Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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there may be mechanisms that allow private communication and exchanges.

The example of the Bacteroides cooperation study, in which the nature of interactions between individual microbes are worked out in culture and then in vivo is emblematic of the kind of bottom-up approach that will be necessary if we are to understand microbiomes in any detail. Another successful example of this approach was recently seen in a study where researchers were able to identify a consortium of four defined microbes that were sufficient to populate the mouse GI tract and prevent colonization by vancomycin-resistant Enterococcus, which is a common cause of infection in healthcare settings (Kim et al. (2019) Nature 572, 665–669). The researchers found that one of the species in the consortium secreted an antimicrobial molecule called a lantibiotic that inhibited the growth of Enterococcus. The other strains help the lantibiotic-producing bacterium to colonize the gut. Interestingly, they found that the amount of the lantibiotic gene in stool samples from patients predicted their chances of developing an Enterococcus infection. Indeed, patient stool samples with high amounts of the lantibiotic gene protected against Enterococcus infection when transplanted into the mouse gut. Together, the results suggest that more rigorous approaches could resurrect both the fecal transplant and probiotic approaches, yielding effective therapies.

Embracing reductionism
The trajectory of the gut microbiome field is similar to other such fields that were born in the ‘omics’ era where the development of technologies, such as high-throughput DNA sequencing, has put a huge amount of data in the hands of investigators. But it seems clear that such data alone will not allow us to understand the incredibly complex interactions between microbes, and organisms in general, in ecological networks. One lesson seems to be that if we want to understand these systems we need to first break down their component parts and study them in isolation. This will no doubt involve a lot of painstaking yet, hopefully, illuminating work. We can expect the road ahead to be slow going but rewarding.

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Feature
Disease in the times of climate change
As human influences change the planet including the composition of oceans and the atmosphere and thus the climate, the microbial world is bound to change and adapt as well. Like individual microbes themselves, these changes are invisible to us. The first indication we are likely to notice is the pattern and severity of diseases affecting wildlife, crops and ourselves. Michael Gross reports.

Since the origins of life, microbes colonised planet Earth and shaped it in the process. After more than two billion years of an exclusively unicellular biosphere, they had created the conditions (including an oxic atmosphere) enabling the evolution of more complex and more energy-hungry multicellular organisms, such as plants and animals, including humans.

Today, microbes are still as important for the steady state of the living Earth as they ever were, but the revolutionary change to the system comes from other quarters. Anthropogenic changes to land, water and the atmosphere are now so pervasive that the Anthropocene is being considered as a new geological epoch (Curr. Biol. (2015) 25, R131–R134).

We are struggling to limit the collateral damage we’re causing to big and highly visible species and ecosystems, such as the forests and the megafauna. And yet, the damage to the invisible world of microbes may ultimately be even worse, and it may fall back on us even harder. A group of scientists recently raised the alarm over the risks we are running.

Warning to humanity
In 2019, Ricardo Cavicchioli at the University of New South Wales in Sydney, Australia, with other microbiologists from more than 30 separate institutes around the world, issued a “warning to humanity” on the dangers arising from the impact of climate change on microbial life (Nat. Rev. Microbiol. (2019) 17, 569–586). Inspired by the Scientists’ Warnings from the Alliance of World Scientists in 1992 and in 2017, the authors wanted to expand the range of those warnings to add a focus on the microbial world and to alert “microbiologists and non-microbiologists to address the roles of microorganisms in accelerating or mitigating the impacts of anthropogenic climate.”

In their consensus statement, the authors highlight ways in which climate change affects microbes, and in which microbes affect climate change in marine and terrestrial biomes as well as in agriculture. The interactions between the microbial world, the environment and human activities are complex and manifold. The danger lies in anthropogenic changes to the environment that may lead to unexpected microbiological feedback reinforcing the change and thus to catastrophic acceleration of the change.

Microbial ecology is typically studied at the small scale, while modellers dealing with global geobiochemical cycles rarely include microbes in their calculations. The authors call on both sides to “improve our qualitative understanding of the global marine and soil microbiome.”

Dangerous feedback effects based on microbial participation in geobiochemical cycles may be difficult to discover let alone to prevent. One area where the impact of climate on microbes is already obvious and its dangers can be addressed is in the spread of pathogens.

Human activities including travel, transport and trade facilitate the rapid spread of pathogens, as the case of the novel coronavirus has impressively demonstrated. In addition, climate change can assist pathogens in a variety of ways. Vector-borne pathogens such as malaria or Zika virus can shift their range if warming moves the range of the vector. For instance, the mosquito Aedes aegypti — the main vector of dengue, Zika, Chikungunya and yellow fever viruses — is currently limited to tropical and subtropical regions because it cannot survive cold winters. Regions that will see milder winters due to climate change will soon become exposed to what used to be tropical diseases. Similarly, tick-borne
diseases such as Lyme disease are predicted to expand in range. Warming oceans cause stress to marine ecosystems and may make them vulnerable to diseases, leading to ecological chain reactions. This has been observed, for instance, in the catastrophic decline of the sunflower sea star (*Pycnopodia helianthoides*) on the Pacific coast of North America, which had trophic effects on sea urchins and kelp forests (Sci. Adv. (2019) 5, eaau7042).

Food security may be affected as climate change favours the spread of crop diseases such as infection of potatoes by *Phytophthora*, a genus of oomycetes causing significant economic damage. A 2013 assessment of more than 600 nematode and insect pests and pathogens affecting crops revealed a range expansion towards the poles that can be attributed to climate change (Nat. Clim. Change (2013) 3, 985–988).

The authors also highlight one issue with direct impacts on human health, namely the spread of resistance genes among microbial populations in the wild. Higher temperatures may facilitate the gene transfer between microbial strains and thus make the spread of resistance traits more likely.

### Diseases spreading

Vertebrates with variable body temperature (ectotherms) including amphibians are already suffering severe impacts of diseases favoured by climate change. Dirk Schmeller at the University of Toulouse, France, and colleagues are studying the disease chytridiomycosis caused by the fungal pathogen *Batrachochytrium dendrobatidis* to examine how interactions between host, host microbiome, pathogen, and the environment influence the disease outcome (Trends Parasitol. (2020) 33, 616–636). This disease has been linked to many population declines and even extinctions in amphibian species in the Americas and around the globe.

In amphibians, the body temperature is dictated by the environmental conditions, so the changing climate can directly affect the growth conditions for both the microbiome and any pathogens settling on the animal. Studies of chytrid disease in amphibians have shown that the outbreak of the disease crucially depends on the state of the host’s skin microbiome.

In the ecological theory of disease, the concept of the disease triangle symbolises the three-way interactions between host, pathogen, and environment. Based on their studies of fungal disease in amphibians, Schmeller and colleagues now suggest to add the microbiome as a fourth corner while keeping everything connected to everything else, which they describe as the “disease pyramid” (although chemists and fans of Plato would think of it as a tetrahedron). With six edges linking the nodes and influencing the disease outcome, this is clearly a complex system that needs to be studied intensively, and for many species that are at risk of similar dangers in a changing climate.

Crop pests and pathogens are threatening to compensate improvements in agricultural production and thereby endanger food security and economic stability especially in tropical countries. Pathogens are typically spread by trade routes, and benefit from large-scale industrialised agriculture. Their likelihood of infecting crops, and of taking hold in a given environment, is also influenced by climate change. Dan Bebber at the University of Exeter, UK, has analysed the role of past climate change in the spread of the Black Sigatoka disease, a fungal infection of banana plants that is currently the most serious threat to this crop. Originating in Asia and accidentally introduced into Honduras in 1972, the disease has now spread across all Latin American banana-producing regions and as far north as Florida.

Analysing detailed climate data, Bebber found that the risk of infection with Black Sigatoka disease (given exposure to its spores) in Latin America and the Caribbean has increased by a median of 44% since its introduction there. “This increase in risk was caused by climate change that improved the temperature conditions for spore germination and growth and made crop canopies wetter,” Bebber writes. Some regions where climate change has led to drought have shown the opposite trend, with infection becoming less likely. Drought may limit the further...
spread of the disease, but then again, it will also affect the host, making it difficult to predict what the future holds for this particular disease triangle. Beyond our food, could climate change also promote human disease by changing pathogens and enabling them to infect us more efficiently? Arturo Casadevall at Johns Hopkins University at Baltimore, USA, warned in 2010 that the adaptation of fungi to a warmer climate could lead to new fungal diseases. Now he suggests that the emergence of Candida auris as a human disease may be the first example to prove his prediction right (mBio (2019) dx.doi.org/10.1128/mBio.01397-19).

First identified in Japan in 2009, Candida auris has caused a growing number of hospital infections in vulnerable patients around the globe. It has become a notable problem because of its intrinsic resistance to many common antifungal products. The most surprising thing about its emergence is that it happened almost simultaneously on three continents involving three genetically distinct strains of the fungus. This finding is based on samples from India, Venezuela and South Africa. Casadevall and colleagues studied the temperature susceptibility of C. auris and its nearest relatives in the wild. They found that it is considerably better adapted to higher temperatures than its nearest relatives. This, the authors suggest, implies the change is a recent one which may have been triggered by rising temperatures. Thus, by adapting to a warmer environment, the fungi may have evolved the ability to settle in the human body and establish themselves as a new human pathogen.

While the paper is published as a hypothesis and the authors admit that a causal link is difficult to prove and other factors may also have played a role, they argue that many such cases could conceivably happen as warming proceeds, and that medical practitioners should be aware of the risks. “Right now, fungal diseases are usually not reportable,” Casadevall said. “So we need better surveillance of these infections in humans — and even in other mammals, where the first warnings of new fungal pathogens might occur.”

Predicting future disease
The complexities produced by the multiple interactions of the disease triangle or Schmeller’s disease pyramid make it difficult to predict future outbreaks and spread of disease even when there are indications that environmental change should drive specific trends. In an effort to cover a disease triangle of host, pathogen and environment in a single prediction tool, researchers have turned to the water flea (Daphnia magna) and its parasite (Ordospora colligata) as a model system. Devin Kirk from the University of Toronto, Canada, with Pepijn Luijckx at Trinity College Dublin, Ireland, and colleagues have applied metabolic theory of ecology (MTE) to the temperature dependence of disease in the water flea (PLoS Biol. (2018) 16, e2004608). This methodology is based on adding up contributory factors such as the temperature dependence of enzyme rates to model the interactions at organism level. Feeding disease-relevant parameters into this model and applying it to the entire temperature range in which Daphnia is viable, the authors succeeded in correctly predicting the disease severity for a given set of conditions.

“What is exciting is that these results demonstrate that linking and integrating metabolic theory within a mathematical model of host–pathogen interactions is effective in describing how and why disease interactions change with global warming,” Luijckx explained. “Due to its simplicity and generality, the method we have developed could be widely applied to understand the likely impact of global warming on a variety of diseases.”

Conceivably this approach could be expanded to relatively simple, controlled systems, such as aquaculture or possibly specific agricultural pests. For animals living in a more complex environment and crucially depending on their microbiome adding a fourth corner and turning the disease triangle into a tetrahedron, however, the future of disease in a changing climate remains difficult to predict. The safest bet would be to take action and stop the climate catastrophe from happening.

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Quick guide
CD-NTases and nucleotide second messenger signaling

Brianna Lowey and Philip J. Kranzusch

What are nucleotide second messengers? Nucleotide second messengers are small, specialized molecules formed from ribonucleotide precursors that function to amplify signaling responses in cells. Cyclic oligonucleotides are a major class of nucleotide second messengers that were first recognized with the discovery of the cyclic dinucleotides c-di-GMP and c-di-AMP in bacteria. c-di-GMP and c-di-AMP are enzymatically synthesized by proteins containing GGDEF- and HDAC-domains, respectively, to control diverse responses in bacteria including growth, osmoregulation, and cell-wall homeostasis. Recent experiments have uncovered a new family of cyclic-dinucleotide-synthesizing proteins in antiviral signaling in both animal and bacterial cells. In response to bacteriophage infection in Vibrio cholerae, the enzyme DncV synthesizes a cyclic GMP–AMP molecule with two canonical 3′–5′ phosphodiester bonds (3′-cGAMP) (Figure 1A). In human cells, a structurally related enzyme named cGAS senses DNA that is mislocalized in the cell cytosol during pathogen replication or in tumor cells. cGAS then initiates a downstream immune response through synthesis of the cGAMP isomer 2′–5′, 3′–5′ cyclic GMP–AMP (2′,3′-cGAMP). cGAS and Vibrio DncV are founding members of a new major family of nucleotide second messenger-synthesizing proteins called cGAS/DncV-like nucleotidyldiphosphatase (CD-NTase) enzymes. Thousands of CD-NTases are encoded in bacterial and animal genomes, revealing an enormous diversity of nucleotide second-messenger signaling systems.

How do CD-NTases function? CD-NTases are a structurally conserved subset of enzymes within the pol-β polymerase superfAMILY that coordinate two metal ions to catalyze