The evolution of bacterial pathogens in the Anthropocene

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Abstract

Humankind has become a primary driver of global environmental and climate change. The extent of planetary change is such that it has been proposed to classify the current geological age as the 'Anthropocene'. Anthropogenic environmental degradation presents numerous threats to human health and wellbeing, including an increased risk of infectious disease. This review focuses on how processes such as pollution, climate change and human-mediated dispersal could affect the evolution of bacterial pathogens. Effects of environmental change on the 'big five' of evolution: mutation rate, recombination (horizontal gene transfer), migration, selection and drift are discussed. Microplastic pollution is used as a case study to highlight the combined effects of some of these processes on the evolutionary diversification of human pathogens. Although the evidence is still incomplete, a picture is emerging that environmental pathogens could evolve at increased rates in the Anthropocene, with potential consequences for human infection.

Introduction

Human-induced climate change, ocean acidification, disruption of the nitrogen cycle, loss of natural habitats, the sixth mass extinction, myriad forms of environmental pollution and depletion of natural resources continue to result in unprecedented planetary change. To formally recognise the impact of man on the global climate and environment, it has been proposed to label the current epoch as the Anthropocene (Steffen et al., 2007) (Figure 1). The Anthropocene is not currently accepted as an official geological timescale, and its exact start (i.e. the 'atomic age', the industrial revolution or the agricultural revolution), or physical marker (i.e. radionuclides, black carbon, plastics or even chicken bones) are still under debate. However, as a concept it has captured the imagination of scientists and non-scientists alike. In addition to often irreversible damage to the natural environment, the Anthropocene also encapsulates major threats to human health and wellbeing, directly (e.g. through increasingly frequent extreme weather events) and indirectly (e.g. through shortages in food and water supplies) (Rockström et al., 2009; Whitmee et al., 2015).

How microbiome composition and function might change in the Anthropocene, and how in turn these changes are expected to affect other components of the biosphere has started to receive increasing attention (Cavicchioli et al., 2019; Gillings and Paulsen, 2014; Jansson and Hofmockel, 2019; Pointing et al., 2016). Microbes play essential roles in all geochemical cycles, including carbon sequestration and greenhouse gas emissions, and so they both affect- and are affected by- climate change (Cavicchioli et al., 2019). Microbial functioning underpins many other crucial processes as well, including ecosystem- and agricultural productivity, and plant-, animal- and human health (Cavicchioli et al., 2019). Climate change can be expected to positively affect pathogen abundance and thereby exposure risks. Higher temperatures result in increased growth rate and persistence in their native range, as well as the extension of geographic ranges (Lindgren et al., 2012). The increase in the frequency and severity of extreme weather events caused by climate change can also translate into an increased risk of human infection (Cavicchioli et al., 2019; Chen et al., 2014; Dayrit et al., 2018) (Table 1). For example, increased turbidity of surface

waters caused by climate change-induced increases in precipitation and deforestation reduces the potential for solar ultraviolet radiation to inactivate pathogens in surface waters (Williamson et al., 2017). Moreover, environmental pollution with biocides, metals and antibiotics results in increased selection and horizontal spread of antimicrobial resistance genes in pathogens (Wellington et al., 2013) making infections harder to treat. At the same time, there is a potential risk of environmental pollution impairing human immunity and the ability to withstand pathogens (Martin et al., 2010).

The ways in which environmental change can affect the ecology of pathogens is increasingly well-documented (Table 1). Much less is known about the effects of a rapidly changing planet on the evolutionary diversification of human pathogens, specifically those that reside in the environment. Although this topic has been expertly discussed previously, most notably by Gillings and co-workers (Gillings, 2017; Gillings and Paulsen, 2014; Gillings and Stokes, 2012; Zhu et al., 2017), a spate of recent studies justifies a new look at this important topic. As a general framework, the five main ‘ingredients’ of evolution will be discussed: mutation, recombination (of homologous as well as non-homologous DNA), migration, selection and genetic drift. The combined action of these evolutionary processes will be explored using a case study of human pathogens colonising plastic debris.

Mutation

A main mechanism of genetic change across the tree of life is mutation. In the best studied bacterium *E. coli*, genomes accumulate around one point mutation per thousand generations (Lee et al., 2012). Although data are still relatively sparse, mutation rates of other bacterial species seem to mostly deviate less than an order of magnitude from the *E. coli* rate (Lynch et al., 2016). How could anthropogenic global change influence bacterial mutation rate? Environmental stressors could result in increased replication errors and DNA damage, resulting in point mutations as well as insertions, deletions and transpositions (MacLean et al., 2013). It therefore can be hypothesised that bacteria in environments polluted with metals and xenobiotic

compounds could have elevated mutation rate, either transiently as a result of stress, or constitutively as mutators selected to adapt to a challenging environment. This is potentially important, as mutator phenotypes may confer an advantage in pathogenesis, allowing a faster response to host-imposed selection pressures (Labat et al., 2005). In addition, mutator strains can evolve antibiotic resistance more readily (Macià et al., 2011) and are able to more rapidly compensate for fitness costs associated with resistance (Perron et al., 2010). Environmental pollution is rife, extending to ecosystems far away from human habitation (Hauptmann et al., 2017), and is expected to positively interact with climate change due to processes such as increased runoff (Rodríguez et al., 2018). However, evidence for an effect of environmental pollution on bacterial mutation rate has been limited (Ilmjärv et al., 2017).

In theory, warming could elevate mutation rate through heat stress, but a recent mutation accumulation study in *E. coli* demonstrated that mutation rate effects are more likely to be mediated by elevated metabolic rate (Chu et al., 2018b). *E. coli* mutation rate was found to be significantly elevated at 37°C, the non-stressful host temperature, compared to 25°C and 28°C (Chu et al., 2018b). Interestingly, elevated temperatures were also associated with a higher proportion of mutations in coding versus non-coding DNA in this experiment (Chu et al., 2018b). Another experimental evolution study involving *E. coli* temperature adaptation found that different growth temperatures resulted in different genome-wide mutational patterns (Deatherage et al., 2017). However, temperature-specific ‘signature’ mutations were not necessarily primarily adaptive in their respective temperature regime and they tended to become less associated with temperature regime over time. Although these results are unlikely to reflect specific temperature adaptations, they do point at a possible more subtle effect of temperature change differentially shaping adaptive paths (Deatherage et al., 2017). The additive and interactive effects of demographic processes such as growth rate (Chu et al., 2018a), growth phase (Loewe et al., 2003), population density (Belavkin et al., 2014) as well as changes in the selective environment (Zhang et al., 2018) on bacterial mutation rates are highly complex. More

work is needed to elucidate the effects of warming on mutation, especially in the presence of chemical stressors.

Horizontal Gene Transfer (HGT)

Arguably a more pervasive force in the evolution of bacteria than vertically transmitted mutations are horizontal transmission events of DNA from other strains and species. Although HGT in bacteria is often represented to be mediated by three main mechanisms, conjugation, transduction and natural transformation, the boundaries between different mechanisms are not always clear-cut and other mechanisms exist too (Gillings, 2017). HGT mechanisms can be divided into a very broad category encompassing those mechanisms that rely on Mobile Genetic Elements (such as plasmids in conjugation and phages in transduction), and a much narrower category of mechanisms that don't (chiefly natural transformation). All HGT mechanisms can either transfer DNA that is homologous to the recipient's chromosome (i.e. representing novel or identical alleles) or transfer DNA that is non-homologous (representing novel genes). Different HGT mechanisms can act alongside each other in the same cell and can be up- or down regulated in response to environmental cues. Importantly, HGT events are likely to engender greater fitness effects than point mutations and could be just as frequent (Vos et al., 2015).

Anthropogenic effects on HGT are likely and varied (Gillings, 2017), especially as the cues determining when bacteria incorporate DNA from other cells are usually specific to the particular life-history of each species. For instance, natural transformation is in some species upregulated as the result of stress (including antibiotic-induced stress (Slager et al., 2014)), but in other species is upregulated as a result of favourable growth conditions (Seitz and Blokesch, 2012). HGT mediated by Mobile Genetic Elements (MGEs) such as plasmids is generally thought to be upregulated as a result of anthropogenic stressors such as antibiotics or metals. For instance, environmentally relevant concentrations of carbamazepine could be shown to increase the transfer of plasmids carrying antibiotic resistance genes within and across bacterial genera (Wang et al., 2019). In another study, bacteria grown in compost amended with metals were

shown to be more permissive to taking up new plasmids (Klümper et al., 2019). However, in one experiment where a strain with a plasmid containing a gene conferring mercury resistance was co-cultured with the same strain lacking this plasmid, the plasmid was found to only spread to the recipient strain in mercury-free media. In the presence of mercury, the recipient was killed before it could receive the resistance plasmid, leaving the donor strain to clonally expand to fixation (Stevenson et al., 2017). This finding thus highlights the context-dependence of the drivers and benefits of HGT.

Migration

Increases in average temperature result in geographic range shifts of (sub)tropical pathogen species (both vector-borne and free-living) towards temperate climes (Table 1). Bacterial distributions can expand relatively rapidly as long-distance migration is aided by ocean- (Hellweger et al., 2014) and air- (Maki et al., 2019) currents, with dust storms especially known to transport pathogens (Soleimani et al., 2019). Increased human-mediated dispersal of bacteria is evident (Zhu et al., 2017) and even taken into consideration as a concern for spaceflight (Nicholson et al., 2005). Long-range dispersal of bacterial pathogens occurred historically through human migration and trade (e.g. (Pepperell et al., 2011)), but presently also occurs as a by-product of the release of invasive species (e.g. (Hayman et al., 2013)), humanitarian operations (e.g. (Frerichs et al., 2012)) and tourism (Schwartz and Morris, 2018). Climate change and human dispersal could act in tandem to alter bacterial migration routes; there is evidence that both the release by ballast water (e.g. (McCarthy and Khambaty, 1994)) and El Niño events have facilitated the intercontinental spread of *Vibrio cholerae* (Martinez-Urtaza et al., 2016).

Migration does not only introduce species to new habitats, it also introduces variants that have evolved in one population into another population, and by doing so, like mutation and HGT, it can speed up adaptive evolution (Morgan et al., 2005). The repeated transport of bacteria from source populations in endemic regions to populations at the edge of this range (or from ancestral niches to novel (host) niches) could aid the evolution of bacterial virulence (Sokurenko et al.,

2006) and antibiotic resistance (Perron et al., 2007) by increasing both population size and genetic variation. The possible effects of migration rates on bacterial evolution in ‘the age of Boeing’ (Cohan and Perry, 2007) has been contemplated for some time, but has truly taken off with the advent of genome-sequencing (e.g. (Domman et al., 2017)). A recent population genomics study demonstrated that the marine pathogen *Vibrio parahaemolyticus* is subdivided into four main geographical populations (Yang et al., 2019a). The Asian population (VppAsia) is not restricted to Asia but is also found in other continents. This study could demonstrate that VppAsia strains in North America had taken up genetic material from local *V. parahaemolyticus* strains. It was possible to estimate that the timescale at which this genetic import has taken place was between 35 to 129 years ago using molecular clock-based methods (Yang et al., 2019a).

Selection and drift

The previous sections described the processes generating genetic variation. The evolutionary fate of this variation is determined by the relative importance of non-random selection and random genetic drift. Natural selection on bacterial pathogens in the context of anthropogenic change can be viewed in three distinct ways. First, anthropogenic pressures can alter the targets of natural selection. An obvious example of this process is increased selection on antibiotic resistance genes through the misuse and overuse of antimicrobials (O'Neill, 2015). As this topic has received considerable attention elsewhere, it will not be discussed here. Second, anthropogenic change can select for greater evolvability. ‘Second-order selection’ (Díaz Arenas and Cooper, 2013) describes selection for mechanisms that generate variation (mutation and HGT) in order to facilitate selection. Some examples have been mentioned above but for an in-depth treatise of the possible effects of anthropogenic pollution on mutation rate and (non)homologous recombination rate see (Gillings, 2017; Gillings and Stokes, 2012).

Third, anthropogenic change could alter the efficiency of selection through changes in population size and structure. Apart from the selective benefit of a new genetic change, the speed at which adaptive evolution occurs is crucially dependent on the effective population size (N_e). N_e

is an important quantity in population genetics representing an idealised population where every individual has the same chance to contribute to the next generation. A larger N_e decreases the importance of random genetic drift and increases the efficacy of selection. The N_e of some environmental pathogens could potentially increase due to an increase in the actual (census) population size, for instance through a positive correlation between temperature on one hand and growth, persistence and range size on the other. In addition, increased migration will erode population substructure and increase N_e . However, N_e could also decrease in some species with a decrease in census population size. Decreases in bacterial population sizes have been well-documented in some taxa as the result of agricultural land management (Clegg et al., 2003; Fierer et al., 2013). Some bacterial species might even go extinct (Louca et al., 2018), especially when they are strongly associated with hosts (Weinbauer and Rassoulzadegan, 2007). However, the effects of anthropogenic disturbance on census and effective population sizes of bacterial species have received little attention. Molecular approaches quantifying both total cell number and actively dividing cells (contributing to the next generation) could potentially be developed to gain a better understanding of effective population sizes in bacteria.

Case Study: the plastisphere

To illustrate one potential hotspot for bacterial pathogen evolution in the Anthropocene this section will discuss the ‘plastisphere’, or the microbial communities on plastic debris (Zettler et al., 2013) (Figure 2). Although plastic mass-production only started after WWII, plastics have so profoundly influenced human society that it is hard to imagine a world without them. However, the low cost of production and durability that have made plastic such a success, also have the downside of resulting in ubiquitous and long-lived waste. A 2017 study estimated that the total amount of plastic in landfills and the environment is 6300 million metric tonnes (Mt), predicted to increase to 12,000 Mt in 2050 (Geyer et al., 2017). Plastic waste eventually breaks down into smaller fragments (of which the <5 mm fraction is classified as microplastics and the <1 μ fraction is classified as nanoplastics (Gigault et al., 2018)) and is readily colonized by microbes from the

surrounding environment (Harrison et al., 2014). Colonization is not random, with certain taxa being overrepresented in biofilms on plastics compared to free-living bacteria in the surrounding environment (Amaral-Zettler et al., 2020; Dussud et al., 2018). Pathogens, both genera associated with faecal contamination (Silva et al., 2019) as well as free-living bacterial genera often associated with pathogenicity such as *Pseudomonas* (Wu et al., 2019), *Vibrio* (Kirstein et al., 2016) and *Aeromonas* (Viršek et al., 2017), have been found attached to microplastics. Pathogens have been found to be overrepresented on plastics compared to the surrounding water (Yang et al., 2020). Furthermore, plastisphere communities have been identified as a reservoir for metal- and antibiotic resistance genes (Wu et al., 2019; Yang et al., 2020; Yang et al., 2019b).

Multispecies biofilms are known to promote HGT between bacteria (Antonova and Hammer, 2011), and microplastic-associated biofilms could therefore serve as HGT hotspots. One study testing this hypothesis indeed found that the uptake of a donor plasmid by lake bacteria was elevated in cells colonising microplastics compared to those in the water column (Arias-Andres et al., 2018). The authors of this study estimate that the horizontal transfer of antibiotic resistance genes could be elevated by many orders of magnitude as the result of pollution with microplastics.

Plastics adsorb chemicals from the surrounding environment, including pesticides (Camacho et al., 2019), metals (Brennecke et al., 2016) and antimicrobials (Fang et al., 2019), and plastisphere biofilms could further promote contaminant accumulation (Wolfaardt et al., 1994). Locally elevated concentrations of selective agents combined with colonising bacteria could potentially facilitate resistance evolution on plastics, but to the author's knowledge no data are available on this process yet. While many plastisphere studies employ 16S rDNA sequencing, they often lack resolution to identify specific pathogenic species. A culture-based study could detect known pathogenic *Vibrio* species on microplastics sampled from the North Sea and Baltic Sea (Kirstein et al., 2016). Enrichment of pathogens on plastics followed by long-range dispersal suggests it is possible that existing population structures of free-living pathogens could be impacted through HGT (as discussed above for the *Vibrio parahaemolyticus* study). Humans can

be exposed to bacteria attached to microplastics through ingestion of bathing- or drinking water or consumption of seafood (Keswani et al., 2016; Smith et al., 2018). However, based on the available data, it could be argued that microplastics might be more significant to human health by accelerating pathogen evolution (Figure 2) than that they are as an actual route of exposure to pathogens.

Conclusion

This review explored some of the diverse effects of anthropogenic change on the basic processes shaping the evolution of bacterial pathogens in the environment. Although the evidence is incomplete and mixed, it is likely that increased temperature and pollution could result in increased evolutionary diversification. Increased dispersal, globally but also locally (specifically through contact between human microbiomes (sewage), agricultural microbiomes (sludge and run-off) and aquatic and terrestrial microbiomes), is of special concern (Zhu et al., 2017). As the frequency of HGT is to a large part governed by a shared ecology (Beiko et al., 2005; Smillie et al., 2011), such mixing will lead to HGT between species that would otherwise not have been in contact, potentially giving rise to more virulent and resistant pathogens (Gillings and Stokes, 2012). Effects on selection through changes in population size and structure are largely unknown but potentially significant.

Importantly, many of the ways in which anthropogenic planetary change can affect bacterial evolution have only just begun to be identified. An example of such a recent discovery is that high CO₂ concentrations can increase levels of plasmid uptake in *E. coli* (Liao et al., 2019a, b). Another example is the finding that mutation rate decreased with decreasing pH in the marine bacterium *Vibrio shilonii* (Strauss et al., 2017). Although in both laboratory studies biological effects were found under conditions well outside those predicted for real-world scenarios, it is a reminder that unanticipated effects of anthropogenic change on pathogen evolution are likely.

Lastly, it is important to realise that species do not evolve in isolation, which is especially true for bacteria which almost always live in highly diverse communities. Evolutionary changes

in one species are likely to affect other species through co-evolutionary dynamics (Padfield et al., 2020), adding another layer of complexity which has not yet received much attention. It is evident there is an urgent need for research designed to uncover the diverse and sometimes unexpected ways in which anthropogenic change can affect the evolution of bacterial pathogens. Such studies will be crucial to mitigate future disease risk.

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Figure Legends

Figure 1: Planetary history and near future represented on a log-scale axis. The log-scale allows plotting of events in deep geological time, pre-historical time, historical time, the present and the future. Selected key events in evolutionary- and human history are indicated. The Industrial Revolution is here taken as the starting point of the Anthropocene. RCP 8.5= Representative Concentration Pathway delivering global warming at an average of 8.5 watts per square meter across the planet, resulting in a temperature increase of about 4.3°C by 2100 relative to pre-industrial time. The logscale representation of planetary history was inspired by jeff smith (<http://matryoshka.org/>).

Figure 2: Observed and hypothesised effects of the plastisphere on the evolution of bacterial pathogens in the marine environment. 1= Schematic representation of a marine planktonic community (blue cells). 2= Anthropogenic pollution results in an influx of terrestrial and host-associated community members into the marine environment (yellow cells), and potentially higher densities due to increased temperature and nutrient levels. 3= A subset of taxa, including pathogens and antibiotic resistant bacteria, form biofilms on microplastics (round cells). 4= Sorption of antimicrobial pollutants (red dots) could lead to locally elevated concentrations and more effective selection for resistance on plastics. 5= HGT rates can be elevated on plastics resulting in cells with novel gene combinations (blue and yellow cells). 6= plastics can act as vectors, transporting plastisphere communities to different environments and communities (green cells).