Climate change and antibiotic resistance: a deadly combination

Jason P. Burnham

Abstract: Climate change is driven primarily by humanity’s use of fossil fuels and the resultant greenhouse gases from their combustion. The effects of climate change on human health are myriad and becomingly increasingly severe as the pace of climate change accelerates. One relatively underreported intersection between health and climate change is that of infections, particularly antibiotic-resistant infections. In this perspective review, the aspects of climate change that have already, will, and could possibly impact the proliferation and dissemination of antibiotic resistance are discussed.

Keywords: Climate change, antibiotic resistance, antimicrobial resistance

Introduction
The world is in the midst of an anthropogenic climate crisis, with implications for the survival of humanity and millions of other species of life on Earth. Climate change is directly linked to human morbidity and mortality, and healthcare itself has a large carbon footprint which urgently needs to be corrected.1–3 However, the primary drivers of climate change are greenhouse gas emissions from fossil fuel use. In addition to being an issue of human health, climate change is an issue of social justice, with marginalized groups at highest risk of experiencing the negative effects of climate change while contributing a relative paucity of greenhouse gas emissions (the wealthiest 10% of the population are responsible for 52% of all carbon emissions).4

Regardless of its etiology, climate change has already and will continue to affect human health, likely in increasingly drastic and severe ways.5 Examples of the effects of climate change on human health include heat-related mortality, food insecurity and reduced crop yields, increased suitability for infectious diseases transmission, rising sea levels, cardiovascular morbidity, mortality from increasingly severe wildfires, and the myriad health effects resulting from other extreme weather events such as floods and droughts.5 These changes will be felt hardest by marginalized groups, including those in low- and middle-income countries and persons from non-White racial backgrounds and/or with low socioeconomic status, that is, climate change is a social justice issue.5

One of the essential pillars that holds up the functionality of our current healthcare system is the availability of effective antibiotics for bacterial infections. Without effective antibiotics, surgeries, cancer treatment, organ transplantation, and community-acquired infections could be fatal, resulting in millions of additional lives lost annually. In addition, some of the gains in childhood survival because of antibiotic availability of effective antibiotics for respiratory infections would be washed away. With the changing climate, this situation will be pushed closer to a breaking point because, as we will demonstrate, climate change and antibiotic resistance are intimately linked. This paper will discuss observations of some of these phenomena already occurring, those that are likely to occur, and those that are possible as the status quo maintainers of the world continue to fail to rise to the challenge of climate change.

Heat and antibiotic resistance
Temperature is intimately linked with bacterial processes and infections.6 Horizontal gene transfer, a major mechanism for the acquisition of
antibiotic resistance, is increased by increasing temperatures. In addition, increases in temperature generally increase bacterial growth rates.7

There is significant evidence that bacterial infection rates are associated with increases in temperature, a discussion of which follows. An international study of 22 cities found that distance from the equator and socioeconomic factors were both associated with risk of Gram-negative bacte-remia.8 Fewer antibiotic-susceptible Acinetobacter infections occur during winter months.9 Another study found that humidity, monthly precipitation, and temperature were all correlated with rates of Gram-negative bloodstream infections in hospitalized patients.10

For the diagnosis of cellulitis, a dose–response relationship between incidence and temperature has been found.11 Similarly, there was a dose–response relationship between hospital admissions due to urinary tract infections and temperature.12 The relationship between temperature and infection rate holds true also for surgical site infections after knee and hip arthroplasty,13 Legionnaire’s disease,14 and other types of surgical site infections.15

Not only are infection rates increased by temperature, antibiotic resistance is associated with increased temperatures. Increasing local temperature and population density both lead to increased rates of antibiotic resistance.16 The relationship between temperature and population density was true for the ubiquitous pathogens Escherichia coli, Klebsiella pneumoniae, and Staphylococcus aureus.16 MacFadden et al. found that the increases in antibiotic resistance were associated with average minimum temperature,16 a value which has been on the rise due to climate change.17 The combination of increased numbers of infections and increasingly antibiotic-resistant pathogens will inevitably lead to more and more antibiotic-resistant pathogens as climate change worsens.

Now we move to one of the most important diarrheal pathogens globally, Salmonella. Heat and humidity both increase rates of salmonellosis,18 which is becoming increasingly antibiotic resistant. In addition, poultry intestinal colonization by Salmonella is increased by heat stress.19 With millions of global cases, the combination of increased case numbers, increased colonization rates in animals, and increasing antibiotic resistance, climate change has the potential to increase significantly the burden and morbidity from salmonellosis worldwide.

Another underexplored consequence of higher temperatures is the effect it will have on human behavior, including prescribers, as higher temperatures increase irritability and reduce critical thinking.20,21 Telemedicine, increasingly used for all types of medical encounters because of the COVID-19 pandemic, has been associated with increased unnecessary antibiotic prescriptions (visits unrelated to the COVID-19 pandemic), which may be a result of time pressure as visits are shorter when antibiotics are prescribed and patients are more satisfied.22,23 As increased use of unnecessary antibiotics and local prescribing practices are known risk factors for antibiotic resistance,16 the association between temperature and behavior could have significant ramifications.

Disasters and infections
As the climate warms, the capacity of the atmosphere to hold water increases exponentially, meaning storms will be more severe and come with more precipitation. More precipitation leads to flooding, flood-related infections, population displacement, refugees, and overcrowding. Overcrowding is associated with increases in infection rates.24–27 Flooding can result in the spread of waterborne infections because of the overflowing of contaminated water from sewage lines or contamination by livestock.

Nitrogen fertilizers increase antibiotic resistance28 and therefore, floodwater pollution by nitrogen fertilizers during severe flooding due to climate change will increase antibiotic resistance. Eutrophication, which can be worsened by flooding, increases antibiotic resistance and can lead to dissemination of resistant pathogens and antibiotic-resistance genes.29 Extreme weather events resulting in flooding will more strongly disrupt weak sanitation infrastructure, increase crowding in already crowded areas, and spread antibiotic resistance from dissemination of sewage, a known reservoir for antibiotic-resistance genes.30 With dissemination of antibiotic resistance, progressive use of...
broad-spectrum antibiotics will be required, resulting in a fatal cycle of the promotion of antibiotic resistance and its spread.

Pollution and antibiotic resistance
More and more intense precipitation will lead to increased runoff and inevitably higher levels of pollution in our water. Pollutants are known to induce expression of antibiotic-resistance genes and bacterial mutagenesis. Increased agricultural runoff (i.e. eutrophication from fertilizers) will increase bacterial blooms in water systems and high concentrations of bacteria will increase opportunities for transfer of antibiotic-resistance genes.

Pollutants, including heavy metals from manufacturing and industrial practices, can be disseminated into the environment with flooding, which will become more severe with the extreme weather events precipitated by climate change. As metals in soil are known to increase antibiotic resistance, this process will result in the dissemination of antibiotic resistance.

Antibiotic resistance, waterborne infections, and sanitation
In addition to flooding discussed above, extreme weather events will lead to drought in some areas. Water scarcity during droughts leads to reductions in sanitation and higher densities of people sharing the same water source. With crowding and shared water, waterborne infections are primed for explosive outbreaks. Water and food scarcity run hand in hand, which could result in poorer nutrition on top of increased diarrheal diseases. Children’s risk of acquiring antibiotic-resistant enteric pathogens is affected by malnutrition, crowding, and poor sanitation. Inevitably this will lead to more severe diarrhea and higher mortality rates, particularly with higher rates of antibiotic resistance preventing the administration of effective therapy.

Microplastics increase gene exchange in bacteria in water sources, which could lead to increased dissemination of antibiotic resistance. As the climate warms, one can envision a nightmare scenario in which Vibrio species increase in prevalence and range due to oceanic warming, become more antibiotic resistant due to microplastics, and lead to outbreaks of antibiotic-resistant cholera and necrotizing fasciitis.

Downstream (indirect) antibiotic resistance
As the climate changes, bacterial and viral infections will be impacted (Table 1). Vector habitats will expand, leading to increased numbers of vector-borne infections. Higher temperatures also increase insect vector activity. Drought leads to elimination of mosquito predators, allowing them to multiply unhindered in the residual pools of stagnant water. With exposure of previously naïve populations, there will be increases in the number of hospital admissions from vector-borne diseases. The result of increased hospitalizations, particularly for those with severe illness requiring intensive care, will be more days with invasive devices and hospital-acquired infections, which are often antibiotic resistant. In addition, patients with critical illness are more likely to be discharged to nursing homes or rehabilitation facilities, which are breeding grounds for antibiotic resistance. Increased throughput through this pathway (i.e. from vector-borne diseases) could result in more antibiotic-resistant infections. The population at risk for vector-borne diseases as a result of climate change is only expected to increase, with estimates of 500 million more people at risk by 2050.

As the range of malaria vectors increases, more persons will acquire the infection, again in persons who are previously naïve and have a higher chance of severe infections (and downstream hospital-acquired infections). With expanding vector range, the areas where antimalarial resistance has been relatively contained will extend and spread, increasing the global burden of antimalarial agent resistance. In malaria-endemic areas with greater than average rainfall due to climate change, there may be increased opportunities for mosquito proliferation due to increased standing water. Climate change has already resulted in the spread of malaria to places previously not endemic.

Another form of antimicrobial resistance related to climate change that is worth mentioning is tuberculosis. Crowding increases transmission rates of tuberculosis and with climate refugees and increased population density/crowding inevitably there will be increased spread of antibiotic-resistant tuberculosis. The co-occurrence of poverty, antibiotic-resistant tuberculosis, and
lack of access to medical care and diagnostics could potentially result in a huge outbreak of antibiotic-resistant tuberculosis. Regarding antibiotic-resistant tuberculosis, one study found that reduced humidity (which could occur in areas affected by climate-induced drought), had higher rates of antibiotic-resistant tuberculosis. In addition to aiding the spread of tuberculosis, population density is associated with antibiotic resistance in other organisms.

As a result of climate change, some areas will have more rainfall, whereas others will have more drought, and with drought, wildfires. In addition to human casualties and the loss of biodiversity from massive wildfires, respiratory problems will occur in survivors. A substantial body of evidence demonstrates that particulate counts result in increased cardiovascular morbidity and mortality both in the short term and the long term. In addition, direct exposure to fire can result in permanent lung-scarring and lead to bronchiectasis. Patients with bronchiectasis are known to harbor antibiotic-resistant infections bacteria and to have multiple infections/exacerbations, another tributary to the common final pathway linking climate change with antibiotic resistance.

As climate change creates a resource bottleneck, farming and livestock producers will be increasingly pressured to maximize their crop and animal yields. In the past, this has often been achieved with antibiotics. Though by no means is unnecessary antibiotic use in farming/livestock a thing of the past, pressured resources could cause resurgence and increase dissemination of antibiotic resistance within ecosystems.

Lastly, to touch on the COVID-19 pandemic. Climate change increasingly brings humans and animals into contact and has and will continue to result in outbreaks of zoonotic and vector-borne diseases with pandemic potential. With the pandemic, we have seen shortages of personal protective equipment and resultant increases in hospital-acquired infections. As diseases continue to emerge and potentially overlap, these shortages and resultant increases in hospital-acquired infections (which tend to be antibiotic resistant) will only increase. As to the effects of climate on COVID-19 outcomes, the data are mixed, with some studies showing effects of temperature on mortality and others finding no association. However, climate change, with its concomitant extreme weather events and particulate matter pollution, contributes to cardiopulmonary morbidity, a known risk factor for poor COVID-19 outcomes. Regardless of the nature of the interaction, because of its ubiquity, climate change is likely to affect the COVID-19 pandemic and its victims.

### Conclusion
Climate change is a social justice issue and its unmitigated progression will disproportionately affect the health and well-being of persons in low- and middle-income countries across the globe. In this time, we must take action at every level to reverse the tide of impending climate disaster. There is no fitness cost to bacteria of being antibiotic resistant and therefore, we must prevent antibiotic resistance due to climate change now, rather than try to fix it later. Antibiotic resistance and climate change are intimately linked and as a profession we have a duty to address both to protect the health of our patients and our planet.

### Conflict of interest statement
The author declares that there is no conflict of interest.

### Funding
The author received no financial support for the research, authorship, and/or publication of this article.
References

1. Chung JW and Meltzer DO. Estimate of the carbon footprint of the US health care sector. *JAMA* 2009; 302: 1970–1972.

2. Lenzen M, Malik A, Li M, et al. The environmental footprint of healthcare: a global assessment. *Lancet Planet Health* 2020; 4: e271–e279.

3. Eckelman MJ and Sherman JD. Estimated global disease burden from US health care sector greenhouse gas emissions. *Am J Public Health* 2018; 108: S120–S122.

4. Gore T. Confronting carbon inequality [press release]. Oxfam International, 2020.

5. Watts N, Amann M, Arnell N, et al. The 2020 report of the lancet countdown on health and climate change: responding to converging crises. *Lancet* 2020; 397: 129–170.

6. Philipborn R, Ahmed SM, Brosi BJ, et al. Climatic drivers of diarrheagenic Escherichia coli incidence: a systematic review and meta-analysis. *J Infect Dis* 2016; 214: 6–15.

7. Pietikäinen J, Pettersson M and Bååth E. Comparison of temperature effects on soil respiration and bacterial and fungal growth rates. *FEMS Microbiol Ecol* 2005; 52: 49–58.

8. Fisman D, Patrozou E, Carmeli Y, et al. Geographical variability in the likelihood of bloodstream infections due to gram-negative bacteria: correlation with proximity to the equator and health care expenditure. *PLoS One* 2014; 9: e114548.

9. Burnham JP, Feldman MF and Calix JJ. Seasonal changes in the prevalence of antibiotic-susceptible Acinetobacter calcoaceticus-baumannii complex isolates result in increased multidrug resistance rates during winter months. *Open Forum Infect Dis* 2019; 6: ofz245.

10. Eber MR, Shardell M, Schweizer ML, et al. Seasonal and temperature-associated increases in gram-negative bacterial bloodstream infections among hospitalized patients. *PLoS One* 2011; 6: e25298.

11. Peterson RA, Polgreen LA, Sewell DK, et al. Warmer weather as a risk factor for cellulitis: a population-based investigation. *Clin Infect Dis* 2017; 65: 1167–1173.

12. Simmering JE, Cavanaugh JE, Polgreen LA, et al. Warmer weather as a risk factor for hospitalisations due to urinary tract infections. *Epidemiol Infect* 2018; 146: 386–393.

13. Anthony CA, Peterson RA, Sewell DK, et al. The seasonal variability of surgical site infections in knee and hip arthroplasty. *J Arthroplasty* 2018; 33: 510–514.e1.

14. Simmering JE, Polgreen LA, Hornick DB, et al. Weather-dependent risk for Legionnaires’ disease, United States. *Emerg Infect Dis* 2017; 23: 1843–1851.

15. Anthony CA, Peterson RA, Polgreen LA, et al. The seasonal variability in surgical site infections and the association with warmer weather: a population-based investigation. *Infect Control Hosp Epidemiol* 2017; 38: 809–816.

16. MacFadden DR, McGough SF, Fisman D, et al. Antibiotic resistance increases with local temperature. *Nat Clim Chang* 2018; 8: 510–514.

17. National Centers for Environmental Information. Assessing the U.S. climate in August 2018, https://www.ncei.noaa.gov/news/national-climate-201808 (2018).

18. Aik J, Heywood AE, Newall AT, et al. Climate variability and salmonellosis in Singapore – a time series analysis. *Sci Total Environ* 2018; 639: 1261–1267.

19. Farag MR and Alagawany M. Physiological alterations of poultry to the high environmental temperature. *J Therm Biol* 2018; 76: 101–106.

20. Hsiang SM, Burke M and Miguel E. Quantifying the influence of climate on human conflict. *Science* 2013; 341: 1235367.

21. Veilleux JC, Zielinski MJ, Moyen NE, et al. The effect of passive heat stress on distress and self-control in male smokers and non-smokers. *J Gen Psychol* 2018; 145: 342–361.

22. Martinez KA, Rood M, Jhangiani N, et al. Antibiotic prescribing for respiratory tract infections and encounter length: an observational study of telemedicine. *Ann Intern Med* 2019; 170: 275–277.

23. Foster CB, Martinez KA, Sabella C, et al. Patient satisfaction and antibiotic prescribing for respiratory infections by telemedicine. *Pediatrics* 2019; 144: e20190844.

24. Vieira MT, Marlow MA, Aguiar-Alves F, et al. Living conditions as a driving factor in persistent methicillin-resistant Staphylococcus aureus colonization among HIV-infected youth. *Pediatr Infect Dis J* 2016; 35: 1126–1131.
25. Immergluck LC, Leong T, Malhotra K, et al. Geographic surveillance of community associated MRSA infections in children using electronic health record data. *BMC Infect Dis* 2019; 19: 170.

26. Blakiston MR and Freeman JT. Population-level exposures associated with MRSA and ESBL-E. coli infection across district health boards in Aotearoa New Zealand: an ecological study. *N Z Med J* 2020; 133: 62–69.

27. Cardoso MR, Cousens SN, de Góes Siqueira LF, et al. Correlates of multi-drug non-susceptibility in enteric bacteria isolated from Kenyan children with acute diarrhea. *PLoS Negl Trop Dis* 2017; 11: e0005974.

28. Forsberg KJ, Patel S, Gibson MK, et al. Bacterial phylogeny structures soil resistomes across habitats. *Nature* 2014; 509: 612–616.

29. Li XD, Chen YH, Liu C, et al. Eutrophication and related antibiotic resistance of enterococci in the Minjiang river, China. *Microb Ecol* 2020; 80: 1–13.

30. Karkman A, Do TT, Walsh F, et al. Antibiotic-resistance genes in waste water. *Trends Microbiol* 2018; 26: 220–228.

31. Chen J, McIlroy SE, Archana A, et al. A pollution gradient contributes to the taxonomic, functional, and resistome diversity of microbial communities in marine sediments. *Microbiome* 2019; 7: 104.

32. Coates-Marnane J, Olley J, Burton J, et al. The impact of a high magnitude flood on metal pollution in a shallow subtropical estuarine embayment. *Sci Total Environ* 2016; 569–570: 716–731.

33. Knapp CW, McCluskey SM, Singh BK, et al. Antibiotic resistance gene abundances correlate with metal and geochemical conditions in archived Scottish soils. *PLoS One* 2011; 6: e27300.

34. Seiler C and Berendonk TU. Heavy metal driven co-selection of antibiotic resistance in soil and water bodies impacted by agriculture and aquaculture. *Front Microbiol* 2012; 3: 399.

35. Van Huynh C, van Scheltinga CT, Pham TH, et al. Drought and conflicts at the local level: establishing a water sharing mechanism for the summer-autumn rice production in Central Vietnam. *Int Soil Water Conserv Res* 2019; 7: 362–375.

36. Brander RL, Watson JL, John-Stewart GC, et al. Correlates of multi-drug non-susceptibility in enteric bacteria isolated from Kenyan children with acute diarrhea. *PLoS Negl Trop Dis* 2017; 11: e0005974.

37. Arias-Andres M, Klümper U, Rojas-Jimenez K, et al. Microplastic pollution increases gene exchange in aquatic ecosystems. *Environ Pollut* 2018; 237: 253–261.

38. Logar-Henderson C, Ling R, Tuite AR, et al. Effects of large-scale oceanic phenomena on non-cholera vibriosis incidence in the United States: implications for climate change. *Epidemiol Infect* 2019; 147: e243.

39. Estallo EL, Ludueña-Almeida FF, Introini MV, et al. Weather variability associated with Aedes (stegomyia) aegypti (Dengue vector) oviposition dynamics in Northwestern Argentina. *PLoS One* 2015; 10: e0127820.

40. Chase JM and Knight TM. Drought-induced mosquito outbreaks in wetlands. *Ecol Lett* 2003; 6: 1017–1024.

41. Chamchod F and Ruan S. Modeling methicillin-resistant Staphylococcus aureus in hospitals: transmission dynamics, antibiotic usage and its history. *Theor Biol Med Model* 2012; 9: 25.

42. Ryan SJ, Carlson CJ, Mordecai EA, et al. Global expansion and redistribution of Aedes-borne virus transmission risk with climate change. *PLoS Negl Trop Dis* 2019; 13: e0007213.

43. Lafterty KD. The ecology of climate change and infectious diseases. *Ecology* 2009; 90: 888–900.

44. Clark M, Riben P and Nowgesic E. The association of housing density, isolation and tuberculosis in Canadian First Nations communities. *Int J Epidemiol* 2002; 31: 940–945.

45. Liu YX, Pang CK, Liu Y, et al. Association between multidrug-resistant tuberculosis and risk factors in China: applying partial least squares path modeling. *PLoS One* 2015; 10: e0128298.

46. Bruinsma N, Hutchinson JM, van den Bogaard AE, et al. Influence of population density on antibiotic resistance. *J Antimicrob Chemother* 2003; 51: 385–390.

47. Tapia V, Steenland K, Vu B, et al. PM$_{2.5}$ exposure on daily cardio-respiratory mortality in Lima, Peru, from 2010 to 2016. *Environ Health* 2020; 19: 63.

48. Yap J, Ng Y, Yeo KK, et al. Particulate air pollution on cardiovascular mortality in the tropics: impact on the elderly. *Environ Health* 2019; 18: 34.

49. Du Y, Xu X, Chu M, et al. Air particulate matter and cardiovascular disease: the epidemiological, biomedical and clinical evidence. *J Thorac Dis* 2016; 8: E8–E19.
50. Imam JS and Duarte AG. Non-CF bronchiectasis: orphan disease no longer. *Respir Med* 2020; 166: 105940.

51. Mac Aogáin M, Lau KJX, Cai Z, *et al.* Metagenomics reveals a core macrolide resistome related to microbiota in chronic respiratory disease. *Am J Respir Crit Care Med* 2020; 202: 433–447.

52. McMullen KM, Smith BA and Rebmann T. Impact of SARS-CoV-2 on hospital acquired infection rates in the United States: predictions and early results. *Am J Infect Control* 2020; 48: 1409–1411.

53. Rahman M, Islam M, Shimanto MH, *et al.* A global analysis on the effect of temperature, socio-economic and environmental factors on the spread and mortality rate of the COVID-19 pandemic. *Environ Dev Sustain.* Epub ahead of print 6 October 2020. DOI: 10.1007/s10668-020-01028-x.

54. Jamshidi S, Baniasad M and Niyogi D. Global to USA county scale analysis of weather, urban density, mobility, homestay, and mask use on COVID-19. *Int J Environ Res Public Health* 2020; 17: 7847.

55. Islam A, Hasanuzzaman M, Azad MAK, *et al.* Effect of meteorological factors on COVID-19 cases in Bangladesh. *EnvironDev Sustain.* Epub ahead of print 8 October 2020. DOI: 10.1007/s10668-020-01016-1.

56. Meo SA, Abukhalaf AA, Alomar AA, *et al.* Effect of heat and humidity on the incidence and mortality due to COVID-19 pandemic in European countries. *Eur Rev Med Pharmacol Sci* 2020; 24: 9216–9225.

57. Holmes AH, Moore LS, Sundsfjord A, *et al.* Understanding the mechanisms and drivers of antimicrobial resistance. *Lancet* 2016; 387: 176–187.