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Abstract

Aquatic ecosystems subjected to anthropogenic pressures are places of rapid evolution of microbial communities and likely hotspots for selection and emergence of antibiotic resistant bacteria. In urban settings, water quality and the risk of infection are generally assessed in sewers and in effluents of wastewater treatment plants. Physical and chemical parameters as well as the presence of antibiotics, antibiotic-resistant bacteria and genes of resistance are driven by urban activities, with adverse effects on aquatic ecosystems.

In this paper we review the environmental pressures exerted on bacterial communities in urban runoff waters and discuss the impact of these settings on antibiotic resistance. Considering the worrisome epidemiology of infectious diseases and estimated mortality due to antimicrobial resistance in the coming decades, there is an urgent need to identify all environmental reservoirs of resistant bacteria and resistance genes to complete our knowledge of the epidemiological cycle and of the dynamics of urban antibiotic resistance.

Keywords

Urban runoff, anthropic pressures, antibiotic resistance, resistome

1. The global threat of environmental antibiotic resistance

After decades of excessive use of antibiotics (ABs) in human and animal medicine, as well as in animal husbandry and agriculture, the global spread of antibiotic resistance has become a major threat to public health because it compromises our ability to treat infectious diseases. The overuse of antibiotics has led not only to their accumulation in the environment but to even more significant, to the selection of antibiotic resistant bacteria (ARB) and their antibiotic resistance genes (ARGs) (Hughes, 2014).

Studies on ARB and their ARGs first focused on epidemiological and clinical contexts while the environment gradually attracted attention as a potential actor in antimicrobial resistance (AMR). It is now accepted that the emergence of AMR should not be underrated (Wellington et al., 2013) in order to evaluate and then mitigate the risk of exposure to environmental resistance (Pruden et al., 2013). Consequently, diverse environments are currently being investigated as reservoirs and/or as hubs for the spread of ARB and ARGs. In particular, aquatic environments are inhabited by highly diverse autochthonous bacteria that represent a vast reservoir of ARGs and by allochtonous bacteria originating from different sources, including potential pathogens that are already resistant to antibiotics. This makes aquatic environments places where the transfer of ARGs among autochthonous and allochtonous bacteria occurs with the subsequent emergence of ARB (Shao et al., 2018).

Among aquatic environments, wastewater effluents from humans and livestock together with the rivers that receive these effluents have been widely investigated for the presence of antibiotic compounds, ARB and ARGs. Wastewaters and related hydrosystems act as mixing places for different chemical compounds that impose selection pressure on ecosystems (Välitalo et al., 2017). In addition, they act as meeting and exchange places for human and environmental bacteria, either pathogenic or non-pathogenic. All these elements are known to favor the emergence and dissemination of antibiotic resistance (Amos et al., 2018; Hocquet et al., 2016).

Beside wastewaters, urban runoff waters are also partially generated by human activities. Urban runoff is defined here as surface runoff of rainwater and water used for human activities that is subject to the laws of gravity. Runoff waters vehicle sediments, nutrients, bacteria (from human waste) and chemical pollutants (pesticides, drug molecules, petroleum by-products, etc.), most of which come from a wide range of human sources. So, along with wastewater, urban runoff is likely to create conditions able to promote the emergence and dissemination of ARB and ARGs but, surprisingly, investigations of urban runoff waters are rare. This review provides an overview of the major features that demonstrate or suggest that urban runoff plays a role in the spread of environmental AMR. The main objective of our review is to provide strong arguments that urban runoff merits further research in the context of the global spread and threat of antibiotic resistance.

2. Miscellany of microbiological facts to help understand antibiotic resistance in the environment

2.1. Selective pressure and dose-effect of antibiotics in the environment

Bacteria have their own resistance determinants that are intrinsically inherited or acquired by mutation or horizontal gene transfer (HGT) under selective pressure. It is believed that a resistant bacterium is selected by ABs at concentrations lower than minimum inhibitory concentration (MIC) of the bacterium, while all the susceptible bacteria displaying lower MICs are killed. According to this classical theory, the very low concentrations of ABs assumed to be found in surface water and in the environment were supposed to be insufficient to select bacteria resistant to therapeutic doses. However, it is now generally accepted that concentrations of AB below the MIC cause a cellular response with an increased rate of mutation in naturally occurring hypermutator bacteria and with enhanced HGT (Bernier and Surette, 2013; Sandegren, 2014; Scornec et al., 2017). At even lower concentrations, modified gene expression leads to induction of resistance genes and tolerance to ABs (Bernier and Surette, 2013). In addition, very low concentrations may cause minute reduction in growth of the susceptible bacterial community resulting in a disequilibrium in the microbial ecosystem (Almakki et al., 2017a; Gullberg et al., 2011). It is important to note that the very low amounts of ABs measured in water and soil environments may be in the same order of magnitude as the minimum selective concentration (MSC), which is the lowest antibiotic concentration that allows the selection of resistant mutants (Gullberg et al., 2011; Kümmerer, 2009a). MSCs may be up to 140-fold below the MIC of the susceptible bacteria. This finding suggests that very low concentrations of ABs can select resistance (Gullberg et al., 2014) and it is generally accepted that exposure to low concentrations of antibiotics over long periods is an optimal way to enrich communities of resistant members (Gullberg et al., 2011). Moreover, it appears that resistant mutants selected at sub-MICs are generally fitter than those selected at high concentrations suggesting that, in the absence of antibiotic pressure, these mutants will be more persistent in bacterial populations than those selected by high antibiotic concentration, which have a higher fitness cost (Sandegren, 2014). Finally, the impact of antibiotic contamination deserves to be taken into account whatever their concentrations in waters because ABs are not only Darwinian selectors for ARB but also resistance promoters via various mechanisms (Andersson and Hughes, 2017; Blázquez et al., 2002). Moreover, in addition to antibiotics, a wide range of pollutants generated by human activities, like heavy metals or disinfectants, exert selective pressure on bacteria, leading to selection of ARB and thus playing an important role in antibiotic resistance (Baker-Austin et al., 2006).

2.2. Exaptation

Several studies suggest that the determinants of AB resistance in environmental bacteria have primary functions other than deactivating man-made antibiotics. This biological phenomenon consisting in a shift in the function of a trait during evolution is named exaptation. For instance, the β-lactamases that hydrolyze natural and man-made antibiotics of the β-lactam family and the enzymes for cell wall biosynthesis evolved from the same ancestor (Meroueh et al., 2003).

In addition, bacteria that produce natural ABs carry ARGs involved in self-protection mechanisms. Antibiotic producers naturally resist their own antibiotics, for instance, by producing AB-inhibiting enzymes (Kümmerer, 2009a). Consequently, ARGs that largely contribute to clinical resistance to ABs such as aminoglycoside-modifying enzymes and extended spectrum β-lactamases were present in soil resistome before the first therapeutic use of their target ABs (D'Costa et al., 2011; Song et al., 2005).

Efflux pumps are probably the most emblematic examples of exaptation in the domain of AMR. Efflux pumps are complex machines that eject molecules from cytoplasm through membrane(s) and cell wall. This non-specific mechanism expels the different products of bacterial metabolism, but pump mutations or overexpression can expand the repertory of molecules extruded by the efflux system leading to resistance to many xenobiotic compounds including heavy metals, pesticides, ABs and biocides (Alonso et al., 1999; Baker-Austin et al., 2006; Buffet-Bataillon et al., 2016). Therefore, co-resistance to ABs and heavy metals or other co-pollutants is frequently observed (Piddock, 2006) in bacteria in unpolluted and polluted soils.

2.3. Dissemination of resistance via mobile genetic elements and integrons, concepts of resistome and mobilome

The dissemination of various antibiotic resistance mechanisms may be linked to mobile genetic elements (MGE). For instance, large conjugative plasmids are MGE that frequently carry multiple ARGs, as well as genes that confer resistance to biocides and heavy metals. It has recently been shown that a single AB or heavy metal at concentrations well below the MIC (as measured in the external environment) can select large conjugative plasmids carrying multiple ARGs (Gullberg et al., 2014). These low concentrations correspond to the MSC described above and the MSC can be further reduced by the combined effect of several xenobiotics. Multipartite MGE and MSC of a single or a mix of xenobiotics in the external environment thus contribute to the emergence, maintenance and transmission of multiple ARGs on MGE (Gullberg et al., 2014).

Alongside conjugative plasmids, integrons are other multipartite genetic elements formed by several gene cassettes and known for their role in the capture and spread of ARGs, mainly among Gram-negative bacilli and particularly among pathogens (Escudero et al., 2015; Partridge et al., 2018). The integrons themselves are not mobile but they are often carried by MGE. More than 130 cassettes conferring resistance not only to AB families but also to antiseptics and biocides have been described (see Stalder et al., 2012, for a very comprehensive review on the involvement of integrons in the environmental spread of antibiotic resistance). Integrons are found in a wide range of ecosystems. A link between the prevalence of integrons in bacterial communities and AB pressure has been proposed in numerous studies as well as by their higher prevalence in *Escherichia coli* populations near areas of human activities (Stalder et al., 2012). For instance, *Enterobacteriaceae* isolated from urban wastewater treatment plants (WWTPs) and high prevalence of class 1 integrons has been observed in hospital effluents (Ferreira da Silva et al., 2007; Guo et al., 2011). In addition, the prevalence of integron-containing strains is higher in polluted than in pristine waters (Stalder et al., 2014). The link between the prevalence of integrons and ABs in environment has been demonstrated in effluents from both antibiotic-producing factories and WWTPs but their prevalence is also higher in anthropized environments where AB inputs are detected. Again, heavy metals have been shown to play a major role. For instance, (i) adding cadmium to water in microcosm led to a 100-fold increase in integron abundance (Wright et al., 2008); (ii) a class 1 integron carried by Tn*21* transposon contains a mercury resistance operon (Stalder et al., 2014). Quaternary ammonium compounds also contribute to the selection of strains carrying class 1 integrons with quaternary ammonium resistance genes (*qac*) (Stokes and Gillings, 2011). Finally, like conjugative plasmids, class 1 integrons are linked with chemical determinants such as metal contamination and thus may support ARG maintenance via trace element stress (Rosewarne et al., 2010). The correlation between integrons and AMR has been widely studied in clinically-relevant *Enterobacteriaceae* but is still controversial in other bacteria, the quantification of the integrase gene of class 1 integrons is currently proposed as an indicator of bacterial resistance in the environment (Gillings et al., 2015; Ma et al., 2017).

MGEs that contribute directly to HGTs and HGTs are also influenced by bacterial lifestyle and environmental stresses. Bacteria in aquatic systems live in attached biofilms as well as in flocs, i.e.

biofilm-forming bacteria in aggregates. Biofilm-forming bacteria are frequently resistant after prolonged exposure to low concentrations of ABs due to weak diffusion of ABs within the structure of the biofilm (Qi et al., 2016). Thus, biofilms and flocs are considered as reservoirs for ARGs and MGEs, such as class 1 integrons (Drudge et al., 2012), in which the rate of transfer of MGEs carrying resistance determinants, such as resistance to quaternary ammonium biocides and fluoroquinolones is increased due to the proximity of bacterial cells (Buffet-Bataillon et al., 2016). Altogether, biofilm is an ideal environment for the acquisition and spread of resistance genes (Fux et al., 2005).

Considering the influence of external conditions on HGT and the development of resistance, anthropogenic stresses are likely to facilitate transfer of chromosomal resistance genes to the MGE pool and hence to accelerate the evolution and spread of resistant strains (Cattoir et al., 2008). In this context, environmental pollutants such as metals, detergents, and nanomaterials can facilitate the transmission of ARGs by HGT, possibly by increasing cell membrane barrier permeability (Wang et al., 2015). In addition, integrons are involved in the SOS bacterial response. Under stress conditions, integrase expression and the rearrangement and capture of new resistance gene cassettes has been shown to be enhanced (Guerin et al., 2009).

The resistome is defined as the whole pool of genes involved in AMR in a given ecosystem. As ABs, ARGs are considered as emerging contaminants because of their potential adverse effect on ecosystems and human health (Hoa et al., 2011; Ng et al., 2017). They are currently being found at increased levels in sediments and other aquatic compartments, mainly in urban, agricultural and industrial areas. Generally, ARGs are carried by living bacteria but ARGs and fragments of ARGs can also persist freely in environment after bacterial death (Mao et al., 2014) as well as in phages that constitute potential reservoirs and efficient vehicles for these ARGs (Brown-Jaque et al., 2018; Marti et al., 2014). Within the resistome, the total volume of all MGEs that contribute to HGT is called mobilome (Caniça et al., 2015; D'Costa et al., 2011). Gene transfer within a bacterial community is an important and rapidly evolving process that allows niche adaptation, niche extension and colonization of new niches. Thanks to the water continuum, local resistome and mobilome can spread to other distant geographical areas (Allen et al., 2010).

2.4. Waterborne bacteria can act as shuttles for antibiotic resistance

AMR has been detected in several waterborne bacteria including *Aeromonas*, *Rhodospirillaceae*, *Shewanella* and *Vibrio* (Goñi-Urriza et al., 2000; Hernández et al., 2011; Schreiber and Kistemann, 2013) as well as in opportunistic premise plumbing pathogens (OPPPs) (Falkinham et al., 2015) such as *Pseudomonas* and *Stenotrophomonas* (Gupta et al., 2018; Hocquet et al., 2016). In addition, most fecal bacteria of human origin that contaminate water bodies carry ARGs as a result of exposure to antibiotic treatments that select ARB in human or animal guts (Salyers et al., 2004).

Aeromonas spp. are emblematic of autochthonous bacteria that play a role in disseminating AMR. For instance, a survey of AMR along the River Elorn in Brittany (France), which drains a large area of intensive livestock farming and freshwater fish farming, revealed a general bacterial enrichment in addition to increasing rates of resistance to oxolinic acid and oxytetracycline in *Aeromonas* populations (Gordon et al., 2007). Members of the genus *Aeromonas* naturally produce three β-lactamases belonging to class B (carbapenemase), class C (cephalosporinase), and class D (oxacillinase). They can exchange resistance genes with other bacteria in the environment as they possess large quantities of MGEs like class 1 integrons (Henriques et al., 2006) or by horizontal transfer of plasmids that harbor a resistance gene(s) (for instance, fluoroquinolone resistance gene *qnr*) (Cattoir et al., 2008). It has been shown that plasmids encoding multidrug resistance (MDR) isolated from *Aeromonas* can be transferred to other human pathogens like *E. coli* or *Enterobacter aerogenes* (Marchandin et al., 2003; Rhodes et al., 2000).

Above we described miscellaneous but not exhaustive microbiological properties of the traits and tools that allow bacterial adaptation and/or adaptive evolution in environments contaminated by antimicrobial agents. Various environmental factors that drive adaptation and/or adaptive evolution of bacteria also contribute to the emergence of antibiotic resistance and its persistence in reservoirs. After a brief review of the water cycle in urban contexts and of the physical and chemical parameters in urban runoff waters, we review the still under-explored issues and questions of the dynamics of ABs, ARB and ARGs in urban runoff.

3. The urban water cycle

The natural cycle of water mainly involves rainfall, runoff onto soil surfaces, infiltration, storage in the soil or in plants, evaporation and infiltration into the aquifer. As water management is a challenge in the context of rampant urbanization, models are being designed specifically for the urban water cycle which mainly includes water inputs (supply sources and precipitation) and inputs of contaminants (for reviews see (Peña-Guzmán et al., 2017; Yazdanfar and Sharma, 2015)). One way for these contaminants to enter the urban water cycle is via runoff. As schematically represented in **Fig. 1**, human activities can disturb the water cycle both by direct pollution of runoff and by destroying the self-purification capacity of natural ecosystems. The water cycle is mainly disturbed in urban and industrial settings. Cities and conurbations include many impervious surfaces that increase runoff and the risk of stormwater overflow.

Stormwater runoff originates from pervious and impervious surfaces after snow or rainfall events. Runoff from different lands such as forest, agricultural, industrial, urban or mixed areas either flow directly through the natural watershed or are carried separately (or in combination) by sanitary wastewater sewer systems from where runoff is discharged into freshwater bodies. Today, in developed countries, the water cycle is becoming increasingly artificial because it is strongly impacted by the “all in pipes” rationale. Impervious surfaces and pipe networks that increase with urbanization lead to engorgement and floods with recurrent chemical contamination of freshwater (Miquel, 2003) (**Fig. 1**).

In urbanized zones, runoff has diverse origins. The major contributors to urban runoff are stormwater from impervious surfaces like roofs (Adeniyi and Olabanji, 2005; Gromaire et al., 2001;

Lye, 2009), roads (Kayhanian et al., 2012), sidewalks, parking lots (Göbel et al., 2007), etc. **(Fig. 1)**. A comprehensive study on urban runoff in California showed that a majority (76%) of bacterial loading occurs during dry weather conditions (Reano et al., 2015). One explanation is that urban runoff can also be generated by residential activities involving the use of water such as excessive landscape watering, washing vehicles, leaks from plumbing systems and recreational water bodies in domestic or recreational settings (Rashid and Romshoo, 2013; Reano et al., 2015). The runoff linked to these residential and recreational activities accounts for nearly 25% of the overall household water consumption (Reano et al., 2015) **(Fig. 1)**.

Atmospheric pollutants and dust produced by traffic (Kayhanian et al., 2012), industry and other human activities can be deposited in and transported by runoff waters. Urban runoff also contributes to the contamination of receiving water bodies through fecal bacteria of human and animal origin (Selvakumar and Borst, 2006) **(Fig. 1)**. Other bacteria autochthonous to plumbing systems and effluent pipes can also be found in effluent runoff waters (e.g. after washing car or other human activity generating wastewater that don't reach wastewater pipes). Despite the prevalence of microorganisms, including pathogens, in urban runoff, the risks they pose to human health have been less assessed than those caused by chemical pollutants (Chen et al., 2016; Gromaire et al., 2001; Lamprea and Ruban, 2011).

Finally, the biotic and abiotic contaminants in urban runoff are qualitatively similar to those in effluent water but sources contribute differently. Considering that urban runoff waters can be re-used to increase water supplies (Sidhu et al., 2013a), their chemical and bacterial contamination as well as the associated risk for human and environmental health requires careful assessment.

4. Physical and chemical parameters that may impact antibiotic resistance in urban runoff

The human impact represented by the presence of domestic and industrial sewage effluents in runoff has been shown to cause an increase in temperature downstream (Shakir et al., 2013). Temperature has a direct impact on the life cycle of most living beings and particularly on bacterial growth. Obviously, atmospheric temperature and the season influence the temperature of surface waters, but the temperature of runoff water can also be affected by human activities particularly by industrial effluents and urbanization. Urbanization (roads, roofs and other impervious surfaces) captures and transfers heat from the sun to receiving water bodies through stormwater runoff (Hathaway et al., 2016). This increase in water temperature in urban area has been shown to have a negative impact on aquatic ecosystems and to influence bacterial dynamics (Paule-Mercado et al., 2016; Tobias, 2013).

The pH of urban runoff water ranges from 6.8 to 8.2 depending on conditions (Kumar and Prabhabar, 2012). Alkalinity is a positive buffer against acidic pollutants associated with urban development, but an increase in pH also reflects runoff contamination by metal roofs, high pressure caused by tourism and road traffic (Adeniyi and Olabanji, 2005; Lye, 2009; Rashid and Romshoo, 2013).

Electrical conductivity is directly linked to water mineralization and varies according to the concentration of calcium, iron, chlorides, nitrates, etc. Electrical conductivity is correlated with water purity and increases with the level of pollution (Kumar and Prabhabar, 2012). It has been measured in a continuum of wetland differently impacted by urban and agricultural runoffs and a good correlation was found between conductivity and other markers of pollution (Harwell et al., 2008).

Human impacts significantly increase total suspended solids, concentrations of nutrients (phosphate, ammonia, nitrite, nitrate, total nitrogen and total phosphorus), chloride, sulfate, total alkalinity and hardness (Shakir et al., 2013). Beside runoff from agricultural lands amended with fertilizers (Kumar and Prabhabar, 2012), increased population density in large cities is associated with increased nutrient inputs to urban runoff. A study conducted on urban runoff from residential catchments in Florida showed that nitrogen inputs mainly resulted from atmospheric deposition (50%) and fertilizers (30%) while phosphate pollution was caused both by soil erosion and by the degradation of organic fertilizers (leaves and grass) (Yang and Toor, 2017). The amount of total suspended solids in water is an indicator of pollution pressure in urban runoff. Concentrations can be 10- or 100-fold higher than that recommended in water quality standards (25 mg/L) (Lundy et al., 2012). Suspended solids come, for example, from roads and traffic, car parks, roadside gullies, industrial and commercial roofs, and sewage misconnections (Göbel et al., 2007; Helmreich et al., 2010; Kayhanian et al., 2012). A high rate of suspended solids is generally linked to contamination by heavy metals and polycyclic aromatic hydrocarbons (PAHs) (Helmreich et al., 2010; Murakami et al., 2004). These pollutants are particularly concentrated in road dust that comes from vehicle emissions, tires, tarmac, paint road markings, etc. Leaching by rain or human activities such as car washing or street sweeping help pollute urban water (Murakami et al., 2004). Consequently, PAHs and heavy metals are present in both particulate and dissolved phases in urban runoff (Brown and Peake, 2006).

Values of dissolved oxygen in freshwater vary according to many environmental and biological factors like season (temperature), daily cycle, water depth, photosynthesis, and respiration by organisms. (Kumar and Prabhabar, 2012). Water from urbanized zones, especially runoff from impervious surfaces, is usually associated with low concentrations of dissolved oxygen (Duwig et al., 2014; Kayhanian et al., 2012) and high levels of biological oxygen demand (Mallin et al., 2009). A decrease in the concentration of dissolved oxygen has a negative impact on aquatic ecosystems (Rashid and Romshoo, 2013).

Heavy metals are well known contaminants of waters bodies, lead (Pb), zinc (Zn), copper (Cu), cadmium (Cd) and nickel (Ni) being the main pollutants in stormwater (Lundy et al., 2012). Several studies have detected decreased concentrations of lead in recent decades as a result of regulations concerning the use of lead in tires and gasoline in several countries (Huber et al., 2016), confirming the significant contribution of heavy metals from vehicle and traffic to the contamination of runoff water (Göbel et al., 2007; Kayhanian et al., 2012). Even if runoff from roads is still the main contributor (56.3% of stormwater load), runoff from roofs also contributes significantly (35.8%) to lead pollution in stormwater (Gray and Becker, 2002). As an illustration, pollution of runoff caused by rainwater was evaluated in a study conducted in Paris (France), a city with huge extents of metal roofs. The study showed that rooftops were the source of 80% of contamination of the regional sewer system by heavy metals including cadmium, lead and zinc (Gromaire et al., 2001). Along with heavy metals, cobalt (Co) and tungsten (W) are strongly suggestive of contamination due to human activities, mainly traffic, as their natural occurrence in the environment is very low (Bäckström et al., 2003).

PAHs, particularly those containing more than three aromatic rings, are mostly transported by particles in road runoff (Kumata et al., 2000) but PAHs in oil and grease can also directly contaminate urban runoff (Kayhanian et al., 2012). Other outstanding pollutants such as perfluoro-octane sulfonate (PFOS) are also detected in runoff because they are transported by the atmosphere and are widely distributed in dust (Sasaki et al., 2003). Heavy metals, PAHs and PFOS are known to be persistent in the environment, and have adverse effects on aquatic ecosystems as well as being chronically toxic for humans and other living organisms (Nakayama et al., 2005). For instances, the genotoxicity and estrogenic activities of road dust increase with an increase in traffic (Degirmenci et al., 2000).

These changing environmental conditions affecting physical and chemical parameters of urban runoff represent all selective pressure conditions that are likely to both promote exaptation and cause a stress on bacterial communities whose composition and structure influence ARG profiles (Zhou et al., 2017).

5. Antibiotics and antimicrobial agents in water and urban runoff

5.1. Natural antibiotics

Several ABs are produced naturally in the environment by soil microorganisms, for example, β-lactams produced by *Penicillium*, *Cephalosporium* or *Actinomycetes*, and aminoglycosides or tetracyclines produced by *Streptomyces* (Kümmerer, 2009a). The main function of natural ABs is to inhibit the growth of other community members thus favoring their producers in the competition for resources. The concentrations of naturally produced ABs are expected to be low (ng/L), therefore their contribution to environmental contamination is considered as non-significant (D'Costa et al., 2007; Kümmerer, 2009a). It is worth noting that there is no evidence for the production of any AB by waterborne bacteria (Kümmerer, 2009a). The assessment of the contribution of natural ABs to runoff contamination requires the study of pristine sites with no human inputs. In a study by Yang and Carlson (2003), no tetracyclines were detected in a pristine site in Colorado (Yang and Carlson, 2003). As tetracyclines are naturally produced ABs, this result illustrates the low contribution of natural ABs to the global reservoir of ABs in the environment, particularly in urban waters.

5.2. Antibiotics from agriculture, animal husbandry and aquaculture

ABs used in veterinary medicine belong to the same chemical classes as those used in human medicine (Cantas et al., 2013), i.e., β-lactams, tetracyclines, quinolones, and sulfonamides (S. Zhang et al., 2016). ABs are given to animals to treat infections but are still authorized and used as growth-promoting agents through feeding at low concentrations over long periods, although this is forbidden in some places; in Europe, for instance, these practices have been banned since 2006 (Charuaud et al., 2019; Silbergeld et al., 2008). Significant quantities (30-90%) of consumed ABs may be eliminated unchanged or as active metabolites through urinary and/or fecal excretion (Du and Liu, 2012; Shao et al., 2018). One secondary pathway for environmental dissemination of ABs and their metabolites is field applications of manure as fertilizer (Sarmah et al., 2006). ABs can be retained by agricultural soils that act as reservoirs (Lee et al., 2007; Rooklidge, 2004) and then gradually released, enabling them to reach surface water compartments through runoff and drainage and groundwater by percolation (**Fig. 1**). ABs can also leak from manure storage facilities and artificial lagoons storing slurry (Meyer, 2004) or through dust (Hamscher et al., 2003). Beside livestock, the rapid development of aquaculture has led to an increase in AB consumption for both the treatment and to promote the growth of fish (Pruden et al., 2013). Fish farms have a direct impact on water and increase concentrations of ABs and ARB in aquatic environments (Cantas et al., 2013).

Antibiotics are also used in plant agriculture to treat bacterial diseases of some fruits and vegetables and also as fruit growth promoter (Kümmerer, 2009a). Despite their limited use (they account for about 0.1% of the total use of ABs in agriculture in the USA), particular care is required (McManus et al., 2002) as ABs such as streptomycin and oxytetracycline are highly resistant to naturally degrading factors like high temperature, UV irradiation and oxidation. Their persistence in the environment may increase selective pressure and hence the selection of resistant bacteria. Runoff from agricultural fields can subsequently impact downstream urban waters (**Fig. 1**). For example, tetracyclines have been detected along the Poudre River in Colorado where both urban and agricultural influences were present (Yang and Carlson, 2003).

In conclusion, in a watershed, antibiotics used for agricultural, aquacultural or livestock activities exerted upstream an urban area, can reach urban waters (**Fig. 1**).

5.3. Antibiotics in municipal, hospital and industrial wastewaters

Like for animals, 90% of ABs consumed by humans are excreted in urine and feces as parent compounds or as byproducts (Tiwari et al., 2017). Moreover, out-of-date prescriptions also may be discarded directly in the toilet and end up in the sewage system, but are also discarded in garbage cans and then in dumps thereby directly contaminating both soil and water. Most families of ABs have been detected in wastewater worldwide at variable concentrations ranging from ng/L to mg/L (Li and Zhang, 2010). When ABs and their metabolites reach wastewater treatment plants (WWTPs), they may be partially removed by adsorption onto the biomass flocs, biodegradation or biotransformation but also by physical-chemical processes such as hydrolysis, photolysis and volatilization (Li and Zhang, 2010; Pruden et al., 2013). However, wastewater treatment is not sufficient to completely eliminate pharmaceutical compounds, including ABs (Tiwari et al., 2017)

The highest consumption of ABs mainly occurs in hospitals where around half of patients are treated with at least one class of ABs, sometimes for relatively long periods (Baggs et al., 2016). As a result, increased quantities of ABs and their metabolites are excreted in hospital wastewater effluents and then combined with municipal wastewater (Baquero et al., 2008; Oberlé et al., 2012). Although hospital sewage only accounts for about 1% of municipal sewage (Kümmerer, 2009a), hospital wastewater is considered as a main contributor of ABs to municipal WWTPs and to the receiving river (**Fig 1**). Typically, AB concentrations in hospital effluents have been found to be 100-fold higher than those of municipal effluents (Carraro et al., 2016; Kümmerer, 2009b; Santos et al., 2013). For instance, Verlicchi and colleagues (2012) studied a WWTP effluent that included wastewater from a hospital. Their quantification of chemical residues revealed higher concentrations of almost all compounds, in particular ABs like fluoroquinolones, in hospital wastewater than in urban wastewater (Carraro et al., 2016).

Concentrations of ABs in effluents from pharmaceutical factories have been shown to reach therapeutic levels at milligram-per-liter concentrations in some cases (Kristiansson et al., 2011; Li et al., 2009; Pruden et al., 2013). In India, for instance, several studies reported high concentrations of fluoroquinolones in effluents from WWTPs that received effluents from pharmaceutical factories. These authors detected 14 mg/L of ciprofloxacin in the effluent of the WWTP and up to 6.5 mg/L in two local lakes (Fick et al., 2009).

Altogether, antibiotics from wastewaters located upstream an urban area, can reach urban waters and exert selection pressure onto bacterial communities (**Fig. 1**).

5.4. Water pollution by other antimicrobial agents and biocides

In addition to ABs, disinfectants, preservatives, fungicides, and insect repellents also display generalist biocide activity (Liu et al., 2015). They can enter the surface water directly or indirectly through WWTPs and have deleterious effects not only on environmental microorganisms but also on algae (Yang et al., 2008) and fish (Davoren and Fogarty, 2005).

In addition, disinfection by-products i.e. chemical compounds whose activity results from the interaction between chemical disinfectants, mainly chlorine, and organic matter, harm environmental microorganisms. More than 600 disinfection by-products have been detected in drinking water, the most prevalent being chloramines, trihalomethanes and haloacetic acids

(Richardson, 2011). Small water systems usually contain higher concentrations of disinfection by-products than medium and large water systems (Charrois et al., 2004). Of note, the carcinogenic *N*-Nitrosodimethylamine is formed during chlorination and chloramination of water containing the herbicide diuron. This by-product is found in groundwater impacted by agricultural runoff (Chen and Young, 2009).

5.5. Dynamics of antibiotics in urban waters

The concentration of ABs in natural water bodies gradually decreases with distance from the source of contamination, due to dilution factor of the receiving hydrosystem and to natural attenuation mechanisms like photolysis, biodegradation, hydrolysis or adsorption (see for instance, the monitoring of tetracycline and sulfonamide concentrations in a river flowing through urban and agricultural areas in Yang and Carlson, 2003. In a recent study, the prevalence of ABs was investigated in the Yangtze River (China) that flows through industrial and crowded urbanized areas. Out of 20 targeted ABs, 11 belonging to three classes were detected: chloramphenicol, sulfonamides, and macrolides, with higher concentrations at the confluence of rivers and sewage effluents than at coastal sites (Yan et al., 2013). Other authors have detected high concentrations of sulfamethoxazole and trimethoprim in watersheds impacted by human activities (Duwig et al., 2014).

In most studies, higher concentrations of ABs are detected in winter than in summer (Jiang et al., 2011; Kim and Carlson, 2007; Yan et al., 2013; Yang et al., 2011). Such seasonal variations could be explained by low temperatures and limited sunshine in winter, which may reduce microbial degradation and antibiotic photo-degradation, in addition to the increased incidence of infectious diseases and AB consumption in winter (Yan et al., 2013). In a runoff-receiving urban lake, the concentrations of eight antibiotics in surface water or sediment increased after a stormwater event (S. Zhang et al., 2016). These results demonstrate the role of runoff waters in the dissemination of ABs in the environment, at least in the case of significant climate events.

The factor that influences the persistence of ABs and their active by-products in the environment is their stability in soil and/or water, in which some ABs including fluoroquinolones may remain active for a long time (Turiel et al., 2006). The persistence of ABs in soil or their transport to surface water is influenced by many factors including the affinity of ABs (or of their metabolites) for other compounds. For example, tetracycline has a high potential to be transported to surface water due to its low sorption on soil (Kay et al., 2004). Another factor that influences the persistence of ABs is their resistance to biotransformation, as observed for sulfamethoxazole and fluoroquinolones that subsequently pass untransformed into WWTP effluents (Daughton and Ternes, 1999; Roberts and Thomas, 2006). In water, ABs persistence and its impact on microbial communities are influenced by the physical-chemical properties of the water including temperature, pH, and dissolved organic compounds, and environmental conditions including solar exposition (Hirsch et al., 1999; Yan et al., 2013; Yan and Song, 2014).

6. Origin and dynamics of bacteria in urban runoff

6.1. Soil

The most frequently detected bacteria in aquatic ecosystems belong to the phyla *Proteobacteria* (*Alpha-*, *Beta-*, and *Gamma-proteobacteria*), *Actinobacteria*, *Bacteroidetes* and *Firmicutes* (Vaz-Moreira et al., 2014). Microbial community composition and structure are highly diverse and are correlated with the geographic location, season and point-source pollution (Zhou et al., 2017). Bacterial communities in aquatic environment contain both autochthonous members (aquatic bacteria also found in pristine waters) and allochtonous bacteria of different origin, for instance, soil (Lee and Kang, 2016). Soil bacteria are major contributors to aquatic bacterial contamination as they are organized in rich and diverse communities (**Fig 1**). Since most bacteria are clustered in the top soil layer (Lee and Kang, 2016), they are better able to disseminate in water during flood events. On the one hand, soil can thus be considered as a natural reservoir for ABs and ARB and on the other hand, soil is directly involved in further contamination of groundwater by infiltration and contamination of adjacent surface water bodies through surface runoff.

6.2. Human and animal commensals

Beside soil bacteria, aquatic allochtonous bacteria can originate from human beings or animals; they can be mutualistic or pathogenic. Human enteric pathogens have been shown to contaminate water, thus posing a risk to human health as etiological agents of severe infectious diseases including salmonellosis, shigellosis, cholera, enteric viral infections and amoebiasis. Allochtonous bacterial pathogens enter freshwater via runoff mainly in insufficiently treated sewage from overcrowded areas devoid of proper sanitary disposal. In addition, human and animal pathogens can enter surface water in runoff from fields fertilized with manure (Thurston-Enriquez et al., 2005). Large quantities of pathogenic bacteria can enter rivers as a result of extreme climate events like severe floods, especially when the floods affect sewers and sewage treatment plants (Abraham, 2011; Marsalek and Rochfort, 2004). Commensal bacteria from human and animal guts can also spread to the environment via fecal-polluted water and their detection can indicate a risk of fecal-oral infections.

Fecal indicators are routinely used in urban runoff waters as a standard to assess water quality (United States Environmental and Protection Agency, 2015). In developed countries with a good sanitary system, fecal indicators in runoff mainly originate from the feces of domestic animals and wild life. However, when rainwater mixes with municipal sanitary wastewater due to failed infrastructure and cross-connections, fecal pollution of human origin may be detected in urban stormwater runoff (Sauer et al., 2011). Contamination of urban runoff by fecal indicators is particularly troublesome because higher concentrations have been detected in urban runoff than in runoff from agricultural land and land under mixed land uses (Paule-Mercado et al., 2016). The concentration of fecal indicators in stormwater runoff is influenced by many environmental circumstances, including early or late-phase storm events, early or late warm season and various physical or chemical variables (Eramo et al., 2017; Paule-Mercado et al., 2016). Fecal coliforms have been detected in freshwater bodies that receive urban runoff (Selvakumar and Borst, 2006). *Enterococcus* spp., which persist in the environment, have often been detected at higher concentrations and rates than *E. coli* (Krometis et al., 2010; Parker et al., 2010; Sidhu et al., 2012). The abundance of fecal coliforms and enterococci appear to be poorly correlated in runoff waters (Selvakumar and Borst, 2006). Microbial source tracking indicators such as *Bacteroides* HF183, human adenovirus and sweetener acesulfame demonstrated more ubiquitous sewage contamination in the vicinity of major Australian cities than that assessed using standard microbiological indicators (coliforms and enterococci) (Sidhu et al., 2013b).

Despite their wide use as indicators of microbial quality water, fecal bacteria in runoff waters are frequently not correlated with the presence of pathogens (de Man et al., 2014; Selvakumar and Borst, 2006). For instance, a study conducted on Dutch urban sites showed that all urban floodwater samples contained fecal indicators but their concentrations were not correlated with the concentrations of pathogens present in the same samples (de Man et al., 2014). Briefly, the prevalence of pathogens depends on their seasonality and their persistence in relation to the location of flooding. Since these parameters may differ from those of indicators, discrepancies between indicator and pathogen prevalence may be observed (de Man et al., 2014).

Waterborne enteric pathogens are frequently detected in runoff waters in high-density residential areas and during extreme climatic events leading to flooding. They include bacteria, enteric viruses and protozoa, all of which indicate sewage pollution (Noble et al., 2006; Sidhu et al., 2012). Urban runoff waters have been shown to contain higher concentrations (7.94%) of potential pathogens than agricultural runoff (6.52%) or runoff from recreational areas (6.00%) (Ibekwe et al., 2013). Waterborne enteric pathogens in runoff waters are mainly *Vibrio* spp., *Leptospira* spp., *Campylobacter* spp., *Salmonella* spp., *Cryptosporidium* spp., *Giardia*, enterovirus and norovirus (Cann et al., 2013; de Man et al., 2014; Sidhu et al., 2012). Concerning the risk to human health, some studies demonstrated that exposure to stormwater runoff is linked to gastrointestinal diseases (Curriero et al., 2001; Gaffield et al., 2003) but few studies have evaluated the annual risk of human infection associated with concentrations of pathogens in urban runoff. De Man et al. (2014) reported an annual risk of 8% for people exposed at least twice a year to floodwater originating from urban runoff caused by rainfall (de Man et al., 2014).

6.3. Man-made infrastructures

In urban areas in developed countries, the 'all in pipes' rationale creates technological ecosystems such as those observed in premise plumbing (McLellan et al., 2015), which include all water supply systems delivering water to different buildings including homes, hospitals, condominiums, apartments, and office buildings. Despite the use of different disinfection procedures, water circulating through these facilities carries a wide range of microorganisms (Wang et al., 2013). Bacteria in premise plumbing belong to *Proteobacteria*, *Bacteroidetes*, *Actinobacteria* and *Acidobacteria* (Wang et al., 2013). These bacteria are autochthonous to natural waters but the particular conditions found in the pipes favor their colonization and dissemination throughout the system. These microbes include opportunistic human pathogens called opportunistic premise plumbing pathogens (OPPPs), such as *Legionella pneumophila*, *Pseudomonas aeruginosa*, *Stenotrophomonas maltophilia* and non-tuberculous mycobacteria (see Falkinham et al., 2015, for a comprehensive review), that are innately resistant to disinfectants. OPPPs are adapted to growth in premise pipes, mainly because they tolerate low concentrations of organic carbon and oxygen in stagnant ditches, they resist grazing by amoeba and form biofilms, which protect them against disinfectants and other environmental stressors like thermal shocks (Falkinham et al., 2015).

OPPPs are rarely taken into consideration when bacterial contamination of runoff is evaluated. When studied, the numbers of OPPPs do not correlate with the number of fecal coliforms and other standard indicators (Falkinham et al., 2015). Indeed, the dynamics of OPPP concentrations in water systems differs from that of classical fecal-oral pathogens and human-specific markers, whose concentrations are higher in the vicinity of the source of pollution. In contrast, the abundance of

OPPPs increases along a gradient starting from their point of entry in the system because they can multiply in pipes and plumbing systems (Falkinham et al., 2015).

Chemically polluted runoff waters contain OPPPs that are generally resistant to xenobiotics. For instance, high concentrations of *Mycobacterium goodii* and *P. aeruginosa* were found in the Lerma River (Mexico) impacted by hydrocarbons, polychlorbiphenyls (PCBs) and heavy metals (Brito et al., 2015) and in one section of a Belgium river impacted by wastewater pollution (Pirnay et al., 2005).

6.4. Dynamics of bacteria in urban runoff

The total bacterial load in urban runoff water is significantly influenced by land use and land cover (Converse et al., 2011; Selvakumar and Borst, 2006). High human population densities have been found to be associated with higher bacterial loads (Glenne, 1984). For instance, microbial loads from high-density residential areas are higher than those observed in low-density residential and commercial areas (Selvakumar and Borst, 2006). Another factor that affects bacterial concentrations in urban runoff is seasonality, with lower bacterial concentrations measured in winter than in summer (Pirnay et al., 2005; Selvakumar and Borst, 2006). These differences can be attributed to increased dilution of runoff water by rainfall in winter and also to lower growth rates of microorganisms at low temperatures.

Urban runoff water contains a less diversified microbial community than agricultural and municipal wastewaters due to lower nutrient availability (Ibekwe et al., 2016). Most of the bacteria detected were *Proteobacteria* and *Bacteroidetes* (Ibekwe et al., 2013). However, community equilibrium may be disrupted by climate events. For example, higher concentrations of the genera *Aeromonas* and *Bacillus* were observed in the water of receiving lakes in China after storm events (S. Zhang et al., 2016). One explanation could be the resuspension of benthic bacteria from the sediment to the surface water caused by the storm event (Sidhu et al., 2012). Several studies have reported that river sediments contain higher abundances of microorganisms than surface waters (Bai and Lung, 2005;

Fries et al., 2008; Ibekwe et al., 2016). Indeed, large quantities of aquatic microbes live in attached, complex and abundant biofilm communities (Costerton et al., 1995).

7. Antibiotic resistant bacteria in urban runoffs

Local conditions influence the prevalence of ARB in hydrosystems. Resistant microorganisms colonizing sediments can be easily moved through the overlying water column under the influence of river management or of natural events like heavy rainfall (Griffith et al., 2010). High prevalence of multidrug resistant *E. coli* was detected in riverbed sediments of the anthropically impacted Apies River (South Africa), suggesting that river sediments may act as a reservoir for resistant bacteria with subsequent dissemination to the overlying river under certain conditions (Abia et al., 2015). Moreover, a higher number of opportunistic pathogens known for their intrinsic and acquired resistance to ABs (*Aeromonas, Cronobacter, Enterobacter, Klebsiella, Serratia* and *P. aeruginosa*) was detected in freshwater bodies post-monsoon and in the winter season than in summer as a result of additional discharge of terrestrial resistant strains via runoff during heavy rainfall events (Mohanta and Goel, 2014).

In China, it was shown that increased AB concentrations accompanied by increased percentages of ARB and ARGs in two urban runoffs were correlated with urban stormwater runoff (S. Zhang et al., 2016). After the storm event, multi-resistance indices at the bacterial community level increased in samples of both water and sediment (S. Zhang et al., 2016). The ARB detected included *P. aeruginosa*, *Acinetobacter, Aeromonas*, and *Bacillus cereus,* as also observed in a river in South Africa (Carstens et al., 2014). Other reports indicated that about 20% of bacteria isolated from waterways were multidrug resistant harboring resistance to ampicillin, kanamycin, chlortetracycline, oxytetracycline, and streptomycin (West et al., 2011).

There is wide agreement that stormwater transports chemical and biological contaminants and that runoff affects water quality. Consequently, urban rivers that receive both urban runoff and sewage from sewer systems and are likely to overflow during storm events are often selected as sites to study urban water cycles. Very few data are available on ARB present in other forms of urban runoff like puddles on impervious surfaces including roofs, footpaths and roads that then flow through urban areas to join urban rivers or water collection systems. A few original studies have focused on the microbial communities in puddles. Furukawa and colleagues (2018) wanted to know if bacterial communities in puddles can be influenced by the proximity of a hospital, thereby affecting the rate of antibiotic resistance. They showed that puddles contained a wide diversity of bacteria, including potential pathogens such as *Aeromonas, Acinetobacter, Enterobacter, Escherichia, Klebsiella, Pseudomonas*, etc. Even though rates of resistance to some antibiotics were very high (for example, 88% for lincomycin or 80% for amoxicillin), no significant differences between antibiotic susceptibility were found between isolates from puddles that formed near the hospital and in other locations (Furukawa et al., 2018), but a *P. aeruginosa* strain resistant to meropenem was isolated from a footpath outside one of the hospitals studied. In another study focused on the prevalence and characterization of environmental *Clostridium difficile* strains, *C. difficile* was isolated in 14.4% of puddle water samples. Some of these strains were multidrug resistant and 12 of the 15 PCR ribotypes presented a PCR ribotype associated with human and animal hosts (Janezic et al., 2016).

Resistance to β-lactams is of major concern because this family of ABs is the most widely used in human medicine including β-lactams of last resort such as carbapenems (Meletis, 2016). Bacteria producing extended spectrum β-lactamases that hydrolyze a wide range of β-lactams are now endemic in most countries and are also detected in urban waters (Bajaj et al., 2016; Lu et al., 2010; Tissera and Lee, 2013). Carbapenemase-producing bacteria hydrolyze most or all β-lactams and have emerged worldwide in the last few years. These highly resistant bacteria are a major threat because they are associated with therapeutic dead-end. In addition to their recent emergence in clinical settings, they have also been detected in urban water (Almakki et al., 2017b; Sekizuka et al., 2018; Xu et al., 2018).

The percentage of ARB detected in runoff water is generally lower than in WWTP effluents (S. Zhang et al., 2016). However, only a few data are available on ARB in urban runoff but reports on the isolation of bacteria displaying resistance to a wide range of antibiotics including emerging resistances in urban runoff underline the urgent need for more detailed studies.

8. Antibiotic resistance genes and resistome in urban runoff

A comprehensive study of 285 ARGs from a polluted urban river in China showed that the abundance of ARGs was positively correlated with total organic carbon and total dissolved nitrogen (Zhou et al., 2017). In addition, ARG abundance and diversity were greatly altered by microbial community structure, itself influenced by point-source pollution (Zhou et al., 2017).

Studies that investigate ARGs and resistome specifically in runoff waters are rare but several genetic and metagenomic studies clearly demonstrated that discharge of treated and untreated wastewater increased the abundance and diversity of ARGs as well as MGE in urban receiving rivers (Lekunberri et al., 2018; Subirats et al., 2017). Surface waters, wastewater and treated effluents share part of their resistome (21 ARGs), suggesting the spread of ARGs across different environments. However, wastewater contains higher average concentrations of clinically relevant ARGs such as genes coding for extended spectrum β-lactamases and carbapenemases (Ng et al., 2017). The predominant ARGs in WWTP effluents are associated with class 1 integrons or sulfonamide resistance genes (*sul*) (X.-H. Zhang et al., 2016). Hospital effluents are a major source of integron dissemination with a prevalence of *E. coli* strains that decreases from the hospital to the WWTP and the receiving river continuum (Oberlé et al., 2012).

Another indirect example of contamination of runoff water by ARGs comes from the city of Victoria (Australia) where the use of reclaimed water to irrigate a park led to a shift in bacterial community composition with an increase in ARG concentration and to the emergence of particular ARG types, such as *bla*$_{\mathrm{KPC}}$ and *bla*$_{\mathrm{IMP\text{-}2}}$ that encode emerging broad-spectrum beta-lactamases (Han et al., 2016) and degrade carbapenems, last-line antibiotics used to treat patients infected by bacteria resistant to other available antibiotics.

The impact of urbanization on the load of ARGs has frequently been demonstrated. One study revealed a significant correlation between the abundance and diversity of resistance genes, ABs and the anthropogenic footprint in the Pearl River estuary in Australia (Chen et al., 2013). In the Jiulongjiang River in China, the total abundance of ARGs and MGE in urban water samples was over two orders of magnitude higher than that in pristine samples (Ouyang et al., 2015). Another significant comparative study of two urban watersheds with different land-use profiles in Singapore demonstrated the impact of runoff on river water quality. The section of river flowing through an urbanized landscape (with commercial and residential buildings) receiving inputs from the urban drainage system, contained significantly more ARGs than the concentrations measured at the other sampling site which is surrounded by a forest and a golf course (Low et al., 2016).

Concerning climatic events, a recent study showed that the load of five target ARGs (*sul1*, *sul2*, *tetO*, *tetW*, and *ermF*) was significantly higher in an urban river during storm events than during equivalent background periods (Garner et al., 2017). The metagenomic analysis of these samples identified from 37 to 121 different ARGs, underlining the role of storm-driven transport of ARGs in urban contexts (Garner et al., 2017). In another study, the detection of nine ARGs and increased levels of integrons after storm events (S. Zhang et al., 2016) confirmed the potential role of stormwater in dissemination of ARGs from land sewer systems to urban freshwater resources. Peak concentrations of ARGs and fecal indicators also depend on the velocity of the storm events linked with their partitioning as attached versus suspended fractions (Eramo et al., 2017).

9. Conclusion

Urban runoff water currently receives less attention than other water bodies concerning antibiotic resistance. However, the results of the few available studies reveal an undeniable role of runoff in the dissemination of antibiotics, antibiotic-resistant bacteria, and antibiotic resistance genes in urban areas. Given the worldwide modifications of cityscapes, the disequilibrium between rural and urban populations and the high population density in cities, combined with the continuing emergence of new antibiotic resistance mechanisms, runoff water should be considered as a vehicle in the spread and persistence of antibiotic resistance in urban contexts. The impact of storms and other climatic events on the load of antibiotic-resistant bacteria and antibiotic resistance genes has been clearly demonstrated and merits further attention in the context of global climate change.

The current threat of antibiotic resistance to human health and the hypothesis that antibiotic resistance could kill 10 million people annually by 2050 (O'Neill, 2014) call for the development of national and global action plans to tackle antibiotic resistance based on the 'One Health' concept. Environmental health is an integral part of this worldwide strategy to control infectious diseases and the present review underlines the fact that urban runoff clearly falls within the scope of global infection control.

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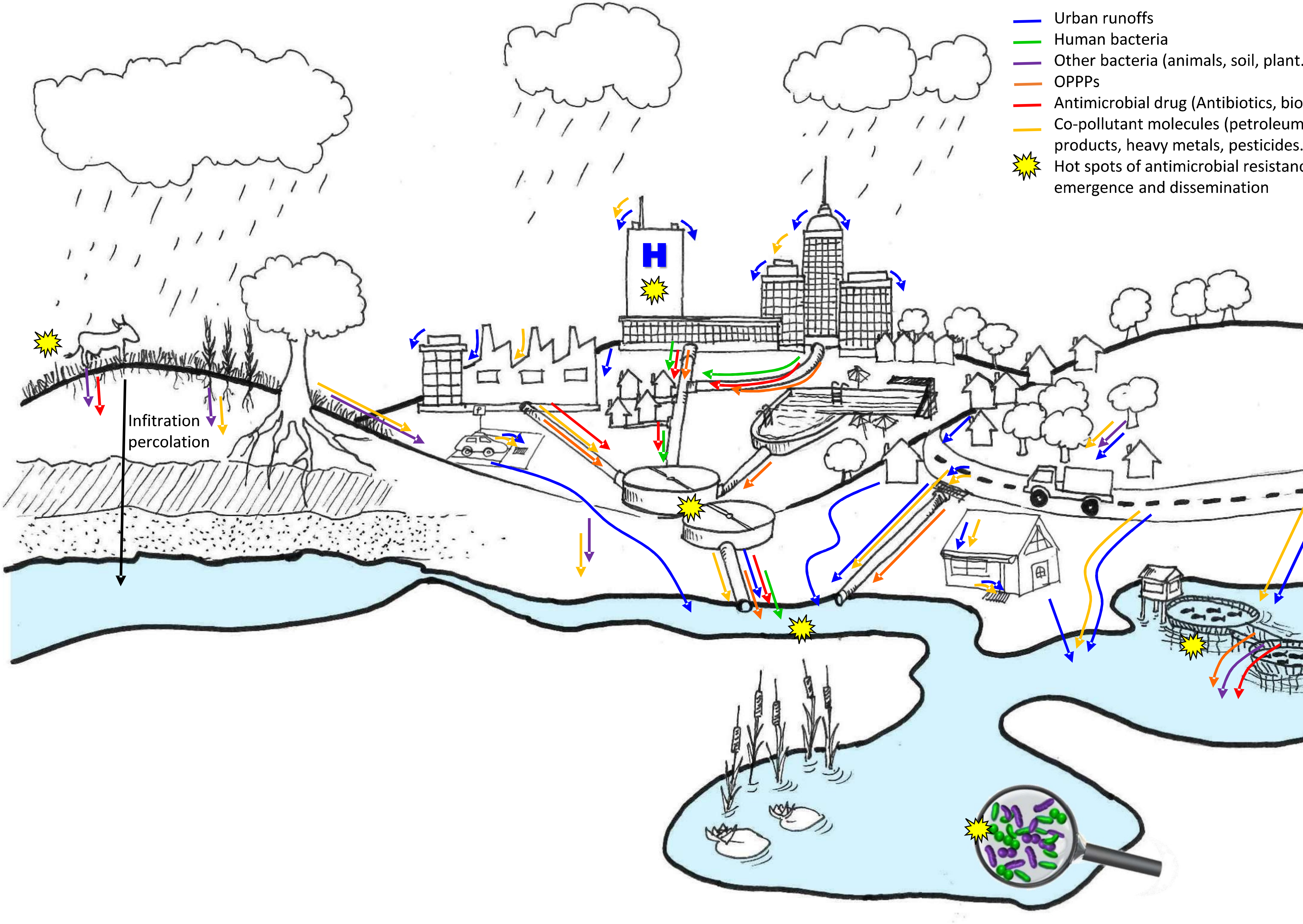
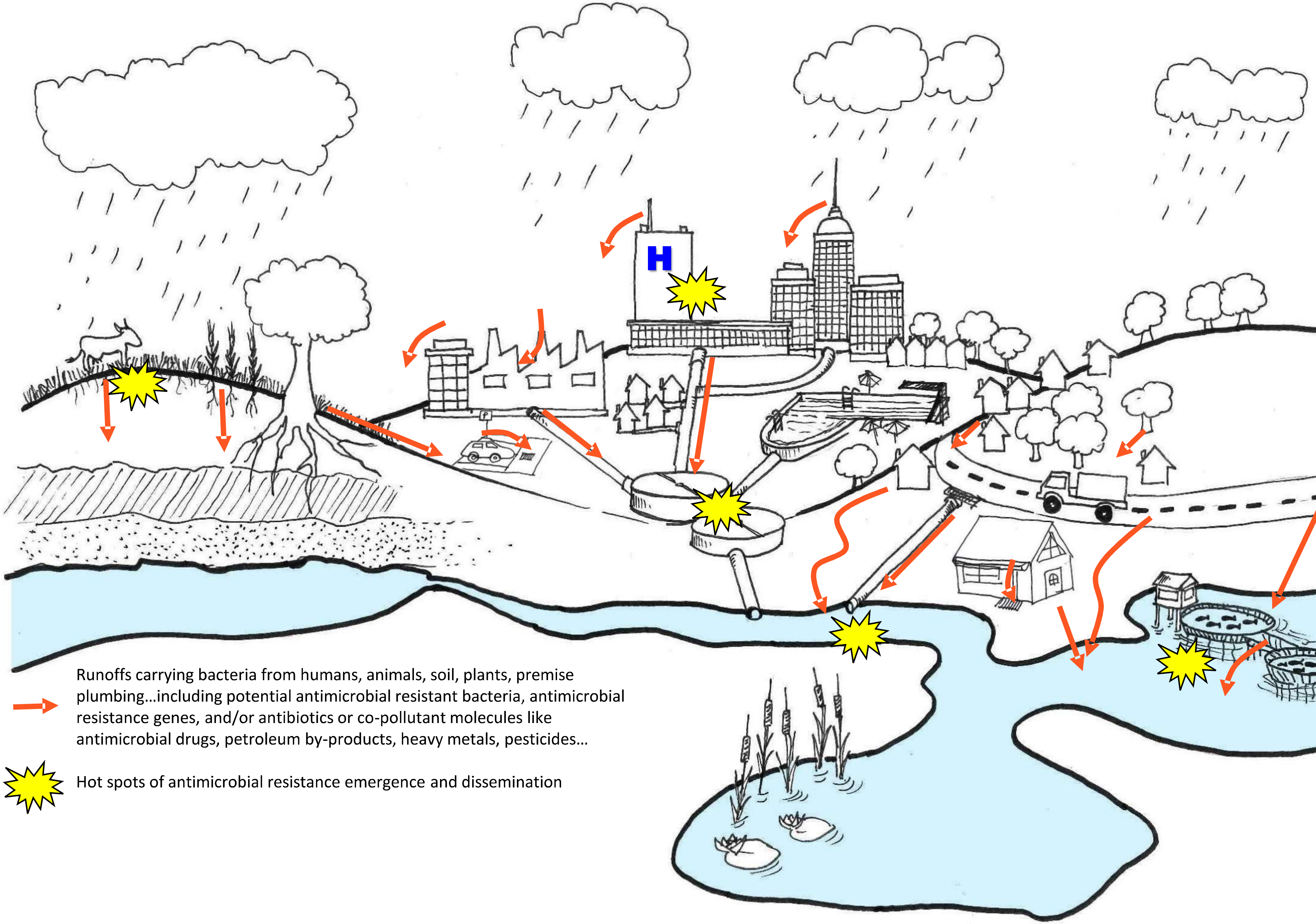
Figure legends

Fig. 1: Urban cycle of water and contaminants. Runoffs and transports of contaminants are indicated by arrows according to the color legend.

Figure 1


Urban runoffs
Human bacteria
Other bacteria (animals, soil, plant.
OPPPs
Antimicrobial drug (Antibiotics, bio
Co-pollutant molecules (petroleum
products, heavy metals, pesticides.
Hot spots of antimicrobial resistanc
emergence and dissemination
Infitration
percolation
H



→ Runoffs carrying bacteria from humans, animals, soil, plants, premise plumbing…including potential antimicrobial resistant bacteria, antimicrobial resistance genes, and/or antibiotics or co-pollutant molecules like antimicrobial drugs, petroleum by-products, heavy metals, pesticides…

✸ Hot spots of antimicrobial resistance emergence and dissemination