediate and minimise the risks associated with their chemical toxicity but often ignored (or not considered) are the biological risks that tend to be associated with past microbial depositions, but also their chronic exposure and adaptations to pollutants. *Should we be concerned with increased bacterial risks due to legacy pollution—in particular, towards the development and dissemination of antimicrobial resistance?*

It is no longer acceptable to state that AMR solely prevails from the selective pressures of antibiotics. Anthropogenic pollution "stress" and geochemical conditions promote genetic dissemination by cross and or co-resistance (Knapp et al. 2017; Ashbolt et al. 2013; Berg et al. 2010; Wright et al. 2006). As such, in this review, we examine the factors that contribute to antimicrobial resistance in environmental bacteria and whether pollution conditions in the estuarine environment could have an impact. We pay particular attention to the possible impact of legacy pollution, which may be: either ignored or unknown; assumed remediated or contained; or remain technologically or economically infeasible to treat.

Industrial pollution in estuaries

Industrial activity, whether contemporary or historical, has often occurred along major watercourses. However, adverse impacts include impaired water quality, habitat loss and diminished resources which results into poor water quality, deleterious changes in ecosystem structure and tropic dynamics, and risks to human and aquaculture health. Examples of investigations of historical environmental pollution events have included: The Clyde (Scotland), Nerbioi-Ibaizabal (Spain), Gironde (France) and Australian estuaries (Hursthouse et al. 1994; Birch et al. 2015; Rodriguez-Iruretagoiena et al. 2016; Larrose et al. 2010; Petit et al. 2015). On the Clyde and its tributaries, subsurface coal and ironstone mining, ship-building, textiles, chemical production and paper and engineering industries have all had a significant environmental impact on sediment quality during the conurbation of Glasgow in the nineteenth and twentieth centuries (Edgar et al. 1999, 2003). Consequently, the river Clyde has received pollution from the onset of the Industrial Revolution (AD 1770) up to the present day (Edgar et al. 2006; Vane et al. 2007, 2011), resulting in elevated PAH (polycyclic aromatic compounds) and PTE (potentially toxic elements, e.g., metal) concentrations.

Sediments are often considered "windows to the past". Deposition layers are created over time with distinct compositional changes and can highlight environmental conditions, e.g., the abundance and composition of siliceous diatom shells in sectioned sediments determine carbon dioxide trends (Friedlingstein et al. 2006). A relevant example is persistent toxic pollutants (e.g., metals) that can be linked to industrialisation as they do not degrade and are not easily mobilised in the sediment layers (Jordi 2016; Farmer 1991; Strzebońska et al. 2017). As such, legacy pollution involves layers of enhanced levels of contaminants from known human activities. They have been investigated to identify responsible parties for past discharges that have become a societal burden and require remediation—for example, Cu (copper), Mn (manganese) and As (arsenic) from abandoned brownfield sites (e.g., Castlebridge-colliery in Alloa, Scotland), and historical industries such as shipyards produce a variety of PTEs, oils, detergents and particulate matter (Papaioannou 2003; Oecd 2010). Additionally, legacy pollutants could include diffuse emissions representing a particular era of human activity, e.g., Pb (lead) from aerially deposited, widely dispersed combustion processes or mishandling of tetraethyl lead-amended petrol.

The existence of pollutants within wider environmental systems, in addition to increasing levels of discharge, is considered important contributing factors influencing antimicrobial resistance (Singer 2017). Their fate and bioavailability to the micro-organisms depend on environmental conditions, the chemical nature of the compound (e.g., sorption constant K_d), affinities to minerals (e.g., Fe–Mn oxides and/or organic matter; (Peng et al. 2009; Konhausera et al. 2002; Akcil et al. 2015; Zaaboub et al. 2015), sediment properties (e.g., grain size, surface area to volume ratio, fine-grained sediments accumulate higher concentrations due to their greater surface area; (Eggleton and Thomas 2004), and additionally

the composition and nature of the bacterial populations, and their innate abilities to resist and/or adapt to pollutant exposure.

Dynamic nature of environmental conditions

Potentially toxic elements (PTEs)

A number of PTEs [e.g., arsenic (As), cadmium (Cd), chromium (Cr), copper (Cu), mercury (Hg), iron (Fe), nickel (Ni), lead (Pb) and zinc (Zn)] (Besta et al. 2013) are included within the Water Framework Directive (2000/60/EC), and are classified as "priority substances" or "priority hazardous substances" in Annex II of Environmental Quality Standards Directive (2008/105/EC) (as amended by 2013/39/EU), and appear on the "key pollutant" list of the European Pollutant Release and Transfer Register (Cuculić et al. 2009; Khan et al. 2017; Larrose et al. 2010). Inputs of PTEs to an estuary depend on the (1) catchment area, (2) geological and soil erosion, (3) precipitation reactions, e.g., Fe/Mn oxides with organic matter, and (4) industry (Table 1). Although these elements are associated with anthropogenic stress on environmental systems, it has been reported that the major PTEs that affect estuarine health are Pb, Cu and Zn (Birch et al. 2015); these have previously been found to be the triad of PTEs associated with anthropogenic influence in other ecosystems (Mclellan et al. 2013).

Using a "metal enrichment index" to determine the magnitude of anthropogenic induced change, Birch et al. (2015) found that human influence on estuarine health is more greatly impacted by high population density than high population; however, this is not always the case as industrial areas (i.e., intense, localised activity with low population density) will exhibit greater anthropogenic influence. Alongside the industrial emissions, infrastructure development affects the hydrodynamic and sedimentation patterns and conditions, therefore, will affect the sediment sorption and pollutant dispersal (Legorburu et al. 2013).

The highest concentrations of PTEs in sediments are found within the "convergence zone" between fresh water and marine water (i.e., within an estuary) due to the high turbidity (PTE sorption to suspended particulate matter) and pH, which affects solubility, sorption and precipitation reactions (Caccia et al. 2003; Berner and Berner 2012; Petit et al. 2015). The association with the solid phase determines bioavailability and re-dissolution to the water column with mobility and bioavailability in the order of Mn > Cu > Zn > Fe (Palleiro et al. 2016; Rodriguez-Iruretagoiena et al. 2016) suggesting that, based on natural versus human PTEs, anthropogenic inputs create greater environmental stress on sediment biota.

Determining the PTE source in estuarine sediments can be difficult due to (1) different sources for the same PTE, (2) bio-turbation between aerobic and anaerobic horizons, (3) continual mixing of top most sediment layer, (4) changing sediment inputs during seasonal changes and (5) dredging and bank restoration disrupting systems and bringing buried contamination to the surface and interfering with legacy tracking (Legorburu et al. 2013; Uncles et al. 2014). Often, multivariate approaches such as principal component analysis (PCA) are used, which allows us to correlate data according to cluster analysis, to elucidate inputs on a site-specific basis.

Polycyclic aromatic hydrocarbons (PAHs)

PAHs are recalcitrant organic compounds that consist of conjoined aromatic rings; they are ubiquitous in the environment (Bosch et al. 2015; Choi et al. 2013) and have pyrogenic, petrogenic and biological sources. Pyrogenic PAHs are formed in high temperature (> 350 °C), low oxygen conditions; biological PAHs are formed during degradation of vegetation material. Petrogenic PAHs are associated with oil maturation process, and major sources in the environment are from oil spills and releases of petroleum, oil and other transportation materials (Abdel-Shafy and Mansour 2016). There are hundreds of PAHs, although the "US EPA 16" is the most commonly studied in environmental systems: naphthalene, acenaphthylene, fluorine, phenanthrene, anthracene, fluoranthene, pyrene, benz[a]anthracene, chrysene, benzo[b]fluoranthene, benzo[k]fluoranthene, benzo[a]pyrene, benzo[g,h,i]perylene, dibenz[a,h]anthracene and indeno[1,2,3-c,d]pyrene; a number of these are listed as "priority hazardous substance" list (2008/105/EC as amended), including anthracene, benzo[a]pyrene, benzo[b]

Table 1 Sources of PTEs within sediments

PTE	Source	Citation
Cr, Cu, Mn, Ni, Pb, Zn	Agriculture: fertiliser application	Caccia et al. (2003)
Cd, Co, Cr, Cu, Sn, Zn	Boat traffic	Caccia et al. (2003)
Mn	Wastewater treatment works	Rodriguez-Iruretagoiena et al. (2016)
Al, Co, Fe, Mg, Mn, Ni	Geology	Birch et al. (2015)
Pb	Leaded petrol	Lenart-Boroń and Boroń (2014)

flouranthene, benzo[g,h,i]perylene, benzo[k]flouranthene, indeno[1,2,3-c,d]pyrene and naphthalene.

The number of rings reflects the origin from which they were derived; i.e., lower molecular weight compounds are typically natural in origin, whilst higher weights tend to be anthropogenic (Yan et al. 2009). Studies have shown that "total PAH" concentrations (i.e., summation of US EPA 16) often increase with sediment depth (Curtosi et al. 2007; Ke et al. 2005) and that up to 89% of these PAHs consisted of four–six rings at all depths (Li et al. 2009)—i.e., anthropogenic sources. Furthermore, PAHs have been proven to increase in industrial areas (Huston et al. 2009). "Total PAH" abundances have been quoted to vary greatly across the world with Scottish sediment studies ranging 150–> 750 μg kg^{-1} (Webster et al. 2001), estuary sediments in Mexico 27–418 μg kg^{-1} (Jaward et al. 2012) and dry sediments in Japan 21–1447 μg kg^{-1} (Onozato et al. 2016).

PAHs have a high tendency to bio-accumulate and cause eco-toxicological concerns (Schwarzenbach et al. 2003; Sawulski et al. 2014; Atsdr, 2005). As a consequence, they have been extensively studied to better understand their environmental fate, distribution and effects (Haftka 2009; Pavlova and Ivanova 2003). The environmental origin of PAHs in sediments typically comes from atmospheric mixtures (and particulate matter–soot), consisting of four rings or more that readily adsorb onto particulate matter and subsequently become deposited into sediment due to weak water solubility (Skupinska et al. 2004).

As a consequence of their non-polar structures, they are unlikely to dissolve in waters. Hydrophobicity increases with the number of aromatic rings, and larger PAHs which have a potential anthropogenic source are less environmentally mobile and bio-available or subject to microbial degradation (Sawulski et al. 2014). Further, in estuarine (and other) systems, the dissolved organic matter (DOM) is the driving force for the absorption of hydrophobic pollutants, and changes in salinity affect the movement of DOM. Increasing salinity causes DOM to partition from water to sediments, and vice versa (Kafilzadeh 2015; Li et al. 2009; Chapman and Wang 2001).

Conversely, smaller PAHs are more soluble and will be bio-available to biota through presence in pore water (Abdel-Shafy and Mansour 2016). PAH degradation into smaller ringed structures allows them to become either bio-available or become part of the pore water matrix and becoming adsorbed onto colloidal organic matter and accumulate in sediment concentrations (Abdel-Shafy and Mansour 2016; Jelena and Maja 2017). Furthermore, their bioavailability can also be dictated according to source and PAH species, e.g., PAHs from oil spills are more available in comparison with those from coal (Wang et al. 2014).

Their environmental behaviour and toxic effects have made them priority substances according to the water framework directive (WFD) (Nikolaou et al. 2009), but effects are PAH specific. For example, benzo[a]pyrene, originally isolated from coal tar in the 1930s, has been linked with carcinogenic properties and been linked to lung cancer (Kasala et al. 2015). Research also shows that certain PAH metabolites can interact with DNA and are genotoxic causing negative and heritable genetic damage (Agency for Toxic Substances and Disease Registry 2012). Some have also been highlighted with potentially carcinogenic properties, e.g., benzo[a]anthracene, chrysene, benzo[b]fluoranthene, benzo[a]pyrene and benzo[g,h,i]perylene.

The source identification of PAHs in sedimentary environments has proven difficult to determine, as the individual compounds cannot easily be distinguished from natural or anthropogenic sources. Typically PAH markers (Stogiannidis and Laane 2015), PAH-ratio methods (Yan et al. 2009), multivariate analysis (Jang et al. 2013) or isotope ratio mass spectrometry (Philp 2007) have been used with the potential to relate to historical industrial pollution (Ma et al. 2016).

Sediment microbiome

The co-discipline of sediment microbiology is concerned with microscopic and macroscopic organisms, including bacteria, protozoa, fungus, algae and soil-dwelling invertebrates (mesofauna) (Paul and Clark 1989) dwelling in sediments down to 2 m (Table 2). Microbial communities are found in habitats as diverse as environmental systems (the microbiome) in the human body, and often with similar interspecies interaction relationships (Drissi et al. 1995). This causes increased concerns that this can become linked to the increased spread and evolution of AMR in the microbiome.

Bacteria form the majority of sediment biomass and are well suited to a sedimentary environment as their size, metabolic versatility, and their collectively diverse nutrient and redox capabilities allow them to flourish in equally

Table 2 Variation of microorganism biomass with sediment depths and percentage decrease from surface adapted from (Bhattarai et al. 2015; Fierer et al. 2003)

Depth (cm)	Microorganism biomass (g/m^2)	% decrease
0–5	9.8 (1.6)	
5–15	4.0 (0.16)	59.18
15–25	2.0 (0.12)	79.59
50	0.63 (0.044)	93.57
100	0.18 (0.030)	98.16
200	0.081 (0.0053)	99.17

Stratified layers of sediments accumulated over a reasonably long period of time, which can be cut in a series of successively receding flat surfaces (Velde and Barre 2010)

diverse environments (Nealson 1997). Numerous conditions affect the presence and quantity of microbial communities (including those species with antimicrobial resistant genes (ARGs) present), and the knowledge of expected key community characteristics can be linked to their responses to physicochemical properties (e.g., conductivity (EC), pH and redox), nutritional quality (e.g., total nitrogen, phosphorus, carbon and minerals), source of carbon—including organic matter (Wang et al. 2016)—and pollutant conditions (including PTE and PAH content) of sediments (Fig. 1). This can create extreme spatial differences of species composition and community structures (Abd-El-Aziz et al. 2017). Fortunately, the advent of community DNA extractions and high-throughput sequencing has provided wealth of information related to this through metagenomics, whether targeted (e.g., via small sub-unit rRNA or specific genes) or "shot gun" (i.e., random).

The communities (and their potential to "share" or horizontally transfer genetic traits—discussed later) are shaped biologically by their ecological interactions. However, the make-up of the microbiome and its functional complexity can be likely influenced by legacy exposures. Like chemical conditions, they too can be archived in the sediment layers. What we will demonstrate is that past stress events, in turn, can have a major impact on the microbiome, but also the resistome—the collection of genes/traits related to resistance, whether latent or active.

Development of antimicrobial resistance

Evolutionary processes have recently been linked with the accumulation of antimicrobial resistance, which include the accumulation and selection of genetic mutations

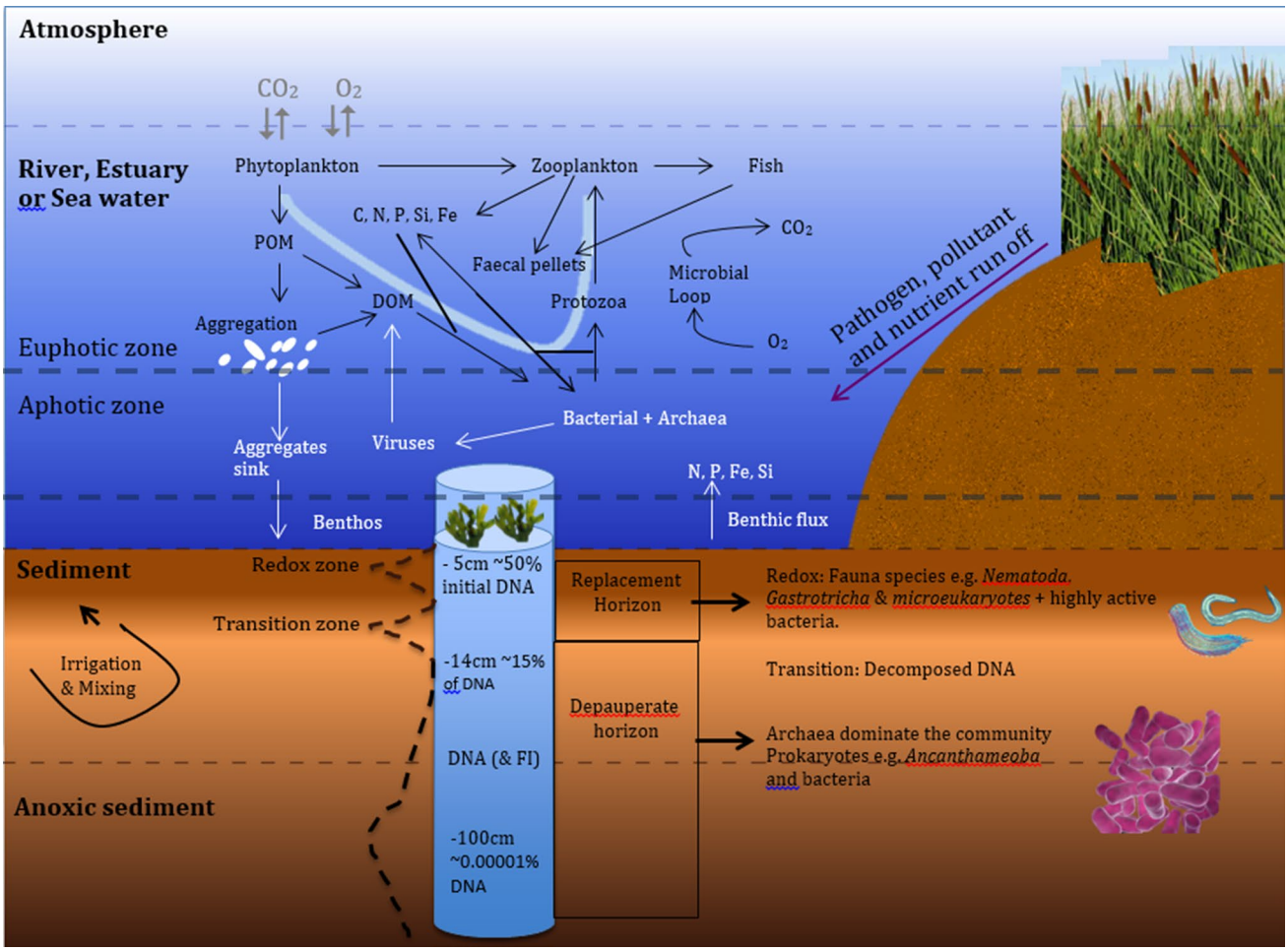

Fig. 1 Microbial structuring of an estuary sediment. Dissolved organic matter is almost exclusively taken up by bacteria and respired as CO_2 or re-introduced into the classical food chain (phytoplankton, zooplankton and fish). This, in turn, alters the carbon cycle that influences the microbiome as well as sediment horizons. The *redox-stratified zone* (0–5 cm) includes a thin layer of oxygen where a few fauna species exist and microeukaryotes in addition to large numbers of highly active bacteria. Below 5 cm is the transition zone; here 50% of the DNA has already decomposed and is found below the sulphate–methane transition

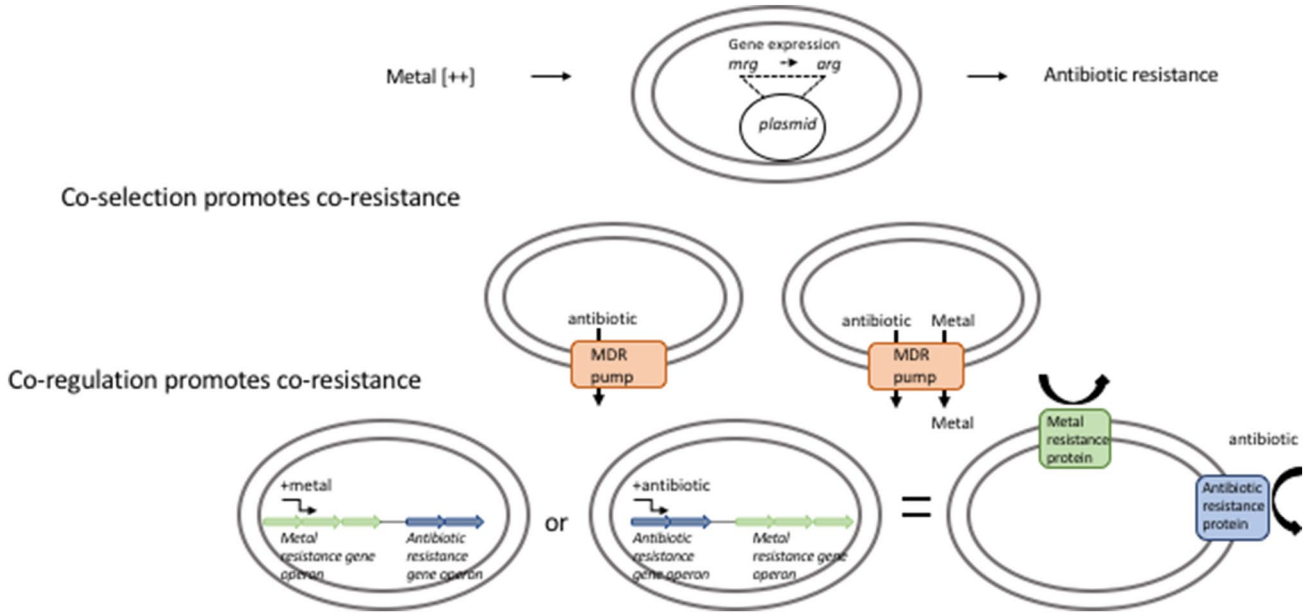

Fig. 2 Hypothesised molecular mechanisms that can result in AMR when antibiotics and metals are introduced into a biochemical system: "Co-selection". Mechanisms such as cross-resistance, co-resistance or co-regulatory resistance can result in AMRs prevalence (adapted from Baker-Austin et al. 2006; Mata et al. 2000)

(Woodford and Ellington 2007) and development and spread of accessory plasmids. Due to difficulties in cultivating sediment micro-organisms (Great Plate Anomaly), it is currently unknown how many types of ARGs exist. However, the development of sequencing-based descriptive metagenomic approaches has provided the means to analyse the occurrence and abundance of previously unrecognised ARGs with examples of successful applications (Li et al. 2015a; Monier et al. 2011; Chen et al. 2017). The extent that environmental conditions impact antimicrobial resistance is becoming increasingly known.

Resistance traits propagate in the presence of a stress factor, which ultimately selects bacterial populations with enhanced survivability. Once a resistance trait is selected, host bacteria can transfer genes between individuals creating an enhanced resistome—collection of latent and active resistance traits in a community. Thus, resistance can spread among micro-organisms once a gene enters a system, either vertically or horizontally.

Vertical transfer involves the increase in resistance trait via inheritable traits and selective pressures. Basically, populations with enhanced genetic traits that confer selective advantage will likely replicate and outcompete other strains; the genes are passed on to "daughter" cells during replication. In this manner, the resistance traits develop greater representation in the microbiome through improved survivability and replication of specific populations.

However, in many microbial communities (e.g., biofilms) the close proximity of bacteria to each other, genetic material can also become horizontally exchanged among different population by various mechanisms (Fig. 2):

- Transformation—the assimilation of free DNA, released from lysed bacteria.
- Transduction—i.e., bacterial phages (viruses) acquire pieces of host DNA and transfer it to the next infected bacterial cell.
- Conjugation—the direct exchange of plasmid DNA.

The increase in ARGs occurs as a consequence of its ability to spread, via transformation or conjugation, between bacteria under antimicrobial stresses (Cottell et al. 2014; Turner et al. 2014); this a nature of many bacteria as part of their SOS response to stress (Beaber et al. 2004). Furthermore the "mobile resistome/mobilome", i.e., the ability for resistant genes to associate and transfer between distantly related bacteria (Wellington et al. 2013) exacerbates ARG presence in environmental matrices and has become a greater focus among current environmental-AMR research, as a potential target for the transfer of resistance traits could be a pathogen.

The determination of antibiotic resistance through identification of antibiotic resistance genes (ARGs) has provided evidence that ARGs have been increasing in environmental systems experiencing anthropogenic stress, e.g., soils, water and sediments in particular since the beginning of the

antibiotic era in 1940s (Chen et al. 2013; Knapp et al. 2010; Graham et al. 2016). The most common entry routes for ARGs in the environment are from sewage outfall (Daughton and Ternes 1999), agricultural fertilisers (Kinney et al. 2006) and veterinary pressures (Blackwell et al. 2007; Topp et al. 2008). The increasing prevalence of AMR/ARG in the "real world" suggests an emerging global human health concern; it is reported that by 2050 global annual mortality is projected to be 10 million if action is not immediately taken to combat antimicrobial resistance (Shallcross et al. 2015).

Role of pollution on resistant genes/AMR

The environmental contribution to the spread of AMR is becoming more commonly recognised, and regulators are beginning to monitor pathways and controlling the release of resistant-driving chemicals, e.g., antimicrobials, metals and biocides (Singer et al. 2016). A common type of resistance that has become a contemporary concern is resistance to antibiotics, but it has recently been observed is that other substances can also select for antibiotic resistance. For example, metal pollution and some persistent organic compounds co-select for antibiotic resistance genes. This co-selection of metal (or other) resistance and antibiotic resistance can occur by one of two processes: co-resistance or cross-resistance. Co-resistance occurs when selection of one phenotype simultaneously selects for genes on the same genetic element. On the other hand, cross-resistance occurs when, for example, the antibiotic and metal have similar paths into the cell, therefore when a resistance response is triggered, cell defence is effective against both metal and antibiotic toxicants. Since metals, e.g., are also widespread in the environment (and probably in elevated concentration in zones of industrial activity) and do not degrade, these toxicants can potentially provide a long-term selection pressure.

Like soils, sediments are considered a reservoir of antibiotic resistance bacteria (Azarbad et al.) and ARGs, with a large variety of novel ARGs and RGs being frequently discovered—representing different types of resistance mechanisms (Nesme and Simonet, 2015), and there are anthropogenic pressures that can exacerbate this. Sources of ARB (and ARG) include the discharge of improperly treated municipal wastewater treatment effluents, agricultural runoff, and wildlife. The bacteria entering the waterways could become bound, and eventually entombed, in the sediments and contributing to the resistome "potential".

However, estuarine systems offer additional complications. Due to the continual changes in salinity, estuarine biota are subject to naturally stressful conditions and become more susceptible to stress from anthropogenic pollution. With the sediments acting as both a sink and source of pollutants, also switching between absorption and desorption reactions due to alternating salinity changes (Chapman and Wang 2001), indigenous bacteria repeatedly become exposed to contaminants. Consequently, they develop survival strategies for stress, including the enhanced transfer of mobile genetic elements. The unfortunate result is these genetic exchanges could include antimicrobial resistance (AMR).

Elevated antibiotic resistance (AR) is evident in environments with high levels of anthropogenic stress (Chen et al. 2013; Knapp et al. 2010) which challenges the common perception that AMR solely occurs as a consequence of antibiotics. A study along the Almendares River/estuary, Cuba demonstrated a high level of resistant genes present despite minimal use of antibiotics, both agriculturally and medically in the country; there were, however, high levels of pollution including metals and other contaminants (Graham et al. 2011; Reid-Henry 2008). Unfortunately, efforts to reduce and control antibiotic use may have limited impact on AR if antibiotics are not the sole cause of AMR in environments.

PTEs and AMR

PTEs within environmental matrices impact microbial communities and represent important vector in the maintenance and proliferation of AMR (Summers 2002; Alonso et al. 2001; Eldon and Smith 2006). The synergistic effects of PTEs and antibiotics have also been shown to influence the development of AMR (Chen et al. 2015; Baker-Austin et al. 2006). For example, the co-exposure to Zn and oxytetracycline increases the microbial community's resistance towards antibiotics (Peltier et al. 2010; Besta et al. 2013). Further the presence of Cu caused microbial resilience, as well as a co-resistance, to ampicillin, chloramphenicol and tetracycline (Berg et al. 2005; Mccluskey and Knapp 2017). Additionally, Ni and Cd have increased the frequency of bacterial resistance in microcosms to chemically unrelated antibiotics including ampicillin and chloramphenicol (Stepanauskas et al. 2006). This suggests that (1) the proliferation of antibiotic resistance can be caused by the presence of PTEs enhancing the enrichment of ARG in indigenous bacterial growth in the microbial communities where ARGs are already present (Chen et al. 2015) or (2) that resistance occurs only in bacteria sensitive to antibiotics which in turn could be induced by synergistic effects of the co-existence of PTEs (Zhu et al. 2013).

PTEs such as Zn, Cu, Mn, Ni, Cr and Fe are essential nutrients for micro-organisms (Lima De Silva et al. 2012) and provide vital co-factors for metallo-proteins and enzymes; however, once concentrations exceed "ideal" levels, PTEs inhibit bacteria by blocking the essential functional sites (Koena Sinah 2005)—whereby metal ions become displaced from their "native" binding site, causing conformation modifications of the molecules (Olaniran et al. 2013). Besides diminished enzyme function, some

could damage DNA. PTEs with no biological role, e.g., Pb and Cd, can cause oxidative stress, lipid peroxidation and mutagenesis (Oyetibo et al. 2010). Further, Cu and Zn are also commonly used antimicrobials (Poole 2017).

Hypothesised mechanisms for metal resistance include PTE accumulation in the form of protein-metal associations, blockages at the level of the cell walls, and enhanced membrane transportation (Hassen et al. 1998), sorption of metals (Chang et al. 1993; Kinkle et al. 1987), and release of organic chelators (Abd-El-Aziz et al. 2017; Lemire et al. 2013). The processes are complex, which are in-turn controlled by a vast variety of variables including, but not limited to PTE presence, nature of environmental medium and/or the microbial species. A number of potential mechanisms causing the increase in ARGs in the presence of PTEs have been evidenced, including in areas resulting from intense industrial activity (Abella et al. 2015; Graham et al. 2011; Hu et al. 2016; Knapp et al. 2012; Stepanauskas et al. 2005; Wright et al. 2006), wastewater treatment outflows (Knapp et al. 2012; Graham et al. 2011; Su et al. 2015), run-off of agricultural wastes (Ji et al. 2012; Li et al. 2015b; Zhu et al. 2013) and direct experiments (Berg et al. 2005, 2010; Knapp et al. 2011; Stepanauskas et al. 2006).

While most evidence is found in areas of elevated human impact, correlations have been found in more "pristine", or baseline environmental levels, as well (Knapp et al. 2011, 2017). The driving force (as mentioned previously) is believed to result from co- and cross-selection processes (Ashbolt et al. 2013; Baker-Austin et al. 2006; Berg et al. 2010; Perry and Wright 2013). Many resistance elements may co-exist on a single genetic element, or bacteria will seek improved resistance traits via lateral gene transfer mechanisms and receive the additional traits. Given that metals do not degrade; selective pressures are likely to persist longer than pharmaceutical compounds which could breakdown in the environment.

PAHs and AMR

Microbial degradation has an important role in the natural attenuation of PAHs in contaminated matrices (Van Dillewijn et al. 2009); however, the presence of PAHs changes the community structure of indigenous bacteria with the number of hydrocarbon-degrading bacteria increases with increasing available hydrocarbons (De Menezes et al. 2012; Zhang et al. 2010; Maila et al. 2005); it is difficult to understand which communities are present in historically contaminated sediments (Azarbad et al. 2016; Singleton et al. 2013). However, many PAH-tolerant bacterial isolates often exhibit strong resistance to metals and antibiotics (Ben Said et al. 2008; Máthé et al. 2012), and ARGs have been found in PAH-contaminated matrices (Chen et al. 2017; Kang et al. 2015).

PAHs have mutagenic properties (Liu et al. 2017; Sun et al. 2015), which could contribute towards AMR—either by directly changing DNA composition, or triggering stress/repair systems. There is little knowledge of specific mechanisms, but metagenomic profiling has demonstrated that PAH-contaminated soils with ARGs is in abundance approximately 15 times more than those less contaminated (Chen et al. 2017).

In comparison with the number of investigations conducted examining other drivers of antimicrobial resistance (e.g., pharmaceutic compounds and PTEs), there have been relatively minimal studies on the effects of PAH contamination to AMR, and few prediction models exist. However, research has demonstrated that naphthalene and phenanthrene exposure were primarily linked to conjugative transfer of genes mediated by class I integrons (Wang et al. 2017); these genetic mechanisms allow bacteria to adapt and evolve rapidly through the acquisition, stockpiling and differential expression of new genes and have been previously correlated with clinical antibiotic resistance (Gillings et al. 2008; Deng et al. 2015; Loot et al. 2017). Genes for PTEs and ARGs have been found in bacterial plasmids and could facilitate the dissemination of these genes under elevated stresses (Li et al. 2015a; Zhai et al. 2016). The effect of the co-exposure is complicated; however, (Lu et al. 2014) found that a moderate dosage of pyrene promotes the microbial prosperity in soils and alleviating metal stress. Previous studies have investigated and shown a co-exposure effect with PAHs and metals which is a consequence of increased anthropogenic activities and contamination; this includes the research of (Gauthier et al. 2014) who summarised that the more-than-additive deleterious effects of PAHs-metal mixtures to microbes.

Conclusion

The genetically diverse array of micro-organisms with their respective metabolisms, as well as the complex array of environmental pollutants, i.e., PTEs, PAHs and their derivatives, makes understanding their combined roles in induced antimicrobial resistance a complicated task. This review highlights that PTEs and PAHs create stressful conditions to exacerbate AMR in the environment and can be used as model pollutants for further public-health risks related to these genetic pollutants. The effects are not just related to current pollution scenarios; rather, legacy industrial effects could be lingering drivers for resistance. The combined effect of various single and multiple mechanisms can be hypothesised to explain the genetic mutation and development of AMR; however, further exploration is required to

elucidate a more causal explanation. No antimicrobial agent will be efficacious forever; however, by establishing a better understanding of the environmental impact and its role in AMR's prevalence may aid in its control. This is critical to combat AMR growth and prevalence across the world, with a target on the prospects for prevention, treatment or remediation.

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