Futures xxx (xxxx) xxx-xxx

Contents lists available at ScienceDirect

Futures

journal homepage: www.elsevier.com

Ontology, difference, and the antimicrobial resistance timeline

J. Anthony Stallins *, Sophie Strosberg

University of Kentucky, Department of Geography, 817 Patterson Office Tower, Lexington, KY, USA

ARTICLE INFO

Keywords:
Complexity
Human microbiome
Antibiotic resistance
Anticipatory system
Coevolution

ABSTRACT

Despite warnings at the start of the industrial antibiotic era seventy years ago, antimicrobial resistance (AMR) is an increasingly intransigent health issue. AMR can be claimed as a social, political, technological, or economic problem. But multidisciplinary, co-evolutionary perspectives are necessary to trace the complexity allowing it to persist. We link the concept of difference to anticipatory systems theory to show how the AMR issue is a negotiation between representations and forces that destabilize them. Drawing from governmental publications and journal articles, we provide examples of representational and non-representational difference spanning the social and biological entanglements of AMR. Just as social theory and future studies recognize a tension between stabilized categories and the latent potentials for their disruption, so does biology in that organisms are adapting yet also robust, capable of change but also stable. We illustrate how the reification of one or the other of these two types of difference can contribute to AMR's entrenchment, yet their interaction also forms the basis for strategies to address it. Difference illuminates how solving AMR is not likely, but knowledge to approach closure requires working simultaneously, even contradictorily, with representational ontologies that provide predictability and the instabilities that unsettle them.

1. Introduction

Novel indoor-based lifestyles, processed foods, improved sanitation, and reduced exposure to soils and animals are now recognized as major influences on the composition and function of the human microbiome. Yet one of the most dramatic changes in the human microbiome initiated with the commercialization of penicillin in the mid-1940s. At this point in time, humans entered the industrial antibiotic era, although the use and commercialization of other resistance-inducing antimicrobials like heavy metals began earlier (Landecker, 2019).

Millions of human lives have been saved by antibiotics. They arrest infection and allow physicians to safely conduct surgery, transplant organs, and deploy cancer chemotherapies. Yet the number of bacterial, viral, fungal, and protozoan organisms exhibiting resistance to antimicrobial drugs continues to increase. Resistant bacteria and their genes now circulate among humans and their built environment, livestock, wildlife, as well as soils and waterways (Davies & Davies, 2010; Finley, Collignon, Larsson, McEwen, & Li, 2013). As the last line of antimicrobials lose their efficacy, warnings about rising mortality rates from formerly low risk procedures and treatable infections have been announced by the Centers for Disease Control and Prevention (2013) the World Health Organization (World Health Organization, 2017), and the United Kingdom (O'Neill, 2014). In Europe, North America and Australia, 2.4 million people are predicted to die from infections with resistant microorganisms in the next 30 years and could cost up to

* Corresponding author.
Email addresses: jast239@uky.edu (J.Anthony Stallins); sophiastrosberg@gmail.com (S. Strosberg)

https://doi.org/10.1016/j.futures.2019.102467
Received 15 May 2019; Received in revised form 20 August 2019; Accepted 8 September 2019
Available online xxx
0016-3287/ © 2019.

US$3.5 billion per year (Organisation for Economic Co-operation & Development (OECD), 2018). The Food and Agricultural Organization of the United Nations and the WHO recently distributed a joint policy statement urging there is 'no time to wait' in order to 'secure the future from drug-resistant infections' (Interagency Coordination Group on Antimicrobial Resistance (IACG), 2019).

However, the dangers of antimicrobial resistance (AMR) have been known for decades (Podolsky, 2018). When Alexander Fleming accepted his Nobel Prize in 1945 for the discovery of penicillin, he warned that "[t]here is the danger that the ignorant man may easily underdose himself and by exposing his microbes to nonlethal quantities of the drug make them resistant." Since then, a wide range of social, economic, and scientific solutions have been proposed. The paucity of success with many of these policies to manage AMR reflects the deep structural impasse AMR poses for public health (Orzech & Nichter, 2008; Wallinga, Rayner, & Lang, 2015). This article takes the position that the multiple, evolving ontologies of AMR contribute to its intransigence. Anticipating the future and responding to AMR is dependent upon our representations of co-evolving human and non-human life forms and processes and the types of causality assigned to them. Responses to AMR reflect representations that are culturally and politically bound, contingent, as well as responsive to underlying novelty (Groves, 2017; Poli, 2010; 2014; Vallis & Inayatullah, 2016).

To illuminate this dynamic, we present examples of the kinds of ontologies animating the AMR issue. We show how they relate to each other in time and space in order to articulate AMR strategies that are more robustly anticipatory. Our examples are distilled from a review of governmental and non-governmental publications as well as journal articles. From them, we discuss how the stabilized representations of entities and processes of AMR reconcile with their disruption in productive and not so productive ways. A query into the unsettled ontologies of AMR is germane because representation and attentiveness to its limits inform the decisions and predictions about the kinds of biomedical research, medical procedures, and governance strategies to prioritize and pursue.

We employ a conceptualization of 'difference' from social theory to convey how the ontologies of AMR are distinguished from one another. This typology of difference encapsulates a prominent tension in knowledge production expressed not only in social theory but also in biology (Austin, 2016; Cockayne, Ruez, & Secor, 2017). It is the tension between representational ontologies and the emergent, non-representational heterogeneity within them. As a way to operationalize difference, we tie it to the concept of anticipation from future studies. Anticipation refers to the capacity of an organized system to incorporate projected future states into its present functioning as a way of orienting or modulating its activity (Rosen & Kineman, 2005). Predictions that utilize anticipatory structure consider sources of novelty and the scenarios they elicit in order to condition the precision of pre-existing representations (Poli, 2010). Following Anderson (2010), representation and non-representation are future 'styles' in that we come to understand the presence of one or many different futures through them. The habits and logics associated with each of them take an abstract category, the future, and shape how it is disclosed and related to. After an overview of AMR in the next section, we define difference in more detail and explain how it is operationalized through anticipation. We then review examples of representational and non-representational difference for AMR, and close with a list of provisos for anticipating its futures.

2. Antibiotics in the anthropocene

Today, antibiotic use in many states in the U.S. exceeds one course per person per year. In 2010, the top seven antibiotic classes were consumed by humans in an estimated 70 billion individual doses, which equates to about 10 pills, capsules, or teaspoons for every man, woman, and child on earth (Blaser, 2016). Yet antibiotics are applied in quantities exceeding those for human health in commercial animal husbandry and agriculture (Orzech & Nichter, 2008; Wallinga et al., 2015). Antibiotics promote weight gain and prevent disease in poultry and livestock while allowing more animals to be raised with less land and labor. Limiting antimicrobial use in agriculture has the potential to reduce antimicrobial resistance in food animals and in humans without major unintended consequences for livestock health (McEwen, Angulo, Collignon, & Conly, 2018; Scott et al., 2018; Tang et al., 2017).

The first widely used antibiotics began exhibiting limited effectiveness shortly after their introduction by the middle of the twentieth century (Brinkac, Voorhies, Gomez, & Nelson, 2017; Davies & Davies, 2010; Landecker, 2016). However, antibiotic therapy does not simply select for increased resistance at the level of an individual bacterial organism. It also selects for the increased prevalence of resistance genes within a microbial community. These can then be transferred to other bacteria through a wide variety of genetic mechanisms unique to bacteria. To date, a relatively small but growing number of bacteria is responsible for most antimicrobial-resistant infections (Centers for Disease Control & Prevention, 2013; World Health Organization, 2017).

Although public health has benefited greatly from past successes in the development of new drugs to thwart the activity of these bacteria, humans now stand at a point where the number of drugs available to stop their effects is shrinking. While the number of patient deaths and hospitalizations due to antibiotic-resistance bacteria has been creeping upward, the number of organizations with demonstrated abilities to gain approval in the U.S. for a new antibacterial agents is at a level not seen since at least the early 1960s (Kinch, Patridge, Plummer, & Hoyer, 2014). Consolidations, bankruptcies, and strategic reprioritization in the pharmaceutical industry have diminished the expertise and economic means to invest in antibiotics. Incentives to develop and sell a new antibiotic are weak (Wallinga et al., 2015). The time it takes to develop and test a new drug can approach a decade, and prices for even non-generic antibiotics are typically lower than other specialty drugs. Antibiotics are viewed as less profitable because they are generally taken only for a short period of time and often only for one course of treatment by any given patient. Their financial shelf-life is often short because newer antibiotics are often held in reserve as drug of last choice. Then once put into use, pressure to make them a generic may increase. Overshadowing this economic unease is the evolutionary inevitability of resistance, the built in self-destruct mechanism for antibiotics (Ventola, 2015).

Increasing drug resistance and fewer new antibiotics have fostered a sense of urgency. Problem-solving frameworks to date have focused mainly on the need for complex interventions in human social behavior. From a game theory perspective, the root dilemma is that individuals pursue antibiotic treatment at the expense of the group (Broom, Broom, & Kirby, 2014; Ho, 2017). Each participant, from patients to doctors to ranchers and farmers, has rational self-interest to pursue a course of antibiotics. However, antibiotics not only affect the individual to whom they are given but also the entire community (Brinkac et al., 2017). With the potential for resistance, overuse of antibiotics is suboptimal for all of us. To address this tragedy of the antibiotic commons Giubilini, 2019; Roope et al., 2019), calls have been made for coordination of global public health initiatives and a carrot and stick strategy to realign cost-benefits such that individuals' interests match those of the collective. Antibiotic stewardship programs have been widely implemented in hospitals, doctor's offices, and on farms in order to monitor and enforce dosing and treatment procedures for humans and for animals.

Given the volume of official reports calling for action, it is tenuous to argue that AMR policy continues to fall short due to lack of evidence (Fleming, Chain, & Florey, 1945; Dubos, 1958; van Aaken & Antonovics, 2016). The failure more squarely resides in the status of AMR as a wicked problem (Andersson & Törnberg, 2018; DeFries & Nagendra, 2017). A wicked system is poorly decomposable and difficult to transform into stable representations. They have ontological uncertainties (Andersson, Tornberg, & Tornberg, 2014). Consequently, no generalizable solution will apply in all cases. Wicked problems require continual learning to formulate the problem and adaptively work toward compromises. Then, as the number and diversity of stakeholders grows, wickedness compounds. Conflict becomes entrenched around ontological priorities. However, wicked problems can be made more comprehendible by giving formal structure to these ontological incompatibilities through a meta-ontology, a framework for co-existing ontologies (Andersson & Törnberg, 2018; Brown, Harris, & Russell, 2010). Difference provides this structure.

3. Difference

Drawing from Deluezian philosophies of life (Proveti 2012), Cockyane et al. (2017) present difference as a meta-framework for linking the static and dynamic features of ontologies. Difference has two components. First there is difference as identity-based, representational categories. Interpretations and judgements are made that distinguish identities and mark them as distinct from or analogous to other identities. This representational typology of difference can also arise through dialectical processes of contradiction and opposition. Representational mediations of the world provide categories like race, gender, species, bacteria with an assumption of stability and a transferability of meaning. They imply precision.

Then there is non-representational difference. It is non-representational in that it is conceptually prior to the construction of identity categories. Difference in this sense derives through the constant potential for novelty and emergence latent within the seemingly finished and fixed. Difference is produced in action rather than through pre-established systems and structures of representation. This 'difference-in-itself' is an escape from representation (Deleuze, 1994). It affirms the excess of life over and above the categories that seek to contain it. Whereas representation targets precision, non-representation encompasses open-endedness and imagination. When these two kinds of difference are taken together, difference becomes a dynamic boundary-ordering device. It encapsulates the process in which humans discriminate, summarize, and apply representations. It also encompasses the process by which these representations decohere in light of new knowledge and in turn coalesce into another set of representations. Difference is invoked whenever categories are distilled from representations of heterogeneous phenomena. It is also in play when these categorizations fail and require revision. Heterogeneity, chance, and exception reside within the uniformity ascribed to representations.

The operational value of difference for AMR is that it distills the tensions among stakeholders vested in stable representations and those whose interests recognize the contexuality and uncertainty of these ontological stabilizations. As a central example, the AMR issue reflects a tension between the mutability of microbes and the necessary representation of them as stable. Bacteria are malleable enough to rapidly acquire resistance to antibiotics, but antibiotic use is predicated upon the representation of bacteria or other microbes as a defined type or class having susceptibility to a fixed chemical compound. Similarly, the concept of infection is more than a binary set of two bounded distinct representations, the host and the pathogen (Hinchliffe, Allen, Lavau, Bingham, & Carter, 2013). Biological differences among hosts and pathogens make infection more or less likely from individual to individual. Yet the concreteness of representations like infected and non-infected is imperative for a diagnosis to be made and treatment procured. These two examples of difference convey how the ontologies of AMR – concepts like bacteria, antibiotic, host, and pathogen – fit into existing categories yet can also exceed them. Through the concept of difference, ontologies proceed from events and situations rather than having any fixed essence (Joronen & Häkli, 2017). This permits more visibility of how stakeholders vested in stabilizing a representation coexist with those whose interests are aligned with its disruption. Although social theorists invoke this conceptualization of difference to illuminate the possibilities of the future when the play of representation and non-representation is unmasked, futurists have done more to formalize its precepts into policy. Difference captures key aspects of anticipatory systems. Like difference, anticipation encompasses predictions based on representations. These representations are fixed out of the past and present and extended into the future as an empirical forecast. The future is constrained to these pre-existing representations. Anticipation also encompasses the 'not yet', the nascent representations that are still performative in nature and unwieldy because they exist latent within existing representations. These non-representational differences require meaning to be inferred or sensed, as the 'not yet' is more semantic than syntactic. As with anticipation, difference is affective as well as actuarial (Adams, Murphy, & Clarke, 2009). Through the lens of anticipation, predictions about AMR are robust insofar as they allow representations and non-representational difference to inform one another (Groves, 2017). Statements about the future condition restricted to either representation or non-representation constrain how the future can be intervened on. Individually, these approaches to the future function through a circularity. Each discloses a set of relations between past, present and future and problematically self-authenticate those relations. To disrupt this circularity requires framing the representational and the non-representational as co-evolving, while remaining cognizant of how their interaction can be steered when one of these two future styles prevail in anticipatory policy over others (Anderson, 2010). To derive examples of representational and non-representational difference associated with AMR, we conducted a multi-disciplinary review of official statements from national governments primarily from North America and Europe, their research units, as well as global consortiums like the United Nations and the World Health Organization. We examined review and synthesis journal articles from sociology, evolutionary biology, anthropology, public health, and environmental biology and epidemiology. Also included were applied studies by microbiologists and molecular biologists at interface of medical practice and drug development. Anticipatory strategies are a broad-based capacity extended through society. Surveying multiple disciplines and institutions of governance insured exposure to the diversity of dialogic spaces (e.g., Guston, 2014) where representational and non-representational styles of framing the future were produced. However, the examples of representational and non-representational difference did not neatly cleave along academic or governmental lines. They are also weighted toward views from countries where antimicrobial overuse is the issue, instead of where health care and access to antimicrobial drugs is more limited.

4. Examples of representational difference for AMR

4.1. War versus peace

Despite our improved understanding of them, the general public are still apt to generalize about bacteria and link them to diseases rather than to the beneficial roles they play in us and in our environment. (Shamarina, Stoyantcheva, Mason, Bibby, & Elhaik, 2017). This is understandable, as historically bacteria have killed many humans and remained largely unidentified until the late seventeenth century. Consequently, war metaphors and catastrophe representations dominate the discourse about AMR (Chandler, Hutchinson, & Hutchison, 2016). Much of this rhetoric has pitched humans in a fight against bacteria, a 'war against superbugs'. The politics of antimicrobial fear have become filtered through the prospect of 'a return to the dark ages of medicine' and the unravelling of modern medicine's achievements (Brown & Nettleton, 2017b). However, representing the AMR issue as a war oversimplifies policy interventions (Nerlich & James, 2009). Analogies to battle justify continued antibiotic development at the expense of incentivizing more adroit multi-pronged strategies (Mendelson, Balasegaram, Jinks, Pulcini, & Sharland, 2017). Yet if the governmental institutions that work to promote public health step back from these strong representations, their efforts to publicize the AMR issue and address antimicrobial overuse may be weakened.

4.2. Good versus bad

Bacteria have become fixed into representations as either competitor or cooperator. There are good bacteria in us when we are well, and bad bacteria when we are sick (Paxson & Helmreich, 2014). As AMR becomes more visible as a health issue, this binary representations of good versus bad bacteria becomes even more entrenched (Chandler et al., 2016). However, potentially pathogenic bacteria are often already on or in us at any given time. Their effects depend upon their phenotype, the nature of the ecological interactions with other bacteria around them, and human physiology (Pitlik & Koren, 2017). Whether a bacteria has a negative or a positive impact can shift from one microbial context to another. Calls have been made to eliminate the term 'pathogen' and to diversify the meaning of 'host' (Casadevall & Pirofski, 2014; 2018). However, diversifying terminology and taking context into greater account may make tracking AMR organisms more difficult for entities like the World Health Organization or the U.S. Centers for Disease Control.

4.3. Us versus them

Othering is a process of moralization that generates representational difference among actors embedded in the AMR issue (Fynbo & Jensen, 2018). Othering is primarily used to characterize as well as stereotype users and prescribers. In the binary politics of blame associated with this 'immunitary moralism' (Brown & Nettleton, 2017a), the behavior of misinformed patients and practitioners requires correction. Doctors become classified as over prescribers and patients as misusers and over-consumers of antibiotics. Blame is passed down such that the AMR issues is oversimplified as just actors behaving irrationally and overconsuming or not finishing their course of antibiotics (Chandler et al., 2016). These moral designations of accountability downplay the logic of taking antibiotics at the level of an individual when there may actually be few other alternatives. Representations originating out of this immunitary moralism can have unintended, stigmatizing and socially divisive consequences that complicate contextual responses to AMR.

4.4. Medicines versus people

As antibiotics become ineffective, vulnerable people have been replaced by representations of medicines as vulnerable. However, calls for saving antibiotics entrench the representation of antibiotics as miracle drugs (Levy, 1992; Rosen, 2017). These vulnerable miracle medicines are also supposed to have particular properties. Patient-customers expect easily obtainable and inexpensive antibiotics, thereby reinforcing the inappropriate use of antimicrobials (Wallinga et al., 2015). Entrenched representations of antibiotics can become barriers to effective change. As these examples convey, representational difference can naturalize and privilege certain constructions of problems. Representations imply classification schemes that can limit the range of solutions (Vallis &

Inayatullah, 2016). Although they can productively guide institutional and professional practices, they can become translated into standardized procedures that reduce attention to context. To an extent, it is necessary to allocate a generalized representation to a given class of entities. Designating a bacteria as dangerous or fining a hospital for overprescribing can be a situationally logical choice based on existing representations. However, by not problematizing the underlying discourses and moralizations in these representations, predictions extrapolated from them are incompletely specified. The examples of non-representational difference in the next section focus more on the novelty and surprise that imposes limits on representations. They provide the sense-making and scenario outlooks that triangulate with representational difference to 'undefine' (Inayatullah, 1998) the AMR future.

5. SOURCES OF NON-REPRESENTATIONAL DIFFERENCE FOR AMR

5.1. History repeats itself

The historical dogma was that AMR should not be found where antibiotics have not been used (Davies & Davies, 2010; Singer, Ward, & Maldonado, 2006). However, resistance genes have been discovered from locations with minimal or no exposure to human civilization. AMR genes occur in remote and uncontaminated soils in Antarctica (Van Goethem et al., 2018), in ancient Beringian permafrost (D'Costa, King, Kalan, Morar, & Sung, 2011), and in the bacteria derived from the culturable microbiome of an isolated cave in New Mexico (Bhuller et al. 2012). Some of these bacteria were capable of thriving on synthetic antibiotics unlikely to occur in nature. This environmental reservoir of resistance is a component of the 'resistome', the collection of resistance elements from which bacteria draw. Antibiotics are produced by bacteria as part of their ecological interactions. Thus the origin of many modern resistance genes in pathogens may be benign environmental bacteria, including antibiotic-producing organisms that have existed for millennia (Perry, Waglechner, & Wright, 2016). The discovery of resistance in bacteria unexposed to human antimicrobials suggests there are limits to the representation of AMR as only a problem of medical practice and governance. The categories comprising any new problem solving framework to address AMR will be embedded in billions of years of evolutionary experimentation and its products (Lebreton et al., 2017).

5.2. Radical mobility

The mobility of bacteria and resistance genes challenges representational stability. One of the omes of postgenomics[1] is the mobilome, the mobile genetic elements of bacterial genomes. Bacteria, their genes, and AMR resistance mechanisms have the capacity to disperse over large distances. This spatial element of AMR can involve the mobility of humans as well as non-human animals (MacPherson et al., 2009; Wang et al., 2018). International travel and immigration contribute to the spread of AMR (Häsler et al., 2018; Kuenzli, 2016). Consequently, resistance does not correlate neatly with industrialization and antibiotic use (Brito et al., 2016; Pehrsson, Tsukayama, Patel, Mejia-Bautista, & Sosa-Soto, 2016). The mobility of AMR genes may be exacerbated in how humans shed millions of bacterial cells per hour into the environment (Lax, Nagler, & Gilbert, 2015). Rooms take on the microbial properties of those who enter it. Buildings such as hospitals develop their microbiomes through the flows of people and materials through them (Arnold, 2014). These mobilities will likely shape bacterial adaptation and evolution in ways that will continue to challenge fixed representations of the entities and processes involved with AMR.

5.3. Anthropogenic reservoirs

The anthropogenic environment diversifies the sources of AMR (Tripathi & Cytryn, 2017). Antimicrobial-resistant bacteria are found in hospitals, but they also reside in other built environments (Fitzpatrick & Walsh, 2016). Farms are sources of resistance genes because of antibiotic use to promote livestock growth. Antibiotics fed to animals can pass directly into their waste. Spreading this manure on land increases the abundance of transferable resistance genes present in soil and aquatic systems. Human wastewater treatment (Singer, Shaw, Rhodes, & Hart, 2016), urban sewage (Su et al., 2017), and drinking water (Ma et al., 2017) are also vectors for AMR genes. Other industrial chemicals, some produced in larger quantities in the past (Landecker, 2019), contribute to AMR. Biocides in personal and hospital hygiene-related products, cleaners and detergents, and heavy metals in industry effluents and traffic-related emissions contribute to AMR (Singer, 2017).

5.4. Community interactions

Bacteria exhibit more rapid adaptive potential than macrobial life forms. This plasticity arises in part because bacterial biological activity can exhibit organized cell-to-cell interactions as a biofilm, a spatially organized, fully metabolically integrated community of different bacterial types (Sauer, Rickard, & Davies, 2017). A biofilm imparts protection from the penetration of antimicrobial agents. Yet exposure to antibiotics can expedite the acquisition of AMR by triggering adaptive changes in gene transfer and expression of

[1] In postgenomics, mapping of the spatial and temporal contexts and circumstances surrounding DNA, rather than DNA sequence alone, has become prioritized. Consequently, scientific and economic value in postgenomics accrues through the enclosure and mapping of the 'omes'. These include the more familiar epigenome and microbiome, but also the mobilome (Stallins, Law, Strosberg, & Rossi, 2017).

bacteria in a biofilm (Schroeder, Brooks, & Brooks, 2017). Resistant bacteria in a biofilm can protect its susceptible companions (Jalasvuori & Penttinen, 2017). This community context weakens interventions dependent upon representations of bacteria as simple, singular entities acting in isolation. Yet over time, the study of AMR has grown from focusing on single pathogenic organisms in homogenous cultures to studying AMR at the level of microbial communities and human-environment contexts (Crofts, Gasparrini, & Dantas, 2017; Niehus & Mitri, 2018).

5.5. Evolving evolvability

Antibiotics are chemicals produced by bacteria for communication but at much lower concentrations than produced by their pharmaceutical equivalents. This saturation of the environment with antimicrobial compounds triggers higher mutation rates as well as greater gene transfer and genetic recombination. These are processes that can lead to directional selection toward bacteria that readily express these adaptive responses. Consequently, antibiotic use may not only lead to an increase in resistance, but also an increase in the propensity for evolutionary adaptation (Gillings & Stokes, 2012). Some antimicrobial-resistant bacteria can even 'trade up' instead of 'trading off', by acquiring resistance without a cost that puts them at a disadvantage in competitive interactions with other bacteria. (Reznick & King, 2017; Schroeder et al., 2017). By potentially effecting adaptive responses throughout the microbial biosphere, the evolution of evolvability disrupts representations of the very problem of AMR as having definable boundaries. Once humans entered the era of industrial antibiotics, we began changing the very conditions of possibility for evolution.

6. Difference and the AMR timeline

As these examples convey, existing bacterial potencies to shape human health are magnified through individual as well as institutional practices. Representational difference provides structure to conceive and develop responses to the emergence of AMR (Fig. 1). However, this structure is limited in light of non-representational difference, the inherent propensity for bacteria and our relationships with them to usurp our representations (Fig. 2). In this way, representational and non-representational difference in tandem convey an evolutionary view of AMR that spans the social and the biological. The recent history of humans and microbes conveys this evolutionary dynamic, starting from the first observations of microbes, through germ theory, and up to the present-day insights about the human microbiome. On this timeline of how bacteria have been studied and linked to human health, the type of difference that attains precedence has shifted back and forth

In the *Pasteurisation of France* Latour (1993) describes the victory of a microbial theory of disease over miasma theory. An ontological shift was negotiated from thinking of microbes as an amorphous pool of bad air emanating from rotting organic matter or swamps to one in which they became represented as individual entities called microbes that could be taken up into medical, political, and economic discourse. During this ascendance of germ theory, bacteria became an object of avoidance and control. Clean became healthy.

However, these representations have been overturned of late with the realization that exposures to bacteria in the environment can tune the developing immune system. The Old Friends hypothesis (Rook, Raison, & Lowry, 2014; Scudellari, 2017) posits that the timing of childhood exposures to environmental microbes can be beneficial later in life. Similar to earlier miasma representations, there is again far less categorical, representational guidance for microbial health. The present marks a return to an emphasis on openness, dynamism, and exposure. Immunity has changed from a stabilized set of criteria about clean versus dirty to an engagement with the messiness and difference-in-itself of the bacterial world.

Developmental biology has undergone comparable integrations of difference over time. In the late nineteenth century many still believed, including Darwin, that bacteria could be spontaneously generated. Microbes were thought to be unstable and thus interchangeable in form and function, or 'pleomorphic'. This gave way to the Kochian view in which bacteria behaved as single cells and representable as species with predictable properties, evolving like species of animals or plants. However, with the advent of molecular techniques to comprehend horizontal gene transfer, the turn has been back toward a more unpredictable 'neo-pleomorphism' (Doolittle, 2013). Bacteria have reclaimed some their earlier instability and interchangeability as we learn more about the mobility of bacteria genes and bacterial evolution. Drawing inspiration from Koch, the primary focus of early antibiotic research was on single pathogenic organisms in monocultures and on the specific classes and categories of drugs to arrest them. More recently, we have shifted our attention again to unpredictable elements like the resistome and the mobilome. We have gone from an interchangeabilty in microbes to the individuality of Koch, and now back toward an open-ended difference-in-itself. These shifts in difference, back and forth from 'diversity' and 'purity' in microbial ontology are an alternative to the accelerationist, building block models of progress in science (Grote, 2018).

Yet unique to the AMR issue today is the simultaneity of both views of microbes. The diversity of the microbiome coexists with a purity arising from the technical capacity to pinpoint bacterial gene sequences and explore how they work. This confluence reflects how AMR stands apart from earlier periods in the history of human-microbe relations (Sardar, 2015). The new sources of non-representational difference illuminate global and historical facets of the AMR issue unavailable and unimaginable in earlier warnings. How should the futures they evoke inform the representations from the past and present that typically dominate predictions about AMR? What does the interaction of both types of difference suggest about the future? We offer these anticipatory guidelines:

1 **Responses to AMR should be pragmatic.** Pragmatism here implies that context defines what is true or best to do more than any single universalizing solution. Debating whether to rely solely on one type of difference over the other masks the true problem in-

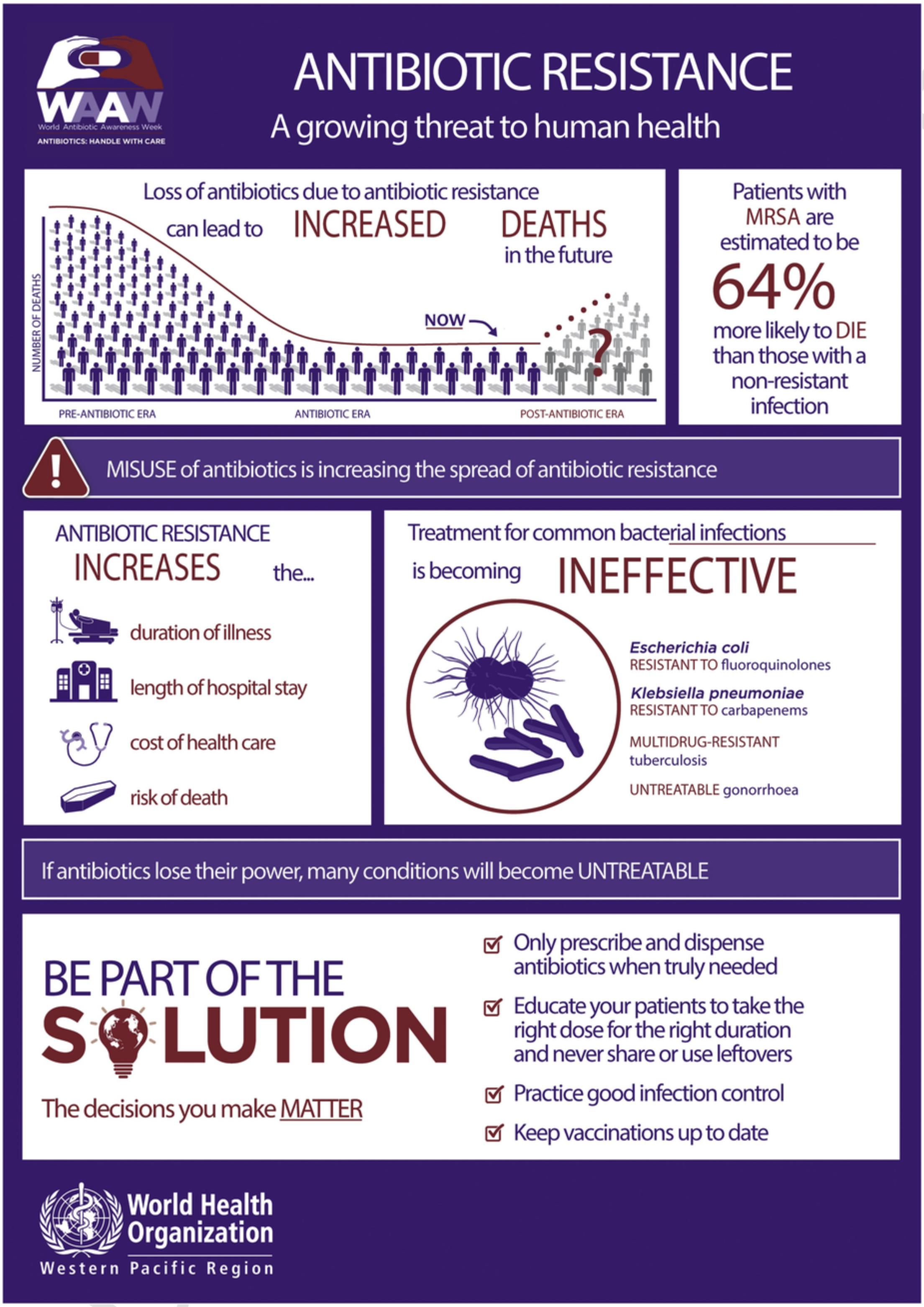

Fig. 1. . Examples of representational difference for AMR from a World Health Organization (2016) poster. The imagery and the actuarial content convey representations of AMR required to mobilize responses to AMR. A singularly representational approach oversimplifies the dynamism of issue. Through the kind of future they make present, representations can limit the range of responses.

Fig. 2. Examples of non-representational difference from journal cover at Elsevier Publishing. Bacteria and microbial processes have a latent fluidity that challenges existing stabilized representations (Brannon & Mulvey, 2019). While microbial evolvability can provide insights about how to address AMR, futures made present solely through the non-representational lack the stability to mobilize widespread responses on existing knowledge. Accessed 19 August 2019, https://www.sciencedirect.com/journal/journal-of-molecular-biology/vol/431/issue/16.

herent to working with the complex causality that defines AMR, which is how useful any particular deployment of difference is in its context. Problem solving with AMR should operate in a way in which things are prioritized as representational or non-representational in accordance to the requirements and obligations following from how the problem is posed at any given time or place.

2 **Reifications of difference are barriers to effective change.** Fleming et al. (1945) warned unsuccessfully about the cost to the community of antibiotic resistance. Other microbiologists at that time held similar views. But like Fleming, they lacked the strong social networks that other scientists, governments and large corporations could mobilize to sell antibiotics, inform policies and regulation, and influence the public. These economic interests were more successful in developing and then solidifying the representation of antibiotics as miracle drugs. In part, the reason Fleming's warning and others like his were not effective was due to the limitations of scientific knowledge at that time. This also empowered the economically-motivated representations that stabilized antibiotics as not having any drawbacks. Because biological phenomena cannot perform the task of asserting their own consequence then or now, it will only be through our labs and discourses that bacteria can be made known. Their existence and properties – their difference – are thus vulnerable to issues of power and influence within the communities that work with them and communicate knowledge about them (Podolsky, 2015; Will, 2018). The universality and certainty of representations can be exaggerated. Heterogeneity and unpredictability can also be reified in order to weaken the representations required to alter antimicrobial practices. Addressing AMR becomes contingent upon relations between institutions with vested interests in reifying particular representational and non-representational framings. For example, from the perspective of some food producers, the inherent ambiguity of what defines and represents livestock health can be invoked to dismiss calls by public health agencies to reduce the use of antimicrobials for meat production. Recognizing who makes these reifications and the motivations for them is imperative for effective responses to AMR.

3 **Surprise and novelty are not just properties of microbes.** Microbes are unpredictable, capable of surprise, as exemplified in the recent global emergence of highly-resistant forms of the yeast *Candida auris* (Nett, 2019). Yet human affective responses are also non-representational. How people understand bacteria, use antimicrobials, and respond to antibiotic stewardship programs involves affect and context (Broom, Broom, Kirby, Gibson, & Davis, 2017; Hardon & Sanabria, 2017). Individuals can vary in what kind of a psychological strategy is effective in promoting positive antibiotic behaviors (Will, 2019). Fleming's discovery of penicillin was accidental, and selection of a particular moldy cantaloupe from Illinois played an outsize role in the early commercialization of antibiotics. To manage AMR requires attentiveness to the obstacles and opportunities imposed by the spontaneity not only in microbes but also in the human sphere, where innovation and creative moments are not entirely predictable. For example, neither the invention of the gene editing technique CRISPR Cas-9 nor its potential to address AMR could have been easily predicted.

4 **Responding to AMR requires an evolutionary perspective.** Institutions, human behaviors, and biological processes interact, adapt, and change as a complex socioecological system. A co-evolutionary perspective can account for how human and non-human aspects of the AMR issue are eventful and creative as well as expressive of longer-term forms of stability and obduracy. Microbes exhibit the properties of being adapted but are also capable of adapting to new conditions. Concepts and practices in the human social realm can analogously be stable and persistent but also have the potential to reconfigure to accommodate new circumstances.

5 **The effectiveness of responses to AMR will be temporary and open-ended.** It is not possible to extricate ourselves from the microbial biosphere. Because of the malleability and adaptivity of microbes, addressing AMR should be expected to be an ongoing process whose results are never permanent stable states, but periodic commentaries on relationality. Although temporary and incomplete, our representations can approach something more reliable. Explanation with AMR can be expected to move from the simple and representable to the unpredictable and heterogeneous and back to the simple over and over (Pascual, 2005; Wimsatt, 2007).

6 **The heterogeneity within representations can be leveraged for benefit.** The act of representation is a performance invoking contingency and context. It can mask heterogeneities that may inform us of novel ways to respond to AMR. For example, even what we would define as healthy individuals can harbor pathogenic bacteria. These bacteria reside in and on us but have no negative impacts because of ecological interactions and environmental conditions (Dorman & Short, 2017). The human body as well as livestock are now considered a potential source of new antibiotics (Challinor & Bode, 2015; Oyama, Girdwood, Cookson, Fernandez-Fuentes, & Prive, 2017).

7 **AMR requires multiple and often oppositional political and economic responses.** Non-representational difference suggests that solutions to AMR are out there amid diverse evolutionary and human social processes. The vitalism of these generative interactions and the entrepreneurial pursuit of technologies and drugs embedded with them has appeals to liberalism, diversity, and market economics. On the other hand, strong representational responses herald autocratic governmental controls and issues of surveillance and regulation. Although not a formal source for our examples of difference, the portrayal of a post-antibiotic Britain in the graphic novel *Surgeon X* (Kenney & Watkiss, 2017) conveys how representation links to governmental regulation. Yet aspects of the biology of microbes and medical practices can and need to be stabilized by representations. Addressing AMR from a coordinated perspective will require the deployment of strong representations and regulatory control in some contexts, and prioritizing of the non-representational, contextual attributes of microbes and human health in others. However, large contrasts exist among and within countries in their access to antimicrobial drugs, their regulation, and in the burden of disease (Podlosky et al. 2015; Ayukekbong, Ntemgwa, & Atabe, 2017; Klugman & Izadnegahdar, 2018). Much like global climate change, uneven development will be a pivotal challenge for AMR (Roope et al., 2019). Any type of anticipatory action will only provide relief, or promise

to provide relief, to what life value has been attached, not necessarily all of life (Anderson, 2010). Given the human coupling to microbial processes and the pervasiveness of microbes in our environment, even those humans living far from routine medical care in low-income countries are enmeshed in the AMR issue. Analogous to how the atmosphere everywhere bears the imprint of anthropogenic influence, all humans are stakeholders with AMR within their own contingent degrees of awareness of its existence and the representations that develop from it.

7. Conclusion

AMR is like climate change in its appeals to urgency and in how it presents choices about how to frame problem solving in the present in order to promote collective benefits in the future (Hulme, 2009). Knowledge and ignorance can be variously strategized (e.g., McGoey, 2012; Will, 2019) in these choices. Yet AMR is not so much a puzzle to be solved and set aside as it a call for a major transition in how antimicrobials are used and how human and non-human health is defined (Chandler, 2019). Representational and non-representational difference are future 'styles' anticipating this transition. Portraying AMR through strong, fixed representations produce an anticipatory affect, a way of making the futures of AMR present so they can be acted upon today. Yet anticipatory affect can also be achieved by appeals to contingency and surprise, abrogations of representation that also make the future present and to be acted upon. When coupled together, difference conveys how predictions about AMR based on assumptions of constancy and inert representation need to be questioned in order to seed new insights latent in uncertainty and complexity (Bergmann, 2016; Levins, 2014).

In this way, addressing the wicked problem of AMR will require greater connectivity between precision and imagination (Cilliers, 2005; Ulanowicz, 2016). Precision is decision-making based on representations of AMR that extend out of the past and into the present. It implies working with categories and their specificity. Imagination is to take measure of the broader environmental and biological capacities AMR is embedded within. It encompasses the moving window of our comprehension of the linkages among antimicrobial drugs, human bodies, and the biosphere. Imagination is sense-making and being alert to the unfolding non-representational future. This connectivity of representational and non-representational difference illustrates how the AMR timeline could be more robustly anticipatory (Poli, 2014).

References

Aaltonen, M., 2009. Multi-ontology, sense-making and the emergence of the future. Futures 41 (5), 279–283.

Adams, V., Murphy, M., Clarke, A.E., 2009. Anticipation: Technoscience, life, affect, temporality. Subjectivity 28, 246–265.

Anderson, B., 2010. Preemption, precaution, preparedness: Anticipatory action and future geographies. Progress in Human Geography 34 (6), 777–798.

Andersson, C., Tornberg, A., Tornberg, P., 2014. Societal systems - Complex or worse?. Futures 63, 145–157.

Andersson, C., Törnberg, P., 2018. Wickedness and the anatomy of complexity. Futures 95, 118–138.

Arnold, C., 2014. Rethinking sterile: The hospital microbiome. Environmental Health Perspectives 122 (7), A182–7.

Austin, C.J., 2016. The ontology of organisms: Mechanistic modules or patterned processes?. Biology & Philosophy 31 (5), 639–662.

Ayukekbong, J.A., Ntemgwa, M., Atabe, A.N., 2017. The threat of antimicrobial resistance in developing countries: Causes and control strategies. Antimicrobial Resistance and Infection Control 6 (1), 47–54.

Bergmann, L., 2016. Toward speculative data: "Geographic information" for situated knowledges, vibrant matter, and relational spaces. Environment and Planning D, Society & Space 34 (6), 971–989.

Blaser, M.J., 2016. Antibiotic use and its consequences for the normal microbiome. Science 352 (6285), 544–545.

Brannon, J.R., Mulvey, M.A., 2019. Jekyll and Hyde: Bugs with double personalities that muddle the distinction between commensal and pathogen. Journal of Molecular Biology 43 (16), 2911–2913.

Brinkac, L., Voorhies, A., Gomez, A., Nelson, K.E., 2017. The threat of antimicrobial resistance on the human microbiome. Microbial Ecology 74 (4), 1001–1008.

Brito, I.L., Yilmaz, S., Huang, K., Xu, L., Jupiter, S.D., Jenkins, A.P., et al., 2016. Mobile genes in the human microbiome are structured from global to individual scales. Nature 535 (7612), 435–439.

Broom, A., Broom, J., Kirby, E., 2014. Cultures of resistance? A Bourdieusian analysis of doctors' antibiotic prescribing. Social Science & Medicine 110, 81–88.

Broom, A., Broom, J., Kirby, E., Gibson, A., Davis, M., 2017. Antibiotic optimisation in' the bush': Local know-how and core-periphery relations. Health & Place 48, 56–62.

Brown, N., Nettleton, S., 2017. Bugs in the blog: Immunitary moralism in antimicrobial resistance (AMR). Social Theory & Health 15 (3), 302–322.

Brown, N., Nettleton, S., 2017. There is worse to come': The biopolitics of traumatism in antimicrobial resistance (AMR). The Sociological Review 65 (3), 493–508.

Brown, V.A., Harris, J.A., Russell, J.Y., 2010. In: Brown, V.A., Harris, J.A., Russell, J.Y. (Eds.), Tackling wicked problems through the transdisciplinary imagination. Taylor and Francis, New York.

Casadevall, A., Pirofski, L., 2014. Microbiology: Ditch the term pathogen. Nature News 516 (7530), 165.

Casadevall, A., Pirofski, L., 2018. What is a host? Attributes of individual susceptibility. Infection and Immunity 86 (2), e00636–17.

Challinor, V.L., Bode, H.B., 2015. Bioactive natural products from novel microbial sources. Annals of the New York Academy of Sciences 1354, 82–97.

Chandler, C., 2019. Current accounts of antimicrobial resistance: Stabilisation, individualisation and antibiotics as infrastructure. Palgrave Communications 5 (53), 1–13.

Chandler, C., Hutchinson, E., Hutchison, C., 2016. Addressing antimicrobial resistance through social theory: An anthropogenically oriented report. Accessed 3 May 2019 London School of Hygiene & Tropical Medicinehttp://researchonline.lshtm.ac.uk/id/eprint/3400500.

Cilliers, P., 2005. Complexity, deconstruction and relativism. Theory, Culture & Society 22 (5), 255–267.

Cockayne, D.G., Ruez, D., Secor, A., 2017. Between ontology and representation: Locating Gilles Deleuze's 'difference-in-itself' in and for geographical thought. Progress in Human Geography 41 (5), 580–599.

Centers for Disease Control and Prevention, 2013. Antibiotic resistance threats in the United States. Accessed 11 Feb 2019 US Department of Health and Human Serviceshttps://www.cdc.gov/drugresistance/pdf/ar-threats-2013-508.pdf.

Crofts, T.S., Gasparrini, A.J., Dantas, G., 2017. Next-generation approaches to understand and combat the antibiotic resistome. Nature Reviews Microbiology 15 (7), 422–434.
D'Costa, V.M., King, C.E., Kalan, L., Morar, M., Sung, W.W., et al., 2011. Antibiotic resistance is ancient. Nature 477 (7365), 457.
Davies, J., Davies, D., 2010. Origins and evolution of antibiotic resistance. Microbiology and Molecular Biology Reviews 74 (3), 417–433.
DeFries, R., Nagendra, H., 2017. Ecosystem management as a wicked problem. Science 356 (6335), 265–270.
Deleuze, G., 1994. Difference and repetition. Columbia University Press, New York.
Doolittle, W.F., 2013. Microbial neopleomorphism. Biology & Philosophy 28 (2), 351–378.
Dorman, M.J., Short, F.L., 2017. Genome watch: Klebsiella pneumoniae: When a colonizer turns bad. Nature Reviews Microbiology 15 (7), 384.
Dubos, R.J., 1958. The evolution of infectious diseases in the course of history. Canadian Medical Association Journal 79 (6), 445.
Finley, R.L., Collignon, P., Larsson, D.G., McEwen, S.A., Li, X.Z., et al., 2013. The scourge of antibiotic resistance: The important role of the environment. Clinical Infectious Diseases 57 (5), 704–710.
Fitzpatrick, D., Walsh, F., 2016. Antibiotic resistance genes across a wide variety of metagenomes. FEMS Microbiology Ecology 92 (2).
Fleming, A., Chain, E., Florey, H., 1945. Sir Alexander Fleming-Nobel lecture: Penicillin (Accessed 11 February 2019). http://www.nobelprize.org/nobel_prizes/medicine/laureates/1945/fleming-lecture.html.
Fynbo, L., Jensen, C.S., 2018. Antimicrobial stigmatization: Public health concerns about conventional pig farming and pig farmers' experiences with stigmatization. Social Science & Medicine 201, 1–8.
Gillings, M.R., Stokes, H.W., 2012. Are humans increasing bacterial evolvability?. Trends in Ecology & Evolution 27 (6), 346–352.
Giubilini, A., 2019. Antibiotic resistance as a tragedy of the commons: An ethical argument for a tax on antibiotic use in humans. Bioethics 33 (7), 776–784.
Grote, M., 2018. Petri dish versus Winogradsky column: A longue duree perspective on purity and diversity in microbiology, 1880s-1980s. History and Philosophy of the Life Sciences 40 (1), 11.
Groves, C., 2017. Emptying the future: On the environmental politics of anticipation. Futures 92, 29–38.
Guston, D.H., 2014. Understanding 'anticipatory governance'. Social Studies of Science 44 (2), 218–242.
Hardon, A., Sanabria, E., 2017. Fluid drugs: Revisiting the anthropology of pharmaceuticals. Annual Review of Anthropology 46 (1), 117–132.
Häsler, R., Kautz, C., Rehman, A., Podschun, R., Gassling, V., Brzoska, P., et al., 2018. The antibiotic resistome and microbiota landscape of refugees from Syria, Iraq and Afghanistan in Germany. Microbiome 6 (1), 37.
Hinchliffe, S., Allen, J., Lavau, S., Bingham, N., Carter, S., 2013. Biosecurity and the topologies of infected life: From borderlines to borderlands. Transactions of the Institute of British Geographers 38 (4), 531–543.
Ho, D., 2017. Love in the time of antibiotic resistance: How altruism might be our best hope. Philosophical issues in pharmaceutics. Springer, 257–271.
Hulme, M., 2009. Why we disagree about climate change. Cambridge University Press, Cambridge.
Inayatullah, S., 1998. Causal layered analysis - Poststructuralism as method. Futures 30 (8), 815–829.
Interagency Coordination Group on Antimicrobial Resistance (IACG), 2019. No time to wait: Securing the future from drug-resistant infections. Report to the Secretary-General of the United Nations (Accessed 4 April 2019). https://www.who.int/antimicrobial-resistance/interagency-coordination-group/final-report/en/.
Jalasvuori, M., Penttinen, R., 2017. What can evolutionary rescue tell us about the emergence of new resistant bacteria?. Future Microbiology 12 (9), 731–733.
Joronen, M., Häkli, J., 2017. Politicizing ontology. Progress in Human Geography 41 (5), 561–579.
Kenney, S., Watkiss, J., 2017. Surgeon X. Image Comics, London.
Kinch, M.S., Patridge, E., Plummer, M., Hoyer, D., 2014. An analysis of FDA-approved drugs for infectious disease: Antibacterial agents. Drug Discovery Today 19 (9), 1283–1287.
Klugman, K.P., Izadnegahdar, R., 2018. Antibiotic prophylaxis—Preventing severe infections and saving lives in poor countries with very high mortality risk. PLoS Medicine 15 (6).
Kuenzli, E., 2016. Antibiotic resistance and international travel: Causes and consequences. Travel Medicine and Infectious Disease 14 (6), 595–598.
Landecker, H., 2016. Antibiotic resistance and the biology of history. Body & Society 22 (4), 19–52.
Landecker, H., 2019. Antimicrobials before antibiotics: War, peace, and disinfectants. Palgrave Communications 5 (1), 45.
Latour, B., 1993. The pasteurization of France. Harvard University Press, Boston, Mass.
Lax, S., Nagler, C.R., Gilbert, J.A., 2015. Our interface with the built environment: Immunity and the indoor microbiota. Trends in Immunology 36 (3), 121–123.
Lebreton, F., Manson, A.L., Saavedra, J.T., Straub, T.J., Earl, A.M., Gilmore, M.S., 2017. Tracing the Enterococci from Paleozoic origins to the hospital. Cell 169 (5), 849-861 e13.
Levins, R., 2014. The road to wholeness in medicine and public health. International Critical Thought 4 (2), 221–240.
Levy, S.B., 1992. The antibiotic paradox: How miracle drugs are destroying the miracle. Springer.
Lorimer, J., Greenhough, B., Grenyer, R., Hodgetts, T., McLeod, C., Dwyer, A., 2019. Making the microbiome public: Participatory experiments with DNA sequencing in domestic kitchens. Transactions of the Institute of British Geographers https://doi.org/10.1111/tran.12289.
Ma, L., Li, B., Jiang, X.T., Wang, Y.L., Xia, Y., Li, A.D., et al., 2017. Catalogue of antibiotic resistome and host-tracking in drinking water deciphered by a survey. Microbiome 5, 154.
MacPherson, D.W., Gushulak, B.D., Baine, W.B., Bala, S., Gubbins, P.O., Holtom, P., et al., 2009. Population mobility, globalization, and antimicrobial drug resistance. Emerging Infectious Diseases 15 (11), 1727–1731.
McEwen, S.A., Angulo, F.J., Collignon, P.J., Conly, J.M., 2018. Unintended consequences associated with national-level restrictions on antimicrobial use in food-producing animals. The Lancet Planetary Health 2 (7), 279–282.
McGoey, L., 2012. The logic of strategic ignorance. The British Journal of Sociology 63 (3), 533–576.
Mendelson, M., Balasegaram, M., Jinks, T., Pulcini, C., Sharland, M., 2017. Antibiotic resistance has a language problem. Nature 545 (7652), 23–25.
Nett, J.E., 2019. Candida auris: An emerging pathogen "incognito"?. PLoS Pathogens 15 (4), e1007638.
Nerlich, B., James, R., 2009. The post-antibiotic apocalypse" and the "war on superbugs": Catastrophe discourse in microbiology, its rhetorical form and political function. Public Understanding of Science 18 (5), 574–590.
Niehus, R., Mitri, S., 2018. Handling unpredictable ecosystems. Nature Ecology and Evolution 2 (8), 1207–1208.
O'Neill, J., 2014. Review on antimicrobial resistance. Antimicrobial resistance: Tackling a crisis for the health and wealth of nations. HM Government, UK.
Organisation for Economic Co-operation and Development (OECD), 2018. Stemming the superbug tide. OECD health policy studies. Accessed 11 Feb 2019 OECD Publishing, Paris, https://read.oecd-ilibrary.org/social-issues-migration-health/stemming-the-superbug-tide_9789264307599-en#page4.
Orzech, K.M., Nichter, M., 2008. From resilience to resistance: Political ecological lessons from antibiotic and pesticide resistance. Annual Review of Anthropology 37 (1), 267–282.
Oyama, L.B., Girdwood, S.E., Cookson, A.R., Fernandez-Fuentes, N., Prive, F., et al., 2017. The rumen microbiome: An underexplored resource for novel antimicrobial discovery. NPJ Biofilms Microbiomes 3, 33.
Pascual, M., 2005. Computational ecology: From the complex to the simple and back. PLoS Computational Biology 1 (2), 101–105.
Paxson, H., Helmreich, S., 2014. The perils and promises of microbial abundance: Novel natures and model ecosystems, from artisanal cheese to alien seas. Social Studies of Science 44 (2), 165–193.
Pehrsson, E.C., Tsukayama, P., Patel, S., Mejia-Bautista, M., Sosa-Soto, G., et al., 2016. Interconnected microbiomes and resistomes in low-income human habitats. Nature 533 (7602), 212–216.
Perry, J., Waglechner, N., Wright, G., 2016. The prehistory of antibiotic resistance. Cold Spring Harbor Perspectives in Medicine 6 (6).
Pitlik, S.D., Koren, O., 2017. How holobionts get sick-toward a unifying scheme of disease. Microbiome 5 (1), 64.
Podolsky, S.H., 2015. The antibiotic era: Reform, resistance, and the pursuit of a rational therapeutics. Johns Hopkins University Press, Baltimore.
Podolsky, S.H., Bud, R., Gradmann, C., Hobaek, B., Kirchhelle, C., Mitvedt, T., Santesmases, M.J., Thoms, U., Berild, D., Lie, A.K., 2015. History teaches us that confronting antibiotic resistance requires stronger global collective action. The Journal of Law, Medicine & Ethics 43 (3-Supplment), 27–32.

Podolsky, S.H., 2018. The evolving response to antibiotic resistance (1945–2018). Palgrave Communications 4 (1), 124.
Poli, R., 2010. An introduction to the ontology of anticipation. Futures 42 (7), 769–776.
Poli, R., 2014. Anticipation: What about turning the human and social sciences upside down?. Futures 64, 15–18.
Poli, R., 2017. Introducing anticipation. In: Poli, R. (Ed.), Handbook of anticipation: Theoretical and applied aspects of the use of future in decision making. Springer International Publishing, pp. 1–14.
Protevi, J., 2012. Deleuze and life. In: Smith, D.W., Hall, H.S. (Eds.), The Cambridge companion to deleuze. Cambridge University Press, pp. 239–264.
Reznick, D., King, K., 2017. Antibiotic resistance: Evolution without trade-offs. Nature Ecology & Evolution 1 (3), 66.
Rook, G.A., Raison, C.L., Lowry, C.A., 2014. Microbial' old friends', immunoregulation and socioeconomic status. Clinical & Experimental Immunology 177 (1), 1–12.
Roope, L.S., Smith, R.D., Pouwels, K.B., Buchanan, J., Abel, L., Eibich, P., et al., 2019. The challenge of antimicrobial resistance: What economics can contribute?. Science 364 (6435).
Rosen, J., Kineman, J.J., 2005. Anticipatory systems and time: A new look at Rosennean complexity. Systems Research and Behavioral Science 22 (5), 399–412.
Rosen, W., 2017. Miracle cure: The creation of antibiotics and the birth of modern medicine. Penguin.
Sardar, Z., 2015. Postnormal times revisited. Futures 67, 26–39.
Sauer, K., Rickard, A.H., Davies, D.G., 2017. Biofilms and biocomplexity. Microbe-American Society for Microbiology 2 (7), 347.
Schroeder, M., Brooks, B.D., Brooks, A.E., 2017. The complex relationship between virulence and antibiotic resistance. Genes (Basel) 8 (1).
Scott, A.M., Beller, E., Glasziou, P., Clark, J., Ranakusuma, R.W., Byambasuren, O., Bakhit, M., Page, S.W., Trott, D., Del Mar, C, 2018. Is antimicrobial administration to food animals a direct threat to human health? A rapid systematic review. International Journal of Antimicrobial Agents 52 (3), 316–323.
Scudellari, M., 2017. Cleaning up the hygiene hypothesis. Proceedings of the National Academy of Sciences of the United States of America 114 (7), 1433–1436.
Shamarina, D., Stoyantcheva, I., Mason, C.E., Bibby, K., Elhaik, E., 2017. Communicating the promise, risks, and ethics of large-scale, open space microbiome and metagenome research. Microbiome 5 (1), 132.
Singer, A., 2017. Antimicrobial resistance: More than just overusing antibiotics. The Pharmaceutical Journal 298 (7898)https://doi.org/10.1211/PJ.2017.20202286.
Singer, A.C., Shaw, H., Rhodes, V., Hart, A., 2016. Review of antimicrobial resistance in the environment and its relevance to environmental regulators. Frontiers in Microbiology 7, 1728.
Singer, R.S., Ward, M.P., Maldonado, G., 2006. Can landscape ecology untangle the complexity of antibiotic resistance?. Nature Reviews Microbiology 4 (12), 943.
Stallins, J.A., Law, D.M., Strosberg, S.A., Rossi, J.J., 2017. Geography and postgenomics: How space and place are the new DNA. GeoJournal 83 (1), 153–168.
Su, J.Q., An, X.L., Li, B., Chen, Q.L., Gillings, M.R., Chen, H., et al., 2017. Metagenomics of urban sewage identifies an extensively shared antibiotic resistome in China. Microbiome 5 (1), 84.
Tang, K.L., Caffrey, N.P., Nóbrega, D.B., Cork, S.C., Ronksley, P.E., Barkema, H.W., Polachek, A.J., Ganshorn, H., Sharma, N., Kellner, J.D., 2017. Restricting the use of antibiotics in food-producing animals and its associations with antibiotic resistance in food-producing animals and human beings: A systematic review and meta-analysis. The Lancet Planetary Health 1 (8), 316–327.
Tripathi, V., Cytryn, E., 2017. Impact of anthropogenic activities on the dissemination of antibiotic resistance across ecological boundaries. Essays in Biochemistry 61 (1), 11–21.
Ulanowicz, R.E., 2016. A call for metaphysical reform. Ludus Vitalis 17 (32), 459–463.
Vallis, R., Inayatullah, S., 2016. Policy metaphors: From the tuberculosis crusade to the obesity apocalypse. Futures 84, 133–144.
van Aaken, A., Antonovics, J., 2016. Too big to handle? Interdisciplinary perspectives on the question of why societies ignore looming disasters. Global Policy 7, 1–4.
Van Goethem, M.W., Pierneef, R., Bezuidt, O.K.I., Van De Peer, Y., Cowan, D.A., Makhalanyane, T.P., 2018. A reservoir of' historical' antibiotic resistance genes in remote pristine Antarctic soils. Microbiome 6 (1), 40.
Ventola, C.L., 2015. The antibiotic resistance crisis: Causes and threats. Pharmacy and Therapeutics 40 (4), 277–283.
Wallinga, D., Rayner, G., Lang, T., 2015. Antimicrobial resistance and biological governance: Explanations for policy failure. Public Health 129 (10), 1314–1325.
Wang, R.L., van Dorp, l. P., Shaw, P., Bradley, Q., Wang, X., Jin, L., et al., 2018. The global distribution and spread of the mobilized colistin resistance gene mcr-1. Nature Communications 9 (1), 1179.
Will, C.M., 2018. Editorial: Beyond behavior? Institutions, interactions and inequalities in the response to antimicrobial resistance. Sociology of Health and Illness 40 (3), E1–E9.
Will, C., 2019. The problem and the productivity of ignorance: Public health campaigns on antibiotic stewardship. Sociological Review. In: http://sro.sussex.ac.uk/id/eprint/81753.
Wimsatt, W.C., 2007. Re-engineering philosophy for limited beings: Piecewise approximations to reality. Harvard University Press, Cambridge, Mass.
World Health Organization, 2016. Campaign tools and materials for world antibiotic awareness week. Accessed 19 August 2019 https://sites.wpro.who.int/antibiotic_awareness/?page_id = 1062.
World Health Organization, 2017. Critically important antimicrobials for human medicine. Accessed 11 Feb 2019 World Health Organization, Geneva, https://apps.who.int/iris/handle/10665/255027.