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nature sustainability

Antibiotic and pesticide susceptibility and the Anthropocene operating space

Living with Resistance project[1]

Rising levels of antimicrobial and pesticide resistance increasingly undermine human health and systems for biomass production, and emphasize the sustainability challenge of preserving organisms susceptible to these biocides. In this Review, we introduce key concepts and examine dynamics of biocide susceptibility that must be governed to address this challenge. We focus on the impact of biocides on the capacity of susceptible organisms to prevent spread of resistance, and we then review how biocide use affects a broader suite of ecosystem services. Finally, we introduce and assess the state of what we term the Anthropocene operating space of biocide susceptibility, a framework for assessing the potential of antibiotic and pesticide resistance to undermine key functions of human society. Based on current trends in antibiotic, insecticide and herbicide resistance, we conclude that the states of all six assessed variables are beyond safe zones, with three variables surpassed regionally or globally.

Humans have, throughout history, modified the environment to reduce vulnerabilities, but in the process sometimes created new risks that must be managed[1]. Large-scale human adoption of pesticides to control plants and arthropods, and of antimicrobials to control microorganisms, are prime examples of such niche construction (Fig. 1). With the adoption of these biocides—chemical substances intended to control other organisms—susceptible pests and pathogens suddenly became beneficial to society, or at least more beneficial than those resistant to treatment. Unfortunately, as a result of biocide use, the abundance of susceptible organisms has declined as our need for them has risen, making biocide treatments increasingly ineffective and biocide resistance a threat to modern biomass production and medicine[2,3].

The effectiveness of biocides depends entirely on the dominance of susceptible organisms over resistant organisms. Given favourable, relatively biocide-free environments, susceptible organisms have the ability to outcompete or prevent colonization by resistant ones. The latter is analogous to the ability of biodiverse environments to suppress outbreaks of pests or pathogens, which is widely regarded as an ecosystem service—a benefit to human societies derived from nature[4].

Making clear that biocide susceptibility can act as an ecosystem service may help to foster a broader understanding of direct and indirect drivers, and a wider range of potential solutions, than those emerging from currently dominant discourses on antibiotic and pesticide resistance[5]. Such discourses often implicitly neglect the value of susceptible organisms to human society and focus instead on the large costs of ineffective biocides and resistance[5,6]. Yet the notion of the need to preserve 'biocide effectiveness' neglects the actual changes in system properties and in so doing pre-defines a limited solution space: an antibiotic or pesticide that has lost its effectiveness has not changed in its chemistry. What has changed is the composition of the biological communities, with a general depletion of susceptible types.

Better understanding of the dynamics of biocide susceptibility can lead to a broader set of solutions to antibiotic and pesticide resistance, grounded in environmental sustainability. In this Review, we seek to lay a foundation for fostering such solutions. We review the ecosystem service properties of biocide-susceptible organisms and the main factors influencing their resilience. We focus on biocide use, including its effects on associated ecosystem functions. To highlight where efforts to preserve antibiotic and pesticide susceptibility are urgent, we introduce the concept of the Anthropocene operating space of biocide susceptibility (Fig. 1) and provide a first assessment of its state for major groups of organisms.

What kind of service?

Biocide-susceptible organisms are of benefit to human society both locally, in the short term, and at the global level, across generations. Locally, susceptibility aids the short-term control of target species, as we will discuss in the next sections. Globally, a broadly susceptible community of pests or pathogens represents option values[7] for future generations to treat infectious disease and manage pest outbreaks. The Intergovernmental Science-Policy Platform on Biodiversity and Ecosystem Services (IPBES) mentions resistance evolution in the context of preserving options for the future. However, it neglects the role of susceptible organisms in providing and regulating those options by aiding control and by competing with resistant organisms, respectively[8]. This omission may be a reflection of general tendencies in the literature on ecosystem services to oversimplify by characterizing species and services as either 'beneficial' or 'harmful'[9,10].

Wider recognition of the instrumental value of susceptible organisms requires changes in how values are assigned to species and the natural world so that we increasingly recognize their context dependence. Species can have a variety of positive, neutral and negative impacts on the health and well-being of people and the resources on which we depend[11–13]. For example, many strains of resistance-prone bacteria, such as *Staphylococcus aureus* and *Escherichia coli*, are ubiquitous and in most cases harmless or even beneficial to humans, but are problematic when, for example, they enter the bloodstream, particularly in elderly or immunocompromised persons[14]. In agriculture, species often have multiple functions: they can have net-positive impacts in one crop and net-negative impacts in others, and pest species can be more or less likely to occur in

[1]A full list of authors and affiliations appears at the end of the paper.

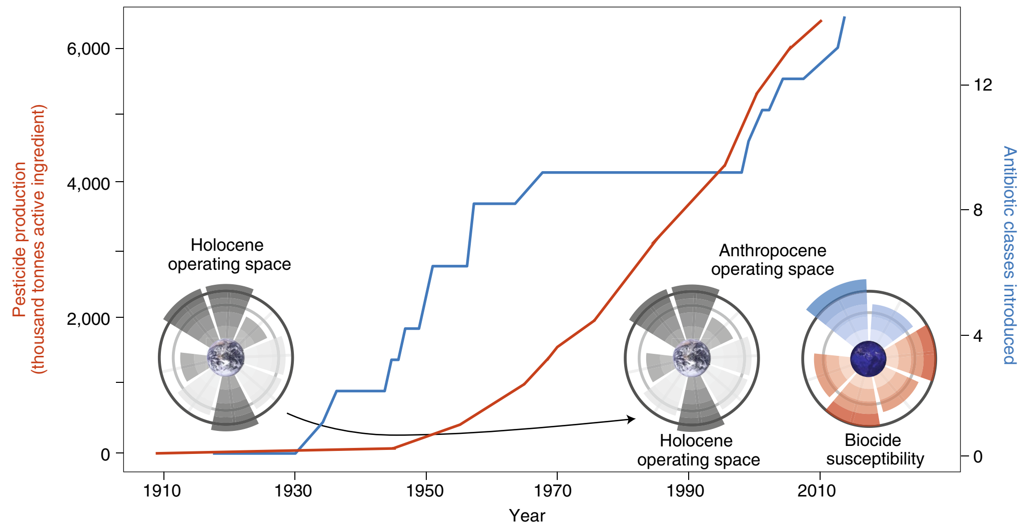

Fig. 1 | Niche construction of the Anthropocene operating space of biocide susceptibility. Global annual pesticide sales (red) and introduction of antibiotic classes (blue) illustrate the progressive adoption of biocides[128,129]. This large-scale adoption of antibiotics and pesticides around the middle of the twentieth century added biocide susceptibility as a new, Anthropocene dimension (bottom right, blue and red diagram) to the Holocene environmental operating space (exemplified by the planetary boundaries, grey diagram[114,115]). Credit: Earth by night, NASA Earth Observatory image by Robert Simmon, using Suomi NPP VIIRS data provided courtesy of Chris Elvidge (NOAA National Geophysical Data Center); Earth by day, NASA Johnson Space Center Gateway to Astronaut Photography of Earth

a cropping system depending on the growing strategy and the biological community that it supports[12,13].

Underscoring the need for viewing susceptible organisms as an ecosystem service, we are unlikely to be able to make species we perceive as beneficial resistant and species perceived as detrimental susceptible to treatment at a general level. And even if it were theoretically possible to limit or eradicate some pathogens and pests at a global scale, the environmental and health costs associated with doing so could be high. More broadly, the challenge is therefore not only to preserve susceptibility, but at the same time to promote the long-term benefit that we can derive from microorganisms, plants and arthropods[5].

Biocide susceptibility differentiates itself from other ecosystem services in terms of the ways in which actors gain access to its benefits (Fig. 1) and the way it is depleted. Despite the presence of susceptible organisms for millions of years, our ability to benefit from them is entirely contingent on access to relatively advanced technologies in the form of mass-produced antibiotics and pesticides. Although others have highlighted the role of technology in co-producing ecosystem services[15], biocide susceptibility represents an extreme example. As access to antibiotics and pesticides often is limited to those who can pay for them, this technology-enabled access contributes to potential global inequalities in the ability to derive benefits from biocide susceptibility[16].

Susceptibility is depleted by evolutionary responses to selection instead of through direct human extraction or pollution as is otherwise common for many provisioning and regulating ecosystem services, such as timber supply and crop pollination, respectively. Over time, this evolutionary mode of depletion can result in coevolutionary biochemical arms-races between human society and the organisms exposed to biocides[3]. Addressing problems associated with susceptibility therefore requires understanding the evolutionary dynamics that underlie the relative abundance of susceptible organisms, but also the cultural evolution underlying human responses to resistance[17]. The growing interest among researchers and some policy-makers in governing evolutionary dynamics for the benefit of society[8,18–22] could help to address the challenge of preserving susceptibility.

Regulating resistance

Preserving biocide susceptibility rests on providing conditions that support the capacity of susceptible organisms to withstand the colonization and spread of resistant ones (colonization resistance), as well as the capacity to replace resistant organisms after their spread (recovery resilience; Fig. 2a). The most critical factor threatening these two components of resilience is the concentration of biocides in the environment, which helps to determine the relative fitness of susceptible and resistant organisms[2,3,23–25].

As resilience is a property that any system can possess, care is required in clearly specifying the species and the contexts in which it is studied[26]. For antibiotics, the focus on resilience of susceptible communities is necessary, instead of the resilience of a few desirable species, because resistance genes can be shared across species[27]. If generally beneficial species acquire resistance in response to sustained biocide use, the risk increases of them passing on their resistance genes to potential pathogens.

A better understanding of the resilience of biocide-susceptible organisms is challenged by insights from a relatively narrow range of studies, such as specialized research on gut[27,28] and soil microbiota[29,30]. Change in gut microbiome composition following antibiotic use shows how biocide use undermines the colonization resistance of susceptible organisms. Non-pathogenic, 'commensal' gut bacteria help to limit the spread of (potentially resistant) pathogens by directly targeting pathogens; by altering the gut environment to be less favourable for pathogens; and by triggering immune responses[31]. However, a few courses of antibiotics can have the effect of shifting the human gut microbiota to an alternative stable state[28] (Fig. 2c). This state is characterized by an increased number of resistance genes as well as an increased risk of infections, compromised immune tolerance and deregulated metabolism[28,32].

The degree to which susceptible organisms can recover after protracted biocide use remains an important unknown[33] (Fig. 2a). Although resistance sometimes has a fitness cost, which can keep resistant organisms from completely replacing susceptible ones, resistance can become resident with continued biocide use[33,34]. At the very local level, the ability of gut microbiomes to recover from exposure to antibiotic treatment is highly individual. Recovery from

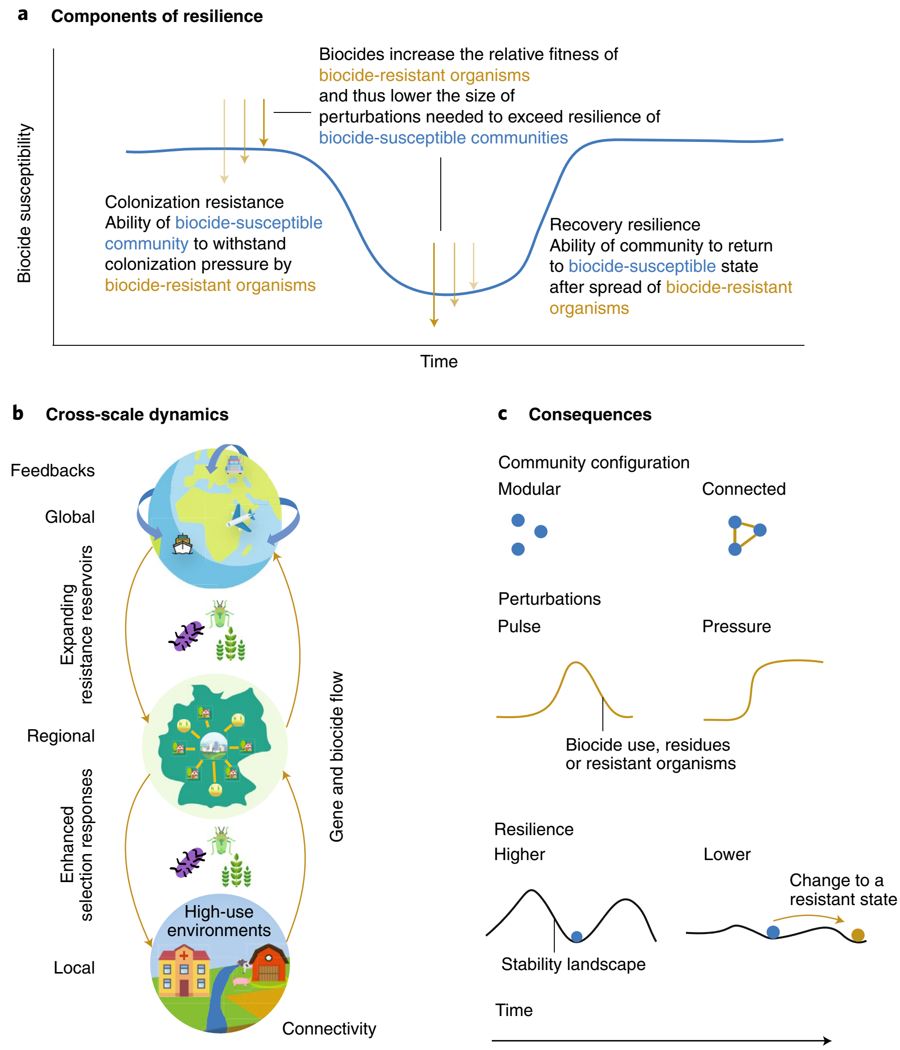

Fig. 2 | Resilience of biocide-susceptible organisms. a, Resilience is expressed through colonization resistance and recovery resilience, with biocides reducing both. **b**, Increasing connectivity leads to global cross-scale feedbacks in resistance evolution by expanding reservoirs of resistance genes and enhancing local selection responses. **c**, Consequently, the resilience of susceptible communities is eroded through a combination of increased connectivity and disturbance from continued biocide use. Credit: icons by Freepik from www.flaticon.com

a small number of antibiotic courses can take 2 to 4 years[28]. In some cases, microbiomes seem to increase their ability to recover over time, whereas in others this ability declines with each antimicrobial course[28]. The former case is often associated with the spread of resistance genes and therefore carries with it the risk of spreading them to potential pathogens[32].

Indirect evidence of the limited ability of the human gut microbiome to recover from resistant infections is provided by the growing importance of faecal microbial transplantation in the treatment of recurring infections with resistant *Clostridium difficile* (for example ref. [35]). Here, recovery increasingly hinges on human restoration. Similar lines of evidence come from mice in which human-mediated colonization with specific commensal bacteria aids recovery from infections with vancomycin-resistant *Enterococcus*[36].

Various strategies can optimize biocide use to preserve the resilience of susceptible communities and lower the probability of the emergence and spread of resistance. First and foremost, environmental heterogeneity can favour susceptible organisms, for example in the form of biocide-free refuges, as can mixing of biocides, or varying biocide use over time[2,3,37,38]. In practice, however, these strategies are rarely fully successful in preventing spread of resistance, as they require a high level of coordination. Co-selection of resistance from other biocidal compounds—such as heavy metals and detergents like triclosan for antibiotic resistance—can also hinder the success of these primary strategies[39–41]. Hence, except in cases of highly simplified, controlled or modular systems such as genetically modified Bt crops (crops modified to produce toxins from the soil bacterium *Bacillus thuringiensis*) in Australia and Arizona, these tactics are primarily expected to delay rather than prevent or control resistance[2].

Factors influencing resilience. To preserve susceptibility, a deeper understanding is needed of the factors affecting the resilience of susceptible organisms. These factors vary in their rate of change, their geographical scale and whether they have a direct or indirect impact (Fig. 2)[27]. Of these, the slow-acting, longer-term drivers are of critical importance for the global supply of susceptibility; yet as noted above, most of our understanding is confined to local, proximate factors[42,43]. Ultimate drivers include the role of functional response diversity and the degree of spatial connectivity[44,45] (Fig. 2b). Although these factors can strengthen the resilience of susceptible organisms under certain conditions, their general direction of development, together with increasing biocide use, is likely to have contributed to undermining the resilience of biocide-susceptible communities (Fig. 2c).

Functional response diversity, the diversity of strategies present in ecosystems to respond to perturbation, is a well-known contributor to the resilience of ecosystem function[46–51]; however, few studies have investigated its influence on the resilience of biocide susceptibility, leaving us with indirect evidence. Although previous studies have found that low gut microbial diversity is associated with what could in part be the result of dwindling regulating services from the gut microbiome—obesity and irritable bowel syndrome—direct measures of the relationship between the biodiversity of the gut and its functional diversity are few[28]. Other studies indicate that the depletion of particular functional groups of bacteria during antibiotic treatment aids the expansion of potentially resistant infections, such as *Salmonella*[52].

In some cases, diversity measures themselves may not capture the underlying dynamics. For example, studies have shown that the overall diversity of the gut microbiome does not predict colonization resistance to resistant *C. difficile*[53]. Thus, often, the influence of community composition on resilience must be understood through the context of an area's ecological history. In human bodies, this history includes an individual's lifetime of dietary choices[54]. In soils, the physico-chemical structure can influence resilience through effects on microbial community composition and physiology[30] and thereby possibly support the ability of indigenous soil microorganisms in preventing the spread of antibiotic resistance genes from manure to soil[29].

The preservation of susceptibility is increasingly threatened by the transmission of resistance genes through horizontal gene transfer and global transport of resistant organisms through travel and trade (Fig. 2b). We now understand that horizontal gene transfer over time has played a key role in transferring important resistance genes from commensal species in the broader environment to potential human pathogens[55,56] and that it could also play roles in insects and plants[45,57,58]. As global connectivity increases, new resistance genes are recruited from an expanded pool of locations, species or functions[45,56] (Fig. 3). The thousands of plant species that have been exchanged between continents are a proxy for the scale of this connectedness and its increase[59] (Fig. 3a). Increasing numbers of intercontinental transfers of important and potentially resistant herbivorous insects have also been documented, including the rapid spread of the fall armyworm from the Americas to Africa[60–64] (Fig. 3b). Finally, the combined impact of horizontal gene transfer and intercontinental connectivity is readily illustrated by the apparent spread of horizontally transmissible antibiotic resistance genes (Fig. 3c; for example NDM-1[65], MCR-1[66], KPC[67]), rendering some strains of pathogenic bacteria resistant to all available antibiotics. Given the importance of horizontal gene transfer in shaping current and likely future dynamics of antibiotic susceptibility, a major challenge lies in identifying the factors limiting the span of these exchanges in microbial communities[68].

An example involving resistant *Salmonella* in Canada illustrates how the above factors interact over time to undermine the resilience of susceptible communities (Fig. 2c). In the beginning of the twenty-first century, resistance to third-generation cephalosporins among *Salmonella* Heidelberg emerged and increased steadily in the province of Quebec. A voluntary ban on their use in broiler hatcheries led to a great reduction in resistance levels in clinical human cases, in retail poultry products and also among non-type-specific *E. coli* from poultry (a Gram-negative indicator organism)[69,70]. However, this was later followed by a rise in resistance[70], including steady increases in resistance in other geographical regions and other food animals[71–74], highlighting the potentially tenuous and short-lived impacts of concerted action from a single group of actors. Further, in the decade since the short-lived decline in Quebec, the repertoire of resistance has expanded to additional plasmids, to multi-drug resistance genotypes and phenotypes, and to many additional genes encoding resistance to extended-spectrum beta-lactams[75]. Thus, in a relatively short period, a largely reversible problem of extended-spectrum beta-lactam resistance has gone from being solvable through a reversal in usage patterns to being intractable and potentially irreversible.

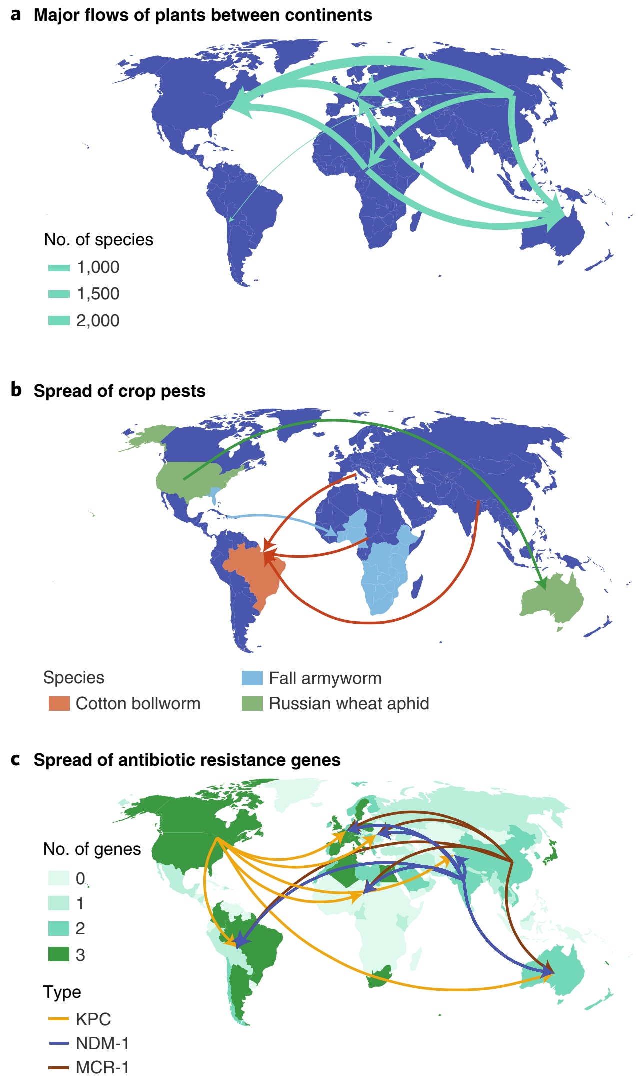

Fig. 3 | Intercontinental spread of non-native plants, agricultural insect pests and antibiotic resistance genes. a, Ten largest flows of non-native plants between continents[59]. **b**, Recent examples of spread of insect pests, including fall armyworm, *Spodoptera frugiperda*, to Africa, probably from the United States or the Caribbean, as well as spread of cotton bollworm, *Helicoverpa armigera*, to Brazil from the Old World, and the Russian wheat aphid, *Diuraphis noxia*, to Australia[61–64]. **c**, Global distribution and spread of three plasmid-borne genes associated with multiple antibiotic resistance and their likely origins (earliest documented presence)[65–67,116]. Map credit: H. Wickham, ref. [130].

Bundles of services

The undermining effects of biocide use on the resilience of biocide-susceptible organisms should not be viewed in isolation. Rather, by altering three key features of biological communities, biocides influence a range of interrelated ecosystem services—ecosystem service bundles[76–79]. These three features are: community diversity

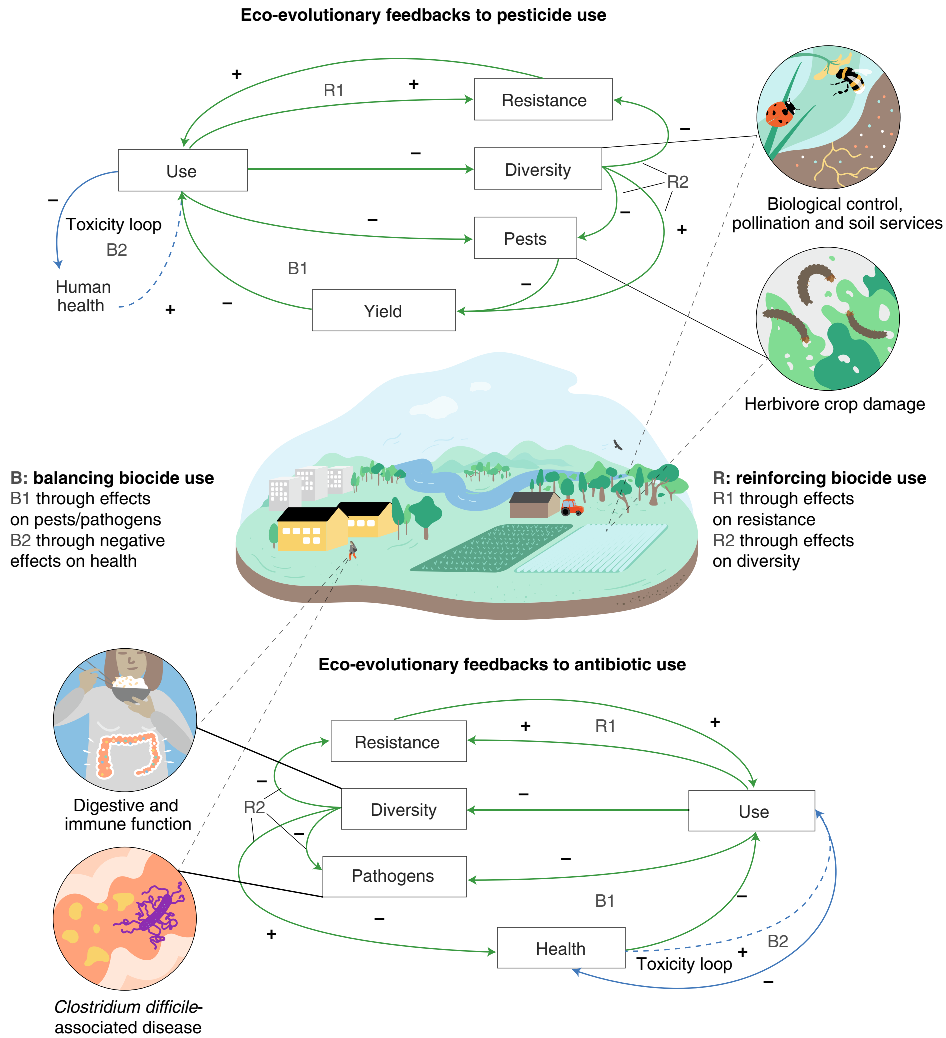

Fig. 4 | The ecosystem consequences of biocide use. Pesticide use (top) and antibiotic use (bottom) influence bundles of ecosystem services and disservices by altering levels of diversity, resistance, and pest and pathogen abundance. Causal loop diagrams show positive (+) and negative (−) influences that lead to balancing (B) and reinforcing dynamics (R) of biocide use. Callouts from each diagram illustrate examples of diversity-associated benefits (upper) and negative impacts (lower) of resistant pests and pathogens. Credit: E. Wikander/Azote

and composition, the abundance of susceptible organisms, and the abundance of species considered pathogens or pests (Fig. 4). Changes in these features in turn alter biocide use through two types of reinforcing (R) and one balancing (B) feedback loop (Fig. 4). In the short term, the ability of biocides to kill pests and pathogens lowers the need for use (B1, Fig. 4) but simultaneously promotes the ability of resistant organisms to outcompete susceptible ones, potentially leading to long-term increases in resistance that reinforces use (R1, Fig. 4). The negative impacts of biocides on diversity may also increase the capacity of (resistant) pathogens and pests to expand and establish themselves in the community, which could increase biocide use (R2, Fig. 4). Finally, the dynamics of susceptibility can also be influenced through the toxicity of biocides for humans—the toxicity loop—in which toxic effects limit biocide use[80] and indirectly promote susceptibility (B2, Fig. 4). Provisioning, supporting, regulating and cultural ecosystem services are all affected as outcomes of these interactions[4].

One of the main regulating benefits derived from the maintenance of diversity and depleted through biocide use relates to the suppression of pests and pathogens (R2, Fig. 4). Non-specific biocides kill species that compete with or consume pests or pathogens, potentially undermining the inherent ability of communities to withstand colonization or spread of these damaging organisms. The disrupting effects of antibiotics on diversity are illustrated at the global level, by the negative correlation between antibiotic resistance genes (indicating the presence of antibiotics) and bacterial diversity[81]. In the gut microbiome, these effects increase the vulnerability of humans and other animals to (co-)infections. The best documented example in humans is the rising epidemic of *C. difficile* (Fig. 4 bottom, R2), an opportunistic bacterial pathogen that in the United States every year infects around 450,000 people and kills 30,000[82]. In animals, antibiotics can facilitate bacterial infections of, for example, *Salmonella* and *E. coli*, and therefore faecal transplants are often provided preventatively to bolster diversity[83–85].

Diversity of agricultural communities similarly influences pest population density and the evolution of resistance. The role of pesticides in altering these dynamics can be illustrated by how the increasing specificity of insecticides has restored the ability of natural enemies to regulate potential pests. The first generation of insecticides typically had broad-spectrum activity and considerable negative impacts on natural enemies, which reduced their overall capacity to suppress pest populations[86] (Fig. 4 top, R2). For example, before the release of Bt crops in Australia, stringent control of cotton bollworm with insecticides decimated the populations of natural enemies that exploit sucking insects. This induced outbreaks of sucking pests, which necessitated more applications of insecticides to control them, and ultimately led to the evolution of resistance to insecticides in sucking pests[87]. More recently, insecticides with greater specificity, such as Bt crops or insect growth regulators, have provided opportunities to reduce impacts on natural enemies[88,89]. Similarly, before the mid-1990s, whitefly, *Bemisia tabaci*, was a serious pest of cotton in Arizona when broad-spectrum insecticides that kill natural enemies were used. After the mid-1990s, replacement of broad-spectrum insecticides with biocides that preserved natural enemies greatly enhanced biocontrol of whitefly, thereby reducing its pest status, the need for insecticides and the risk of resistance[89,90]. Importantly, natural enemies not only suppress pest populations and reduce the need for insecticides, but can also directly accelerate or delay the evolution of resistance when resistant individuals are respectively more or less vulnerable to natural enemies than susceptible individuals[91–93].

Provisioning and supporting services in both agriculture and humans are broadly affected by biocide use. The extent to which pollination acts as a supporting service in agriculture is clear, given estimates suggesting that 75% of cultivated crops are pollinated by insects[94] (Fig. 4 top, R2). One of the most important drivers that affects insect pollination and consequently crop yields is the use of insecticides, particularly neonicotinoids which, even when used at concentrations far lower than recommended, affect the short-term behaviour of pollinating bees[95]. The impacts of insecticides on pollinators at the population level and across ecosystems remain unresolved despite many studies, probably because of an inadequate understanding of the effects of long-term exposure to sub-lethal doses in agricultural ecosystems[96,97]. In soils, studies of the acute and chronic effects of pesticide applications on soil function have been limited and findings mixed. Although microbial activity may be reduced for some time owing to pesticide application[98] and the composition altered, there are also potential positive interactions from reduced tillage and pesticide application, for example in transgenic herbicide-resistant crops[99,100].

With compelling evidence that consumption of antibiotics causes major and sometimes irreversible alterations to the human microbiome[32,101], a rapidly developing research field is how antibiotics affect the microbiome's longer-term supply of health benefits, such as immune and metabolic function[102–104] (Fig. 4 bottom, R2). The composition of the personal microbiome is influenced by both the biodiversity of the environments in which we live and our exposure to them[105,106], while antibiotics also alter the microbiota of these environments[107,108]. The general form of the hygiene hypothesis, the biodiversity hypothesis, argues that missing exposure to microbial biodiversity generally contributes to increasing incidence of autoimmune diseases[106]. Yet, while increasing frequencies of autoimmune diseases[109] and food allergies[105,110] can potentially be linked to sterile environments[102,111], unravelling causal pathways in this highly multidimensional problem, with multiple manifestations and potential mechanisms, is proving challenging[112].

State of the Anthropocene operating space

At the global scale, increasing levels of resistance constrain long-term opportunities to benefit from antibiotics and pesticides in human health and in food, fuel and fibre production. The beginning of the Great Acceleration — the period during which the rate of human impact on Earth system greatly increased — sometimes serves as the point marking the onset of the Anthropocene[113]. Using this starting date, the early Anthropocene in the 1950s was characterized by vast opportunities to apply new and more efficacious biocides. However, as resistance spread to a broader set of available biocides, the operating space provided by biocide susceptibility declined and the risk increased of crossing a threshold beyond which current practices cannot continue. If organisms become resistant to all commonly available biocides, this type of pan-resistance will not necessarily be easily reversed but is likely to continue to be present at some frequency[33,34]. Pan-resistance therefore constitutes a possible tipping point in the opportunity for human society to benefit from biocides and biocide susceptibility. The question arises as to whether we have already crossed the safe zones of the Anthropocene operating space for biocide susceptibility.

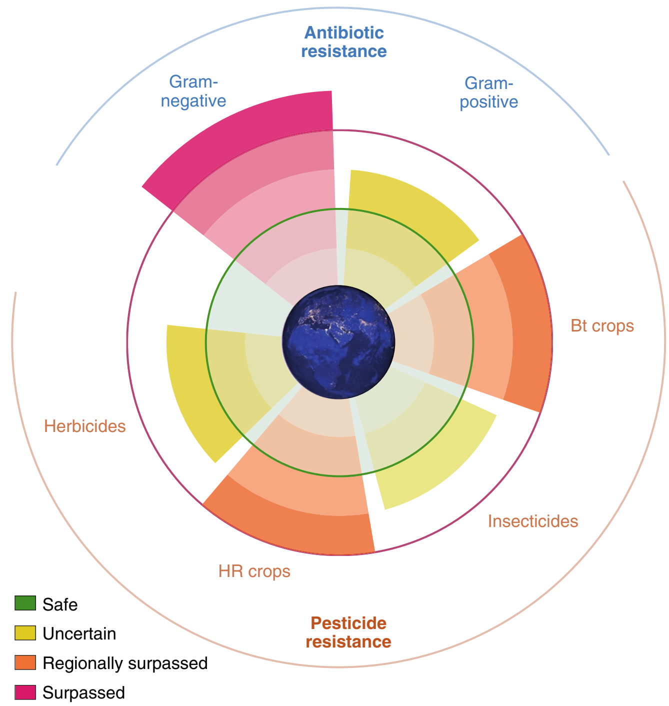

Fig. 5 | State of the Anthropocene operating space of biocide susceptibility. For antibiotics (blue labels), the state is assessed for Gram-negative and Gram-positive bacteria. For pesticides (brown labels), the state is assessed for resistance associated with two types of transgenic crops—herbicide-resistant (HR) cropping systems and insecticidal Bt crops—as well as in general for herbicides and insecticides. Three of the six variables are surpassed regionally or globally; none are in the safe zone. Earth image credit: NASA

To formalize and assess the current state of the operating space in major groups of organisms, we follow the paradigm for the assessment of the planetary boundaries that set out to evaluate key functions and tipping points of the Earth system[114,115]. We set out three zones of increasing risk for current biocide use practices: the 'safe', 'uncertain' and 'surpassed' zones. For antibiotics, we assess susceptibility in Gram-negative and Gram-positive bacteria separately, given their differences in cell wall architecture which helps to determine innate resistance. For pesticides, we assess insect susceptibility to genetically engineered Bt-cropping systems as well as plant glyphosate susceptibility in genetically engineered herbicide-resistant cropping systems. This is supplemented with a general assessment of insecticide and herbicide susceptibility (Fig. 5).

As the relationship between biocide use and resistance can be complex, and depends on historical patterns, it is desirable to use the degree of susceptibility as a control variable rather than the rate of biocide use. We define the safe zone as extending from the state of no relevant resistance to the presence of single biocide resistance at low frequencies and with many other available biocides. The uncertain zone of increasing risk is entered once one of two criteria is fulfilled: (1) multiple biocide resistance is observed and less desirable treatments must be applied, or (2) single biocide resistance is common with some, but few, alternatives. The surpassed zone is entered once resistance is observed to all relevant biocides (pan-resistance). In the case of genetically engineered cropping systems based on use of a single biocide or single group of insecticidal toxins, the surpassed criterion translates to common resistance to that biocide or available crop toxins.

Like the nine planetary boundaries defining the human operating space of the Holocene[114,115], the global pools of resistance and susceptibility genes exhibit varying degrees of connectivity and modularity. Connectivity is highest for horizontally transferable antimicrobial resistance genes, which effectively resembles a global system connected through travel, transport, and trade. It is lower for plant and arthropod susceptibility and resistance gene pools, which exhibit higher regional or local heterogeneity. For the latter, it is therefore also relevant to assess whether we may be in the zone of high risk at a regional level.

Using the above criteria, we assess the Anthropocene operating space for antibiotic susceptibility to be globally surpassed for Gram-negative bacteria and in the uncertain zone for Gram-positive bacteria (Fig. 5). The recent discovery of plasmid-borne resistance genes to carbapenems (KPC[67] and NDM-1[65]) and to colistin (MCR-1[116]) means that some Gram-negative bacteria, in particular of the Enterobacteriaeceae family, are now effectively pan-resistant and join the list of pan-resistant *Pseudomonas aeruginosa* and species within the *Acinetobacter* genus[117]. For example, a well-documented case of pan-resistance occurred in 2015 in a hospital in Nevada, with the bacterium being resistant to 26 out of 26 available antibiotics[29]. More broadly, over 60% of 1,300 infectious disease specialists surveyed primarily in North America report encountering pan-resistant infections[118]. Gram-positive resistant infections are also of increasing concern, especially extremely drug-resistant tuberculosis, multi-resistant *S. aureus* and *Enterococcus*[117]. However, in contrast to Gram-negative bacteria, several new treatments have recently become available for some of these infections or are likely to become available in the near future[119,120]. In addition, several countries have been able to lower resistance levels in some important Gram-positive infections such as methicillin-resistant *S. aureus*[121,122].

Pesticide susceptibility is generally assessed as being in the uncertain zone, but surpassed at the regional level in genetically engineered cropping systems owing to increasing resistance to foundational pesticides (Fig. 5). Insecticide resistance is assessed as being in the uncertain zone, given that multiple insecticide resistance is increasing in several pests, such as diamondback moth, *Plutella xylostella*, and green peach aphid, *Myzus persicae*[123]. Likewise, in plants, multiple herbicide resistance is increasing and leads to an assessment of general herbicide susceptibility as being in the uncertain zone[124]. For Bt crops, the spread of resistance to regionally available Bt-crop toxins in the US mid-west and in India leads to an assessment as regionally surpassed[125]. For herbicide-resistant crops, the increasing spread of glyphosate resistance leads to its assessment as regionally surpassed[124]. Our global assessment therefore indicates that, for all major types of antibiotics and pesticides considered, we are today in a situation where resistance puts current practices at increasing risk (Fig. 5). This is a state that has gradually worsened to be fundamentally different now from when antibiotics and pesticides first were taken into use.

Sustainability in the Anthropocene

Global reliance on pesticides and antibiotics has led to dependence on the environmental supply of susceptible microorganisms, plants and animals. However, after more than half a century of biochemical arms-races wherein increasing levels of resistance have been addressed through the development of new biocides, an assessment of global trends in resistance suggests that we are entering a new phase in which levels of multiple resistance and pan-resistance put the sustainability of current practices at increasing risk. These risks are particularly pronounced for pesticide resistance in highly simplified transgenic cropping systems and for antibiotic resistance in Gram-negative bacteria.

Our assessment illustrates the great need to manage susceptibility to antibiotics and pesticides as an ecosystem service in order to preserve an operating space of biocide susceptibility in the Anthropocene. Promoting communities of susceptible microorganisms, plants and animals could also be a part of a larger effort to seek sustainable development through a de-escalatory strategy that maximizes the benefits of the ecosystem services associated with biocide susceptibility. A critical aspect includes initiatives to build diversity and redundancy to mitigate the risks associated with reliance on one or a small number of strategies for pest and pathogen control.

There is also a need to strengthen monitoring and surveillance of the operating space of biocide susceptibility to aid its management. Currently, globally standardized monitoring of biocide use and resistance levels suffers from large gaps and multiple inconsistencies. For example, for antibiotic resistance, use and resistance data can only be related to each other with the caveat that sales data come from overall use (including the community) whereas resistance data often arise from a hospital setting; these settings exhibit different resistance dynamics. For pesticides, global databases of insecticide and herbicide resistance only report individual cases and only a few countries are systematically monitoring the levels of resistance to insecticides and herbicides.

The unique challenges associated with promoting biocide susceptibility provide an opportunity to learn about coevolutionary dynamics between humans and the environment in a context of rapid ecological, social and technological change. So far, such studies of social-ecological coevolution have focused on the long-term perspective of how society adapts to human-induced environmental changes[1,126,127]. Given that biocide susceptibility can erode rapidly through self-reinforcing dynamics, its study can provide valuable insights for the management of other ecosystem services in the context of rapid change. Finally, the large-scale technological changes associated with the industrial revolution and the Great Acceleration may have created other environmental dependencies that should be considered as part of the Anthropocene operating space. Governing these new dependencies must be a priority for societies in achieving sustainability.

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Author contributions

P.S.J. conceived the manuscript on the basis of four workshops where all authors contributed in person or virtually. P.S.J. wrote the first draft of the manuscript with primary contributions from Y.C., S.D., R.R.D., G.E., G.L., H.M.S. and D.W. P.S.J., Y.C., E.Y.K., D.W. and D.J. performed the assessment of the Anthropocene operating space. P.S.J. and F.K. designed the figures. M.S. and P.S.J. conceived the feedback loops of Fig. 4. All authors commented on and contributed to the writing of the manuscript.

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Living with Resistance project

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