

1 Climate change: any dangers from antimicrobial resistant bacteria?

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16 **Abstract**

17 Antimicrobial resistance represents a threat whereby micro-organisms (particularly bacteria)
18 become resistant to our antibiotics and disinfectants, thus complicating our ability to treat and
19 prevent infections. This is often developed by sub-inhibitory exposures to our drugs and/or
20 disinfectants, but it can be caused by (often negative) changes in the environment as a stress-
21 response mechanism to environmental conditions, such as temperature, salinity, metals
22 (potentially toxic elements), and organic pollutants.

23 Here, we explored possible mechanisms by which climate change could either directly (by
24 changes in temperature and/or precipitation), or indirectly – such as shifts in human
25 populations, disease vectors, agriculture, water availability, glaciation, and hydrology. Each
26 scenario discusses how environmental changes, or stressors, could affect the development or
27 transfer antimicrobial resistance in bacteria.

28

29 Climate change is altering the earth's atmosphere in several ways, being expected to
30 generate altered air temperatures and lead to more extreme changes in precipitation across the
31 globe. The worldwide average surface temperature has increased 0.74 °C over the last century
32 (Rosenzweig, et al., 2007). These effects are not anticipated to be geographically uniform, and
33 has generated multiple changes, including altered frequencies of extreme weather conditions
34 in different parts of the World. The most significant differences in air temperature and climate
35 classification are predicted to occur at more northern latitudes. In comparison, precipitation
36 increases are present at both extreme northern latitudes and also sporadically across regions of
37 the equator, including parts of India, Saudi Arabia, and East Africa (Beck, et al., 2018). These
38 changes in climate will translate to altered conditions relevant to microbial growth, at the scale
39 of both individual microorganisms and at the community level. These changes will be relevant
40 to all forms of microbial life, including bacteria, fungi, and viruses.

41 Climate change will also impact human health, increasing the prevalence of heat related
42 diseases and leading to altered migration patterns. There is limited discussion in the literature
43 regarding the mechanisms through which climate change will alter the development or
44 dissemination of antimicrobial resistance (AMR) in the environment. However, it has been
45 mentioned that global warming contributes to antibiotic resistance (AR) in the environment
46 (e.g., MacFadden, et al., 2018). Rather than attempt to list all previous articles that have been
47 published on the subject, we will instead discuss current issues involving AMR and how they
48 may be impacted by climate change.

49 Both climate change and antimicrobial resistance have been recognized as
50 interdisciplinary problems related to the “tragedy of the commons” (Singer, et al., 2016)—in
51 which, individuals behave according to one’s self interests, but contrary to the common good
52 of others. A major misconception exists that the development of AMR stems from bacterial
53 exposure to antibiotics or synthetic antibacterial compounds; the extent of this can be argued.
54 It has, however, become more evident that anthropogenic pressures accelerate the presence of
55 AMR (Forsberg, et al., 2014), but it can also be presumed that inherent changes in natural
56 landscapes could contribute as well – although these changes may occur at a slower-pace and
57 their contribution may be more difficult to elucidate.

58 There is strong evidence demonstrating that pollution, even at relatively low
59 concentrations, can produce shifts in bacterial communities (the “microbiome). Resistance
60 traits within a microbial community (i.e., the “resistome”) propagate in the presence of a
61 natural selection factor, which ultimately creates resistant populations of bacteria. Once a
62 resistance trait is selected, host bacteria can transfer genes between individuals (horizontal gene
63 transfer) *via* transferrable genetic elements (e.g., plasmids) creating an enhanced resistome
64 (Wright, 2007, 2010). Thus resistance can spread among microorganisms once a gene enters a
65 system, including target organisms that are pathogenic (Dantas and Sommer, 2012).

66 Microorganisms can develop resistance to many environmental factors, including heavy
67 metals, disinfectants, nutrient conditions, and temperature. However, resistance to antibiotics
68 is perhaps that of greatest contemporary concern in society. It has consequences which impedes
69 the efficacy of infection control and treatment – with health-related, economic and societal
70 consequences. It is commonly believed that this type of resistance is only driven by the
71 excessive use of sub-inhibitory concentrations of antibiotics; again, the extent can be argued.
72 While this mechanism remains the major contributor to antibiotic resistance, it has been
73 recently observed that pressures from environmental pollutants can also provide a level of
74 selection pressure.

75 Bacterial communities respond genetically to pollutants *via* evolved mechanisms for
76 their self-protection (Alonso, et al., 2001). For instance, metals (or potentially toxic
77 elements) in the environment may contribute to microbial cellular health as a micronutrient,
78 while at elevated levels generating a stress response and resistance development (Beaber, et
79 al., 2004; Ashbolt, et al., 2013). An example of this response has been observed in the
80 development of copper-resistance mechanisms in bacteria isolated from soil with a high-
81 metal content (Berendock, et al., 2015). Other metals, such as chromium and mercury, have
82 limited biochemical merit and cause oxidative stress. Unfortunately, defence-associated metal
83 resistance genes are often closely associated with those responsible for AMR as both reside on
84 mobile genetic elements.

85 This co-selection of metal resistance (or other resistance mechanisms, e.g., those against
86 toxic organics or disinfectants) and antibiotic resistance can occur by one of two processes: co-
87 resistance or cross-resistance (Baker-Austin, et al., 2006). Co-resistance occurs when selection
88 of one phenotype simultaneously selects for other genes located on the same genetic element.
89 On the other hand, cross-resistance occurs when the antibiotic and metal have similar
90 biochemical pathways or targets in the cell. Consequently, when a resistance response is

91 triggered, the cell defense becomes effective against both metal and antibiotic toxicants. As
92 such, the environment acts both as a reservoir of resistance traits and a bioreactor containing
93 chemical stressors, providing opportunities for genetic exchange. There is, therefore,
94 significant potential for these traits to disseminate to clinically relevant pathogens.

95 The relationship between metal tolerance (or resistance) and AR has been known;
96 reviews can be found in the literature (e.g., Baker-Austin, et al., 2006; Martinez, 2009; Seiler
97 and Berendonk, 2012; Perry and Wright, 2013). However, microorganisms of clinical
98 significance have been found resistant to multiple antimicrobials, including metals, by
99 susceptibility assays (e.g., Marques, et al., 1979; Dhakephalkar and Chopade, 1994; Bass, et
100 al., 1999; Ghosh, et al., 2000; Guo, et al., 2014), suggesting that a link between genetic traits
101 exists.

102 In the environment, relationships between metals and AR proliferation were first
103 noticed in highly contaminated areas, including outflows of insufficiently treated wastewater
104 and biosolids (Graham, et al., 2011; Knapp, et al., 2012; Su, et al., 2015), agricultural wastes
105 (Ji, et al., 2012; Zhu, et al., 2013; Li, et al., 2015), industrially contaminated areas
106 (Stepanauskas, et al., 2005; Wright, et al., 2006; Graham, et al., 2011; Knapp, et al., 2012;
107 Abella, et al., 2015; Hu, et al., 2016; Rodgers, et al., 2017) and direct application *via* metal
108 exposure experiments (Berg, et al., 2005; Stepanauskas, et al., 2006; Berg, et al., 2010;
109 Knapp, et al., 2011). AR presence in these cases has often been indicative of exposure to
110 elevated metal pollution.

111 Less information exists on less-impacted soils and basal (e.g., pristine natural) levels,
112 but evidence suggests that risks still exist. The geochemical nature of soils, collected in the
113 1970s for a national archive, had correlations with various antibiotic resistance genes found
114 among their bacterial communities—including those for tetracyclines, beta lactams, and
115 erythromycin (Knapp, et al., 2011). Similar patterns observed in residential soils, all have

116 sub-regulatory levels of metals (Knapp, et al., 2017). In some cases, the metal content may
117 not directly correlate with AR genes, but increase the mechanisms (e.g., integrases) by which
118 genes may become horizontally transferred to other bacteria—thus increasing the risk *via*
119 frequency of potential exchange.

120 Besides metals, some persistent organic compounds will co-select for antimicrobial
121 (including antibiotic) resistance genes, including pesticides (e.g., Anjum and Krakat, 2016),
122 polychlorinated biphenyls (LoGuidice, et al., 2013), and disinfectants (Tandukar, et al., 2013;
123 Khan, et al., 2016; Zhang, et al., 2016). Additionally, polycyclic aromatic hydrocarbons
124 (PAHs) are ubiquitously found environmental pollutants that have the capability to enhance
125 the abundance of AMR in microbial communities. PAHs are organic compounds with multiple
126 aromatic rings fused in a single compound. PAHs can either be phytogetic—originating from
127 plant materials, petrogenic—from petroleum products or sources, or pyrogenic—resulting
128 from combustion processes. In addition to their potential sources are the distribution and
129 abundance of compounds, and their associated toxicities.

130 The association of PAHs with AMR has been found in lake-sediment pollution (Máthé,
131 et al., 2012), coastal areas (Wang, et al., 2017), and soils (Chen, et al., 2017). Areas with PAH
132 contamination have been reported to have increased prevalence of genes encoding efflux
133 pumps, detoxifying transporters (Chen, et al., 2017), and also conjugative transfer *via* class I
134 integrons (e.g., Wang, et al., 2017).

135 Since metals and certain PAHs (e.g.) are also widespread in the environment and do not
136 degrade, these compounds can potentially provide a long-term selection pressure. Resistance
137 development is not only due to the presence of high concentration of antimicrobials; rather low
138 concentrations of contaminants, which cause cellular stress to microorganisms, could also
139 provide the selective pressure.

140 Climate change and AMR represent contemporary topics of discussion. In a recent
141 meeting among the members of Centre for Water, Environment, Sustainability and Public
142 Health (a University of Strathclyde, Department of Civil & Environmental Engineering
143 research group), various cross-disciplinary researchers had a discussion about the possible
144 impacts of climate change on the patterns of antimicrobial resistance. Some of their thoughts
145 are outlined as:

- 146 1. Pathogen; their fate, prevalence and gene transfer
- 147 2. Agriculture-related changes
- 148 3. Water distribution and quality
- 149 4. Melting glaciers and permafrost thaws
- 150 5. Hydrological changes and legacy pollution

151 Here, we present our thoughts.

152

153 **1. Pathogens**

154 *1.1 Pathogen Prevalence*

155 At the community scale, changes in precipitation levels and temperatures can be expected
156 to alter the spatial distribution of pathogen vectors. These vectors may be biological (e.g., flies),
157 or non-biological (e.g., dust, fomites) (Nordor, et al., 2018).

158 For example, climate alterations have the potential to alter the range of disease-spreading
159 insects such as the mosquito *Anopheles*, a vector for *Plasmodium* – an obligate parasite of the
160 mosquito. Many *Plasmodium* species cause malaria, with *Plasmodium falciparum* putatively
161 linked to carcinogenesis (Lehrer, 2010; Nordor, et al., 2018). Elevated CO₂ and changes in air
162 temperature are climate effects with the greatest potential to alter the distribution of malaria
163 *via* changes in disease vector distribution. Temperature changes will have an indirect impact
164 on soil moisture dynamics, providing a further mechanism to alter the life cycle of malarial

165 vectors. The presence of stagnant water due to increased precipitation rates would also increase
166 the breeding area for the *Anopheles* vector. Therefore, climate change will alter the life cycle
167 of the *Anopheles* vector, along the life cycle of *Plasmodium* itself (Dhimal, et al., 2015; Le, et
168 al., 2019).

169 Changes in distribution of malarial areas are anticipated due to climate change, leading to
170 higher malarial burdens (Campbell-Lendrum et al. 2015). Moreover, climate change is
171 expected to impact a range of other vector-borne pathogens in a similar manner. Examples
172 include dengue fever, west nile virus, tularemia, rabies, chikungunya, and Lyme disease
173 (Green, et al., 2008). The principal vector of Lyme disease – the arthropod *Ixodes scapularis*
174 – is anticipated to experience a 213% increase in suitable habitat area within the North
175 American continent by 2080. This effect is anticipated to be driven largely by expansion of
176 viable breeding territory into Canada due to alterations in temperature caused by greenhouse
177 gas emissions and sulfate aerosols (Brownstein, et al., 2005).

178 Climate change will generate changes in daily life, such as increased use of air conditioning
179 systems due to elevated indoor temperatures (Vardoulakis, et al., 2015). It has been recognised
180 in the past that indoor environments can harbour microbial communities which vary with
181 geographic location. For example, temperate climate zones harbour far more diverse fungal
182 communities than tropical climate zones (Amend, et al., 2010). Significant expansions in the
183 temperate ‘humid continental climate’ (Dfb) are anticipated by 2080, particularly across Russia
184 and parts of India. This would suggest that regions with significant human populations may be
185 exposed to fungal communities of increased diversity due to climate change, with potential
186 impacts on human health.

187 Heating, ventilation, and air conditioning systems as well as settled dust and outdoor air
188 are well recognised as sources of indoor airborne microorganisms (Prussin and Marr, 2015).
189 Airborne fungal particles are of particular concern, as a cause of allergies and even cancers.

190 Climate change may lead to significant effects on global fungal populations, with the spread of
191 thermo-tolerant species being anticipated (Garcia-Solache and Casadevall, 2010). These
192 effects may be amplified in urban areas (McLean, et al., 2005). The reduction in the thermal
193 gradient between environment and mammalian hosts generated by climate change is
194 anticipated to increase the range of potential fungal diseases (Garcia-Solache and Casadevall,
195 2010). Any increased use of domestic air circulation systems due to climate change – for either
196 heating or cooling – may become linked to alterations in aerobiology, with subsequent potential
197 impacts on human health (Fernstrom and Goldblatt, 2013).

198 Specific geographic sites for increased fungal diseases have been identified in North
199 America, with the increase in dry summers and increased precipitation late in the year
200 enhancing the spread of *Blastomyces dermatidis* and *Coccidioides immitis*, both of which are
201 associated with varied health effects, including bone disease (Green, et al., 2008).

202 Within the United States, a 2-4% rise in occurrence of antibiotic resistant bacteria
203 belonging to the genii *Escherichia*, *Klebsiella* and *Staphylococcus* has been associated with
204 regions of elevated local temperature versus cooler areas (MacFadden, et al., 2018). There is a
205 clear link between increased temperature and population density, with increased prevalence of
206 antimicrobial resistance being linked to these elevated temperatures (MacFadden et al. 2018).
207 These effects were observed to be consistent across almost all classes of antibiotics and
208 pathogens, and this association has grown stronger over time. While the selective pressure of
209 antibiotic use is considered to be the largest contributor to the emergence of antibiotic
210 resistance, it has become apparent that climate-change associated factors such as increases in
211 air temperature (Beck, et al., 2018) and increased urban density (Güneralp, et al., 2017) have
212 potential to increase the prevalence of antimicrobial resistance in many bacterial species
213 relevant to human health.

214 The negative effects of antimicrobial resistance are ever-increasing due to the uncontrolled
215 use of antimicrobials for the treatment of various infectious diseases. Changing patterns in
216 pathogen distribution are expected to expand the geographic range and intensity of
217 antimicrobial use. For example, the expansion in the viable area of *Ixodes scapularis* into
218 Canada is likely to increase the use of doxycycline and ceftriaxone to combat the causative
219 pathogenic bacterium *Borrelia*. While the emergence of antibiotic resistance has not been
220 observed in *Borrelia* (Sharma, et al., 2015), the increased use of doxycycline and other
221 antibiotics such as amoxicillin and even macrolide antibiotics may be associated with increased
222 resistance of other species present in the environment, as observed with *Streptococcus*
223 *pneumonia* (Karcic, et al., 2015). Similar effects may be anticipated due to increased use of
224 antifungal treatments in response to elevated levels of fungal diseases linked to climate
225 change,(Fernstrom and Goldblatt, 2013; Prussin and Marr, 2015; Vardoulakis, et al., 2015)
226 leading to altered geographic distribution of antifungal resistance.

227 1.2 Gene Transfer

228 HGT (horizontal gene transfer) is a process through which organisms can exchange genetic
229 information without reproduction. This process allows the exchange of functional genetic
230 material such as virulence, xenobiotic metabolism, and antibiotic resistance genes (ARG). This
231 transfer can occur even at the domain level – such as between bacteria and archaea – and occurs
232 in many different environments, including soil, seawater, and within the human body (Aminov,
233 2011). HGT is linked to emergence of some microbial traits harmful to human health and
234 wellbeing, including antibiotic resistance.

235 Ecology and environmental conditions have been identified to significantly influence the
236 gene transfer among microorganisms (Fuchsman, et al., 2017). Indeed, it is thought that
237 ecology is even more significant an influence than phylogeny (Smillie, et al., 2011). This has
238 been evidenced by the high rates of gene transfer between bacteria and archaea in

239 environments, which are conducive to the growth of species from each of these domains. This
240 effect is particularly pronounced in the extremophilic bacteria and archaea, such as
241 thermophiles and halophiles.

242 Changes in climate are linked with increased salinity in locations such as the Arctic Ocean,
243 (Greene and Pershing, 2007), as well as coastal estuaries and aquifers (Titus, 1989). These
244 effects may expand the geographic distribution of growth sites suitable for extremophiles, with
245 a concomitant increase in horizontal gene transfer between highly varied species of bacteria
246 and archaea.

247 In soils, temperature, moisture levels, pH, and soil type have all been associated with
248 changes in rates of conjugal plasmid transfer (Aminov, 2011). Changes in soil temperature
249 have been associated with climate change, dependent upon geographic location. For example,
250 warming trends have been observed in the Tibetan Plateau (Fang, et al., 2019), Alaska and
251 Siberia (Oelke and Zhang, 2004), and Russia (Zhang, et al., 2001). There is also potential for
252 climate-change associated soil acidification in a number of environments (Rengel, 2011).
253 Associations between climate change and soil moisture are complex, being influenced by
254 changes in precipitation and, therefore, potentially broader climate classification changes
255 (Seneviratne, et al., 2010; Beck, et al., 2018).

256 Increasing pH from 4.5 to 8.5 is linked with a general increase in gene transfer rate at 22
257 °C, with the effect becoming less pronounced at 37 °C (Rochelle, et al., 1989). Similarly,
258 increasing temperature from 22 °C to 29 °C is linked to a decrease in gene transfer rates in
259 *Agrobacterium tumefaciens* (Dillen, et al., 1997).

260 In summary, climate change can be expected to increase the levels of HGT in the
261 environment through a range of mechanisms, such as increased sea and soil temperatures, soil
262 acidification, and changes in ocean salinity. Altered microbial community compositions due to
263 climate change effects may also bring previously disparate microbial species into closer

264 contact. Increased levels of HGT have been directly linked to the generation and spread of
265 antibiotic resistance in the environment (Ventola, 2015). Therefore, climate-change effects
266 have significant potential to increase the spread of antibiotic resistance genes.

267

268 **2. Agriculture**

269 The occurrence and prevalence of antimicrobial- and drug-resistant organisms and genes
270 have been associated with the selective pressures on the usage of antibiotics in both clinical
271 and agricultural sectors (Levy, 1997). Agricultural practices have been considered a major
272 culprit for the increase in antibiotic-resistant strains of bacteria (Silbergeld, et al., 2008;
273 Kennedy, 2013; John, 2014). For instance, in the USA alone, about 13 million kg, or 80% of
274 all antibiotics, have been associated with livestock production annually (Hollis and Ahmed,
275 2013). On a global scale, Van Boeckel, *et al.* (2015) reported that 45–172 mg of antimicrobial
276 agents are consumed annually per kg of animal (e.g., cattle, chicken, and pigs) produced.

277 *2.1 AMA and AMR pathways in agriculture*

278 Agriculture has been recognised to have many reservoirs/hotspots and pathways involved
279 in the dissemination of AMA (antimicrobial agents) and AMR within the agricultural
280 environment and the food processing industry (Thanner, et al., 2016). The general transmission
281 route or pathway is typically from animal (livestock) to animal-derived manure to soil to water
282 and to sediments, with human (farmers) and animals as hosts. Several authors have identified
283 hot spots of ARG (antimicrobial resistance genes) and ARB (antimicrobial resistant bacteria)
284 to include the digestive tract of farm animals and humans, manure, wastewater treatment plants,
285 and the soil or rhizosphere (Zhu, et al., 2013; Wu, et al., 2014; Woolhouse, et al., 2015;
286 Thanner, et al., 2016; Manyi-Loh, et al., 2018). Other possible water-related hotspots for ARG
287 and ARB include: rivers and lakes, sediments, biofilms in aqua-cultural systems, irrigation
288 systems, slaughterhouses, as well as on plant surfaces (Thanner, et al., 2016). Soil and water

289 tend to function as mixing media or sinks for the mobile genetic elements (MGEs), as well as
290 sources of AMR (Riesenfeld, et al., 2004; Xiao, et al., 2016).

291 Antibiotics such as tetracyclines, sulphonamides, lincosamides, aminoglycosides,
292 macrolides, β -lactams and pleuromutilins with potentially adverse effects are administered to
293 livestock globally for treatment or therapeutic purposes, for sub-therapeutic purposes for
294 growth promotion, as prophylaxis and/or metaphylaxis (Mellon, et al., 2001; Apata, 2009;
295 Landers, et al., 2012; Abou-Raya, et al., 2013; Finley, et al., 2013; Pham Kim, et al., 2013; De
296 Briyne, et al., 2014; Baynes, et al., 2016; Manyi-Loh, et al., 2018). This has led to increase in
297 resistant bacteria within the gut flora of livestock and the deposition of antibiotic residues in
298 products such as meat/muscles/fat, milk, eggs, liver, and kidney available for human
299 consumption (Witte, 1998; Aarestrup, 1999; Manyi-Loh, et al. 2018). Further, animal
300 excretions (urine and faeces) containing antibiotic residues, ARBs, and ARGs may be released
301 into the agricultural environment as raw manure often used for soil fertilization (Acar and
302 Moulin, 2006).

303 The dissemination and fate of antimicrobials within the agricultural sector depends on:

- 304 1) the pattern of administration of the antimicrobials, the metabolic activities and
305 transformation processes within the animal, the potential of releasing the compounds
306 into the environment through animal excrements (European Medicines Agency,
307 2018);
- 308 2) their physicochemical properties such as shape, size, molecular structure, solubility
309 and water repellence (Thanner, et al., 2016; European Medicines Agency, 2018);
- 310 3) environmental effects such as changes in climatic conditions, soil types, erosion,
311 hydrology – surface and groundwater (Carlson and Mabury, 2006; Davis, et al., 2006;
312 Kuchta, et al., 2009; Park and Huwe, 2016; Pan and Chu, 2017; European Medicines
313 Agency, 2018);

- 314 4) environmental fate, including sorption properties (Tolls, 2001; Lin and Gan, 2011;
315 Thanner, et al., 2016), abiotic or biotic transformation/degradation processes (Thiele-
316 bruhn and Peters, 2007; Reichel, et al., 2013; Cui, et al., 2014; Manzetti and Ghisi,
317 2014; Duan, et al., 2017); and
- 318 5) uptake by crops or pasture (Kumar, et al., 2005; Dolliver, et al., 2007; Kuchta, et al.,
319 2009; Carter, et al., 2014).

320 Soil acts as a natural reservoir for AMA and ARBs since a wide range of known and
321 unknown (or uncultured) AMR determinants have been detected in non-fertilised soils
322 (Riesenfeld, et al., 2004; Maron, et al., 2013; Marti, et al., 2013; You and Silbergeld, 2014;
323 Xiao, et al., 2016). However, antimicrobial agents are mostly introduced to soil *via* fertilization
324 with raw manure collected from animal sources treated with antimicrobials, bringing
325 metabolites of AMA and microbes with ARG existing on mobile genetic elements (MGE)
326 (Hamscher, et al., 2005; Binh, et al., 2008; Zhu, et al., 2013; Wolters, et al., 2015; Thanner, et
327 al., 2016). Additionally, AMAs are added through the use of irrigation with wastewater and
328 treatment of crop diseases with antibiotics (Finley, et al., 2013; Oluyeye, et al., 2015).
329 Depending on soil temperature, pH, nutrients and oxygen concentration as well as microbial
330 diversity, ARG may be transferred to soil microbes through HGT (i.e., *via* conjugation,
331 transduction and transformation mechanisms), resulting in enrichment of taxa and decline in
332 the population of organisms significant for soil quality (van Elsas and Bailey, 2002; Aminov,
333 2011; Perry and Wright, 2013; Ding, et al., 2014; Fahrenfeld, et al., 2014; Jechalke, et al., 2014;
334 Forsber, et al., 2015). According to the European Medicines Agency (2018), there may be a
335 positive correlation between the factors that promote the persistence of a compound in soil and
336 factors that enhance their potential to select for resistance within the same microbiome. It has
337 been reported that an increase in soil moisture content from 15 to 25% led to a decrease in the
338 half-life of an antibiotic (sulfadimethoxine) from 10.4 to 4.9 days (Wang, et al., 2006); while

339 a similar increase in temperature resulted in the degradation of norfloxacin (Yang, et al., 2012).
340 In contrast, other studies have found that warmer temperatures (30 - 45°C) could enhance the
341 antimicrobial effects and antibiotic resistance of common pathogens and bacterial biofilms
342 (Rachid, et al., 2000; Hajdu, et al., 2010; MacFadden, et al., 2018).

343 The aquatic environment also serves as source and sink of antibiotic-resistant bacteria
344 and resistance genes (Biyela, et al., 2004; Baquero, et al., 2008). Also, antimicrobial agents (or
345 mobile resistant genes) in raw manure can be translocated *via* the action of rainfall runoff
346 and/or soil erosion from the surface of fertilised soils to nearby surface or ground water bodies,
347 depending on the properties of the AMAs, the soil and hydrological effects (Pollard and Morra,
348 2018). Although studies on the mobility and transport of antimicrobials in the environment are
349 scarce, the European Medicines Agency (2018) suggest that these behaviours will vary
350 considerably for different antibiotics.

351 Humans, especially those involved in agriculture (e.g., farmers) typically become hosts
352 to commensal organisms and resistant pathogens via ingestion. Farmers and their families can
353 transmit AMAs to livestock through contact, since the human skin and digestive tract serve as
354 reservoir for some of these pathogens (Acar and Moulin, 2006). However, this route of
355 transmission depends on several factors including geographical location or region, farming
356 system adopted, size of farm, hygiene, ethno-cultural and religious practices (Lozano et al.
357 2016).

358 2.2 *Influence of climate change on agriculture*

359 Climate change will directly impact agricultural climate resources (such as precipitation
360 and temperature) and cause changes in livestock productivity, crop/plant community
361 composition and productivity, soil microbial communities and the general agro-related
362 ecosystem, as well as surface and ground water hydrology (Kim and Lee, 2010; Bardgett, et
363 al., 2013). It has been predicted that climate change will result in further reduced agricultural

364 productivity in regions with hitherto low agricultural productivity levels (Harvey et al., 2014).
365 Some studies report that changes in the amount and quality of feed as well as increased heat
366 stress may result in a 25% decrease in animal production (van de Steeg and Tibbo, 2012; Lewis,
367 et al., 2018) with higher temperatures leading to lower daily milk yield (Verner, 2012).

368 2.3 Possible changes induced by climate change on AMR in agriculture

369 Thanner et al. (2016) provide a comprehensive list of knowledge gaps in AMR in
370 agriculture, justifying the difficulty to reach valid conclusions on the prediction of key factors,
371 like climate change, on AMR prevalence in the agricultural sector. The discussions in the
372 aforementioned sections also show that for the few available studies, there are contradictions
373 in findings regarding the behaviour of AMA/ARG under variable climatic conditions. It has
374 been suggested that global-scale surveillance programmes utilising comparable test methods
375 may be necessary to provide data on areas like the occurrence/abundance, transfer pathways
376 and factors influencing the selection, spread and persistence of AMAs/AMR in the different
377 compartments of agriculture, and the environment in general (Thanner, et al., 2016; Manyi-
378 Loh, et al., 2018). This will contribute towards better understanding, prediction and
379 management of AMR in agriculture.

380 Nevertheless, the socio-economic trends induced by climate change is expected to
381 influence land use patterns (Karmakar, et al., 2016) and general agricultural practices, with
382 possible indirect impacts on AMR. The Food and Agriculture Organization of the United
383 Nations (2016) predicts that climate shocks may lead to economic downturn for farmers,
384 especially small-scale farmers, as productive capital or assets may be sold to absorb the shock.
385 In several countries in the Near East and North Africa region, extreme droughts and climatic
386 events could result in crop failure and lead to food insecurity, malnutrition, famine and
387 starvation (Elasha, 2010; WFP and ODI, 2015). These factors, coupled with the growing
388 population implies that there would be greater demands for food (including animal proteins)

389 across the world, thereby placing pressure on agricultural production (Padol et al. 2015). The
390 tendency to use antibiotics to promote animal growth will become almost inevitable especially
391 in developing countries. Currently, the factors influencing the usage of antibiotics vary
392 considerably across regions and countries (World Health Organisation, 2012). These factors
393 include: land use, sources of contaminated water, animal demography as well as national and
394 international trade and policies (World Health Organisation, 2012). Antimicrobials that have
395 been banned in several countries, including developed countries, are still being used in
396 developing countries, (Moyane et al., 2013; Adebowale and Adeyemo, 2016). It has also been
397 predicted that to meet increasing consumer demands, the use of antibiotics in Brazil, Russia,
398 India, China and South Africa (known as the BRICS countries) is expected to double (Van
399 Boeckel, et al., 2015). China, is reported to be the highest producer and user of antibiotics for
400 humans and animals (Manyi-Loh et al., 2018). A study by Lee et al. (2001) has predicted that,
401 in the future, a significant percentage of animal-derived proteins packaged as food for human
402 consumption would have received some sort of chemotherapeutic or a prophylactic agent.

403

404 **3. Water Distribution and Quality**

405 *3.1 Surface waters*

406 Drought and flood are two extreme conditions, resulting from climate change, that can
407 dramatically affect the water quality, having significant effects in concentration of metals,
408 organic pollutants and pathogenic bacteria (Xia et al. 2015). The increase in the world average
409 temperature could have greater impact on world's water resources and decrease the availability
410 of freshwater resources. There are many direct and indirect effects that could have lasting
411 impacts: 1) re-distribution of water and its availability as a sources of drinking water; 2)
412 changes to the water quality as driven by increased biochemical activities; 3) changes in the

413 fate and presence of pathogens likely involved in the AMR process; and 4) impacts on
414 treatability of water, all of which could impact the risks associated with AMR.

415 Climate change is a major contributing factor in the disruption of water cycle and water
416 supply systems (de Oliveira, et al., 2015), and these strongly relate to elevated temperature
417 (Xia, et al., 2015). Increased temperatures accelerate evaporation and transpiration leading to
418 water loss from soil and plants (Bates, et al., 2008). Many water-supply systems face water
419 scarcity and reduced water quality, and climate change is considered as one of the reasons for
420 this shortage of water (Delpla et al. 2009).

421 Climate change deteriorates water quality (Xia, et al., 2015) by different biochemical
422 processes (Delpla et al. 2009). As we know, microorganisms support the existence of life on
423 the earth, and climate changes depends on the response of the microorganisms to the
424 environment (Cavicchioli et al. 2019), including their key role in different nutrient cycles
425 (Azam and Malfatti, 2007). These biochemical and microbiological reactions are temperature
426 dependent (Whitehead, et al., 2009); for example, higher temperatures reduce the concentration
427 of dissolve oxygen in water. Anoxia, as we already know in eutrophic systems, leads to further
428 changes in water quality, such as the further release of nutrients and metals. This cascades to
429 increased rates of nutrient assimilation and biomass production—including algal blooms and
430 anoxic dead-zones (de Oliveira, et al., 2015). However, long-lasting results may not be clear;
431 while immediate-nutrient effect are observable, studies show that climate change (i.e.,
432 increasing temperatures) may decrease nutrient concentrations in surface river waters (Alam et
433 al. 2013; Hosseini, et al., 2017), caused by cumulative assimilation by biota.

434 Anthropogenic activities tend to have a direct effect on water pollution while climate
435 change can have indirect effects on decrease in water quality in supply system (Bates et al.
436 2008). Water temperatures have dramatic impacts on its treatability for drinking water and may
437 require further treatments to maintain the potability. Increased water temperatures have the

438 unfortunate consequence of requiring higher dosages of chemical disinfectants (e.g., chlorine),
439 and they also result in increased formation of disinfectant by-products after disinfectant
440 treatment—e.g., the formation of chloroform from chloramine-treated water after 3 days at
441 higher temperature (Yang et al. 2007). This not only affects the potability of drinking water,
442 but also the increased disinfectant chemical loadings can impact the microbiome.

443 *3.2 Water distribution*

444 The obvious, but highly unfortunate consequence is that alterations in water availability
445 will lead to the re-distribution of populations; but, it will also encourage the use of waters with
446 reduced quality to meet demand. Thus requiring additional treatment and/or distribution of
447 water .

448 Water distribution systems are complex systems. They often represent environments with
449 low concentrations of antimicrobials, e.g., chemical disinfectants, to maintain a level of
450 assurance that the water remains potable. Chemical disinfectants, like the antibiotic therapies,
451 are designed to exhibit either biocidal or biostatics effects on the bacteria. At elevated
452 concentrations, they may be quite effective. But, disinfectant concentrations and efficacy
453 decline with temperature and deterioration of water quality (e.g., chlorine demand). At some
454 point along the distribution system, or in time, the concentrations could decline to “sub-lethal
455 levels.” Instead of inhibition, we could see population selection. Any surviving bacteria would
456 have undergone selective pressures for resistance traits that contribute to their survival. This
457 could be resistance traits against the disinfectant, but also other chemicals present, including
458 those associated with poor water quality – e.g., metals.

459 Even if bacteria could be removed at the point of treatment, distribution systems still
460 have the risk to become colonized by pathogens having antimicrobial resistance due to
461 limitations in treatment technologies and leakage; this becomes a mechanism and source, by
462 which resistant infections to human beings could result (Buse, et al., 2012). This could be

463 further exacerbated by the prolonged storage of water in (e.g.) building cisterns (Falkinham,
464 2015), where disinfection efficacy declines and the opportunity for contamination increases.
465 Thus, water supply systems could represent an unsuspecting source of AMR, which could
466 become worsen by declining availability, deteriorating water conditions and challenged
467 treatment efficacy. As such, there is a risk of spreading of antibiotic resistant bacteria to human
468 populations via insufficiently treated drinking water (West, et al., 2011).

469 A number of antibiotic resistant genes including *tet*, *sul*, *van* and *amp* have been reported
470 being transported via water bodies, and have been found in treatment plants and distribution
471 systems (Schwartz, et al., 2003; Pruden, et al., 2006; Prado, et al., 2008; Czekalski, et al., 2012;
472 Guo, et al., 2014; Bergeron, et al., 2015; Adesoji, et al., 2016). The bacteria with antimicrobial
473 resistance are not easy to treat (Levy, 2002) and pose a potential health risk for the immune-
474 compromised population (Lee, et al., 2010). Due to their impacts on human health, antibiotic
475 resistance has been announced as global health emergency (Sanderson, et al., 2018), and there
476 is an urgent need to minimize the environmental pollution due to antibiotics (Singer, et al.,
477 2018). Although the use of antibiotics has been reduced in different parts of the world, the
478 problem is not diminishing as their resistance is widely spread among different environments.
479 World Health Organization has started a global action plan to eradicate the problem through
480 public awareness and sustainable investment (WHO, 2015; Singer, et al., 2018). Distribution
481 systems and the complex interactions of source water availability, conditions and treatment
482 exemplify the challenges ahead.

483

484 **4. Melting glaciers and permafrost thaws**

485 Warming climate in glacial areas causes huge physical ($\Delta\sigma > 2000$ MPa), chemical and
486 biological stress to surface and near surface environments. Ice sheets had once wide coverage
487 during the Pleistocene (~2.5 Ma - ~12 ka) reaching ~40 °N in North America. Currently,

488 glaciers and continental ice-sheets cover ~10% of the land; permafrost currently covers ~23.9%
489 (Zhang, et al., 2008) of exposed Northern Hemisphere land surface. The glacial cycle produces
490 large vertical and flexural stress changes to the lithosphere (Lemieux, et al., 2008). Glacial
491 retreat results in hydromechanical changes: isostasy, permafrost melting, ice sheet un-loading,
492 groundwater flow/chemistry, and pore fluid pressure. Deglaciation removes vertical, flexural
493 and hydraulic loads from the lithosphere. Lithospheric rebound occurs, pore fluid pressures
494 change (Neuzil, 2012) in response to the changes in stress. High-pressure heads during glacial
495 advance cause groundwater to migrate from the surface to depth (Lemieux, et al., 2008). When
496 the hydrostatic pressure of ice sheet is removed, exfiltration of deep saline brines occurs. Fresh
497 glacial groundwater becomes input to the groundwater system.

498 Groundwater chemical conditions and subsurface flow pathways change during the glacial
499 cycle, having the potential to mobilise and transport: brines, heavy metals and organics at the
500 surface. Studies of the Laurentide ice sheet, during the Wisconsin and Pleistocene glaciations
501 in North America show brine formation and migration causes changes to ground and surface
502 water chemistry across a glacial cycle. Brine rich in sodium chloride formed from sea water
503 during cold glacial periods under permafrost through a process of cryogenic brine formation.
504 Cryogenic brines form when water freezes (Starinsky and Katz, 2003), solutes are not stored
505 in the ice and concentrate in the remaining water. Cryogenic brines form alongside permafrost
506 (McIntosh, et al., 2011) in the near surface. During static glacial periods brines and mineralised
507 halite remain stable in the subsurface. Warm periods result in permafrost thawing and glacial
508 melt; this results in the up-welling of saline brines (Starinsky and Katz, 2003), which can then
509 reach the surface and soil zone. Deglaciation has the largest chemical impact on groundwater:
510 saline brines are driven to shallower depths. Melt water infiltrates and dissolves halite minerals
511 (deposited during permafrost formation in glacial periods). Infiltrating melt water triggers

512 microbial mediated methanogenesis (McIntosh and Walter, 2005). The effect of glacial cycles
513 results in large swings in the surface and soil water chemical conditions.

514 Conditions in the permafrost differ; Siberian permafrost has high methane and negative
515 redox potential (Willerslev, et al., 2004) indicating a harsh anaerobic condition. Antarctic
516 permafrost has high redox potential and alkaline pH compared with neutral pH in Siberian
517 sites. Thawing of permafrost is documented to release CO₂ as well as methane into the
518 atmosphere (Hodgkins, et al., 2014). However, during the thawing process CO₂ and CH₄ gases
519 will also get dissolved into the melt water. This in turn will lead to lowering of pH in thawed
520 permafrost. As permafrost thawing rate increases over time (Haldorsen, et al., 2010), melt
521 water surrounding patches of permafrost promote further thawing. Release of organic matter
522 and methanogenesis CH₄/CO₂ production will increase exponentially as permafrost thawing
523 rate increases. Increasingly rapid changes to the soil environment will cause stresses to the
524 microbiome as a consequence of the changing climate. Previously trapped and accumulated
525 organic matter in permafrost (Turetsky, et al., 2000) is released into the water system during
526 thawing. The increase in organic matter (OM) input from melting permafrost supplies the OM
527 source used in methanogenesis. OM input from melting permafrost includes primary and
528 secondary metabolites which are biologically available and can be directly up taken by plants
529 and microbes.

530 Melting permafrost, in response to warming climate, releases major ions making them
531 available in the soil zone. Release of major ions increases their concentration in fresh surface
532 water environment affecting aquatic ecosystems. Both major ions (Ca²⁺, Mg²⁺, SO₄²⁻, NO₃⁻)
533 and trace elements (e.g., Ni, Hg, Pb, Cr, As) increase with increased melting of permafrost.
534 Release of toxic trace metals into freshwater environments can have wide reaching impacts on
535 the ecosystem. Increased nitrate, phosphate and sulfate are made available in melting
536 permafrost. High nutrient input and rapid fluctuations stress the aquatic ecosystem. Rapid

537 changes in toxic trace elements and nutrients into the environment will cause shifts in the
538 microbiome, and the trace organics and metal may impact the resistome – or presence of the
539 resistance genes (Colombo, et al., 2018).

540 There are evidences for the release of heavy metals and the consequential presence of AMR
541 (particularly metal). For example, strains of bacteria from permafrost soil samples in china
542 show Pb resistance, and Pb²⁺ biosorption (Li, et al., 2017). Environmental strains of
543 *Acinetobacter lwoffii* from permafrost contain genes for heavy metal resistance (including Cr,
544 As, Hg, Cu, Ni, Co, Zn); the chromosomal resistance genes were homologous to plasmid genes
545 found in *A. lwoffii* (Mindlin, et al., 2016). Mercury resistant bacteria were discovered in
546 permafrost near Kolyma, Canada (Petrova, et al., 2002).

547 While it is expected to have associated resistance traits to elevated metal concentrations,
548 there have been evidences of expanded spectrums. Viable bacteria found in Siberian permafrost
549 showed antibiotic and heavy metal resistance. Resistance is thought to be because of the harsh
550 conditions (constant freezing, poor nutrient availability, inorganic and organic inhibitors) the
551 strong selection pressure (Zhang, et al., 2013).

552 Microbes trapped in permafrost have been shown to have antibiotic resistance genes similar to
553 modern day bacteria (D'Costa, et al., 2011). Thawing ground ice and sediments can release
554 ancient resistant bacteria to the surface environment. There is little evidence to show that
555 increased organic matter is transported to aquatic environments, it instead likely remains in the
556 soil and saturated zones.

557

558 **5. Hydrological changes and legacy pollution**

559 Increased industrial activity in society is an inevitable and on-going process. With a
560 growing demand for goods and services, pristine and rural landscapes have become
561 transformed into urban centres with increased population densities, factories and

562 manufacturing. Other areas become exploited for natural resources (e.g., mining) and
563 exploration and/or generation of energy (e.g., oil and gas industries). Many European and
564 North American countries have experienced this Industrial Revolution during the 18th century;
565 many other countries throughout the world have recently undergone, or undergoing, their own
566 versions of revolution. Whilst development of industries and the technology became a period
567 of societal advancement, it was also inevitably the era of pollution, whereby-products of
568 anthropogenic activities and industry were released into the surrounding environment (Krishna,
569 2007; Reza1, et al., 2010) and became entrained into the soil and sediment layers as legacy
570 pollutants.

571 These legacy pollutants include a variety of potentially toxic elements (e.g., Pb, Cu, Cr,
572 Co, Ni, V and Zn), polycyclic aromatic hydrocarbons (Rodgers, et al., 2019), and bacteria
573 which have been released into sediments due to anthropogenic pollution (Krishna, et al., 2006).
574 Often, these contaminants that remain in the environment are rather recalcitrant, meaning either
575 they do not degrade or do so very slowly. Evidences have been found in recent studies, for
576 instance, Rodgers et al. (2018 and 2019) in the Clyde estuary (UK) highlight that a higher
577 legacy of anthropogenic activity can be found in sediments from historical industrialisation.
578 PCA analysis was used in this study to distinguish between natural and anthropogenic
579 contaminants to identify sites with high industrial depositions. Results indicate high levels of
580 heavy metals and PAHs present near heavily used industrial sites of the estuary, several of
581 which being pollution “hotspots”, indicating pollutant have accumulate over time. Sediment
582 quality were greatly diminished due to these inputs, and alterations in alkalinity and tides have
583 had little to no impact on the concentrations of PTEs present (Rodgers, et al., 2018).

584 Climate change can result in changes in the hydrological cycles, leading to consequential
585 changes in precipitation, water flow, and ultimately erosion of soils or scouring of sediments
586 (Krishna, et al., 2006). Pollutants, for example, captured into the sediment layers could become

587 increasingly more likely to become re-entrained into advective flows, becoming re-distributed
588 downstream creating an additional sources of pressure on environmental and public health.

589 There is not much evidence of risk with antimicrobial resistance resulting from changes
590 in hydrology, but the extent of their presence in the environment and their relation to pollution
591 has become increasingly known over the last few decades. The relationship between
592 environmental conditions and the development and dissemination do apply; the risks could be
593 hidden. We can postulate some scenarios where this may become problematic:

- 594 1. Polluted soils and sediments become a bioreactor for bacteria, subsequently enriching
595 resistance traits. Post-industrial sediments, as mentioned previously, are carriers of
596 adsorbed chemical pollutants that provide additional stress to the microorganisms. The
597 prolonged degradation and retarded release of the pollutant could provide a
598 concentration gradient of exposure, which could provide a wide range of stress
599 conditions, and varied bacterial responses. Populations *in situ* can either become
600 selected for resistance traits (*via* chemical toxicity), genetically modified (*via* increased
601 mutation and genetic selection), or experience increased horizontal genetic transfer.
- 602 2. Entombed in polluted sediments, the bacteria could be co-present at the time. When
603 reviewing the period of industrial revolution (in the UK), it was also the period of poor
604 sanitation and wastewater treatment. Sewage and bacteria were discharged into major
605 waterways that were also major industrial centre. In this case, pathogens associated
606 with human or agricultural disease are present in elevated numbers, and could likewise
607 experience the pollution stress. They then become stored, remaining dormant, in
608 sediment layers with their fully developed resistome.

609 Resulting from either scenario, polluted sediments, harbouring highly multi-drug
610 resistant and potentially pathogenic micro-organisms, become re-introduced into flowing water
611 (Allen, 1977). This creates a biological risk to agricultural, aqua-cultural and human health

612 downstream, as many industries are located on rivers and estuaries due to their necessity for a
613 water source.

614 The best evidence for this is a recent examination of the Clyde estuary where researchers
615 found chemical pollutant profiles in sediment (30-50 cm depths) that corresponded to past
616 pollutant events, especially in terms of zinc, copper and arsenic (Rodgers et al. 2019).
617 Examining the extracted DNA from the microbial communities obtained from slices of the
618 sediment cores, there was a corresponding elevation of antibiotic resistance genes for:
619 aminoglycosides, beta-lactams, FCA (fluoroquinolone, quinolone, chloramphenicol,
620 florfenicol and amphenicol resistance genes), MLSB (macrolide, lincosamide, streptogramin
621 B), tetracycline, vancomycin, sulphonamide, and efflux pumps; additionally genes associated
622 with transposons and integrons, which represent genetic transfer elements, were also increased
623 (Rodgers et al. 2018). Additionally, Tonner et al. (2019) successfully recovered viable isolates
624 from the deep sediment layers, consisting mostly of aquaculture pathogens: *Pseudomonas* spp.
625 and *Aeromonas* spp. resistant to several heavy metals (e.g., Zn, Cu, Cr) and antibiotics (e.g.,
626 many beta lactams).

627 Hydrology in this context refers to the nature of waterways (i.e., rivers, channels,
628 tributaries, and estuaries) and their natural flow pattern or regime near areas of industrial
629 legacy. Many of these areas, which have the continuous stress of variation in salinity and pH's,
630 have been exposed to a myriad of pollutant effluents affecting, one way or another, the presence
631 of bacterial pathogens and the character of their resistome.

632 Unfortunately, variations in the flow of waterways can become influenced by alteration
633 of the surrounding environment which can be triggered by climate change. The alterations can
634 disrupt soils and sediments and cause potentially pathogenic bacteria to be re-introduced into
635 in-stream processes. This leads to a decrease in the quality of the water in nearby sources such
636 as estuaries subsequently posing a potential threat to human health. In summation, it is

637 important to evaluate the health risks of post-industrial soils and waterways and their potential
638 risk to human life. The hazards of bacteria, which have developed from industrial legacies, are
639 yet to be fully understood.

640

641 **6. Summary**

642 Climate change represents a shift in the balance, and the outcomes and links are
643 complex—and rather difficult to predict. It can only be best speculated based on the indirect
644 results by the changes in the factors that may contribute to the development and dissemination
645 of resistance traits; changes in the chemical composition of the environment that may create
646 additional stress on the microorganisms (e.g., metals and polycyclic aromatic hydrocarbons);
647 changes in the character of the lithosphere (e.g., soils) and water; changes in human behaviour
648 (e.g., agriculture) and distribution; or the distribution of pathogens. One common theme that
649 may mitigate the impact of AMR would be (and currently is) the reduction of environmental
650 stress. Further research is needed to understand the microbiome, the resistome, and the impact
651 shifting environmental (e.g., chemical and temperature) stressors—these approaches could be
652 applied to agricultural wastes and soils, wastewater treatment, pathogens discharged into the
653 environment, and the evolution and dissemination upon exposure to ecological stress.

654

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