The Anthropocene Operating Space for Antimicrobial Resistance: tipping points in treatability of priority pathogens

Tiscar Graells^{1*}, Christine Heinzl^{2,3}, Peter Søgaaard Jørgensen^{1,2}

¹Global Economic Dynamics and the Biosphere, Royal Swedish Academy of Sciences, Stockholm, Sweden

²Stockholm Resilience Centre, Stockholm University, Stockholm, Sweden

³Department of Geography, Rheinische Friedrich-Wilhelms University Bonn, Bonn, Germany

* Correspondence:

Tiscar Graells, PhD

tiscar@kva.se; tiscar.graells@e-campus.uab.cat;

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Abstract

Evolution of antimicrobial resistance, especially antibiotic resistance, results from complex dynamics between microorganisms, stressors and the environment itself, where non-linear dynamics are present with unpredictable impacts on treatability, and therefore, on society. The Anthropocene Operating Space for Antimicrobial Resistance is a recent framework for risk-assessment of tipping-points in treatability by combining information about the level of resistance and the effects of available antimicrobials. Here, we develop this framework at an increased level of resolution and extent compared to previous analysis adding three sub-zones to the original three zone framework and applying it to 20 priority pathogens, constituting its first application at the pathogen level, including fungal pathogens. In doing so, we also provide updated definitions of each zone and sub-zone together with an overview of mechanisms and contexts contributing to treatability of tipping point risks. We find that 7 out of 20 assessed priority pathogens (6 out of 11 Gram-negative bacteria) are in the zone of highest risk where widespread tipping points in treatability are most likely (surpassed zone). Namely, *Acinetobacter* spp., *Pseudomonas* spp., *Enterobacteriaceae* (*Escherichia coli* and *Klebsiella pneumoniae*), *Neisseria gonorrhoeae* and the yeast *Candida auris* are those assessed exceeding our current resources. Meanwhile, *Mycobacterium tuberculosis*, *Clostridioides difficile*, *Staphylococcus aureus*, *Enterococcus* and *Salmonella* are classified at very high risk of crossing the tipping point in treatability. The problem of antimicrobial resistance is often described as a future threat in the so-called post-antibiotic era. However, our assessment concludes we may have surpassed the threshold in some of the scenarios, and that we are on the edge in others. The proposed framework, being easy to implement across sectors, while requiring little or no economic investment, unifies criteria to be used between different key actors joining two important parameters in antimicrobial resistance: the epidemiological state of priority pathogens and treatment sustainability. In the future the framework can be expanded to other pathogens and repeated assessments will be useful as an indicator of tracking trends in treatability tipping-point risks.

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1. Introduction

The effectiveness of antibiotics has been waning since they were introduced into modern medicine over 70 years ago. Today our inability to treat infections compromises clinical practices previously taken for granted (e.g. prophylactic use in surgery, cancer or dialysis) and affects negatively patient outcomes including higher mortality and/or morbidity. Antimicrobial resistance (AMR) increases costs in the healthcare system due to (i) more extended periods in facilities, (ii) infection control interventions and (iii) need for more costly alternative therapies (Wernli et al., 2017; Kousouli et al., 2019). Although governments have recently committed to take action and mitigate the effects of AMR, the consequences for human health are likely to worsen given the global increase in antibiotic use (50 % between 2000 and 2015) (Klein et al., 2018), the projected increase in antibiotic use for livestock production (Van Boeckel et al., 2017) and the extensive and often un-reported use of antimicrobials in the growing aquaculture sector (Henriksson et al., 2018). AMR ranks alongside climate change as a global environmental challenge (Laxminarayan et al., 2016; Jørgensen et al., 2018) with antibiotic resistant infections involved in the deaths of hundreds of thousands of people every year (Laxminarayan et al., 2016; US CDC, 2019) and healthcare associated costs estimated in billions of dollars (for direct, additional costs and lost productivity) per year in the United States alone (van Duin and Doi, 2017).

Previously known susceptible strains have acquired resistance (Van Hoek et al., 2011) typically due to selection pressure of antimicrobials and their residues that select for advantageous mutations that affect strains clonally (intraspecific) within microbial populations (Aslam et al., 2018). Although this happens naturally, environments influenced by anthropogenic forces (e.g. the release of antimicrobials or their residues in natural settings) become ‘hotspots’ due to strong ecoevolutionary dynamics between human activity and the environment (Jørgensen et al., 2020). ‘Hotspots’ are those ecosystems where emergence, spread and persistence of resistance is likely to happen. Examples are hospitals, farms, wastewater or pharmaceutical facilities (Andersson and Hughes, 2011; Gullberg et al., 2011; Kristiansson et al., 2011; Kraemer et al., 2019). Microorganisms live in complex ecosystems where they interact simultaneously with each other, with the environment and on multiple levels. This can lead to different responses to the same condition making outcomes uncertain and hindering long-term predictions. This aperiodic behaviour due to non-linear dynamics (Strogatz, 2007) in microorganisms (**Table 1**) can perpetuate, spread or hinder resistance (Holmes et al., 2015; Jørgensen et al., 2018). This lack of periodicity with little or no correlation over time is what prevent to predict the behaviour of variables and components in microbial communities and ecosystems (Strogatz, 2007). Many projects study AMR following linear dynamics (e.g. growth curves studies), while systems in reality are non-linear remaining poorly understood. Acquired resistance, from acquisition of foreign resistance genes often located in mobile genetic elements passed vertically and horizontally (intra- and interspecific) within the same or related species of bacteria (Martínez and Baquero, 2014; Kraemer et al., 2019), is an example of such aperiodic non-linear behaviour. Horizontal gene transfer (HGT) makes resistance genes available among microbial communities that temporarily or permanently share habitat and location (Martínez, 2012; Bengtsson-Palme et al., 2018) with unpredictable exchanges and outcomes. HGT is among the most important non-linear dynamics in resistance evolution (**Table 1**) jointly with long-distance transmission of strains because of trips and social connectivity (Frost et al., 2019; Hernández-García et al., 2019) (**Table 1**). Other complex dynamics also lead to treatment failure with similar clinical outcomes as resistance (**Table 1**), but they are often not being considered to assess the risk in treatability for global public health

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as there are gaps of knowledge within and among them and the majority are still being studied, such as heteroresistance (Andersson et al., 2019).

Careful surveillance of AMR is fundamental to understanding the current context and public health situation. ESKAPE list (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and *Enterobacter spp*) (Rice, 2008; Boucher et al., 2009) is among the initial frameworks of problematic priority microorganisms to surveil worldwide but tracking lists have been enlarged since 2008 and monitored pathogens can vary across locations depending on resistance rates (<https://resistancemap.cddep.org/AntibioticResistance.php>).

In addition to monitoring AMR phenotypically, knowledge of mechanisms and specific genetic resistances involved, including well described detection guidelines, is also crucial for understanding the AMR context (Martinez- and Simonsen, 2017).

Increasing AMR has put in the spotlight frameworks for resistant microorganisms that urgently need innovative therapies or new drugs (CDC_2019; WHO_2017). Despite that, industry and large pharmaceutical companies are not investing enough in this research and these tasks have been devolved upon public universities or public research organizations (Vila et al., 2019).

Table 1: Non-linear dynamics in antibiotic and antimicrobial resistance and their role in treatment failure or clinical adverse outcomes.

TYPE OF DYNAMIC	SIGNIFICANCE	REFERENCES
Horizontal Gene Transfer (HGT) of resistance genes	Transference of antibiotic resistance gene(s), whose acquisition allows growth at high concentrations of the antibiotic irrespectively of the time and exposure duration, through mobile genetic elements between different strains within the same or different species.	(Stokes and Gillings, 2011; Perry and Wright, 2013)
Co-selection of resistance	Other stressors present in a defined environment (antimicrobials, heavy metals or biocides) co-select for antibiotic resistance as resistance genes to these are often located together in mobile genetic elements.	(Gullberg et al., 2014; Cheng et al., 2019)
Cross-resistance to other antimicrobials	A specific biocide or drug resistance select also for resistance to other antimicrobials or antibiotics. It often affects, but not only, antimicrobials with similar targets or inside the same class.	(Ferretti et al., 2016; Hashemi et al., 2019)
Selection at very low concentration of antimicrobials	Selective pressure towards antibiotic resistance at several hundred fold below the lethality for susceptible cells which can be found in natural environments, sewage plants, body and cell compartments.	(Gullberg et al., 2011; Wistrand-Yuen et al., 2018)
Tolerance	Induced dormancy or cease of an essential process of a whole bacterial population that is triggered by stressful conditions. It enables temporary survival to bactericidal antimicrobials at concentrations that would be lethal.	(Brauner et al., 2016; Levin-Reisman et al., 2019)
Persistence	Reversible phenotype characterized by slow metabolism or dormancy of a subpopulation inside a main population of bacteria. It enables survival of the persister subpopulation(s) despite having genetic susceptibility, and after the stress, persisters grow normally and they can re-establish infection.	(Brauner et al., 2016; Fisher et al., 2017)
Heteroresistance	Unstable phenotype caused by reversible spontaneous genetic modifications that lead to antimicrobial susceptibility reduction. This reduction affects subpopulation(s) of a main bacterial population and it could contribute to adverse clinical outcomes.	(Andersson et al., 2019; Nicoloff et al., 2019)
Biofilms	Structures where bacteria surround themselves with a polymeric matrix that grows thicker and embeds other microorganisms developing to a complex structure where cells are protected. Most chronic infections involve biofilms, as only antibiotics are often ineffective with them.	(Monroe, 2007; Ciofu and Tolker-Nielsen, 2019; Cabrera et al., 2020)
Long-distance transmission	Travels and high connectivity allow bottom-up scale transmission of infectious diseases from local to global and between distant places in short periods of time.	(Frost et al., 2019; Hernández-García et al., 2019)

Without new antimicrobials in the market, emergence and rapid spread of resistance in the last decade set the need for common worldwide classifications to describe microorganisms becoming problematic. The first framework widely used standardized the definitions for multidrug-resistant (MDR), extensively drug-resistant (XDR) and pandrug-resistant (PDR) bacteria using guidelines of clinical breakpoints for *Staphylococcus aureus*, *Enterococcus spp.*,

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Enterobacteriaceae (except for *Salmonella* and *Shigella*), *Pseudomonas aeruginosa* and *Acinetobacter* spp. (Magiorakos et al., 2012). Other pathogens such as mycobacteria, *Salmonella* spp., or *Neisseria gonorrhoeae* can also be classified by it (Parry and Threlfall, 2008; Hendriksen et al., 2009; Richter et al., 2009; Tapsall et al., 2009; Magiorakos et al., 2012). Acquired non-susceptibility to at least one agent in three antimicrobial categories describes MDR. Acquired non-susceptibility to at least one agent in all but two or fewer antimicrobial categories defines XDR, whereas non-susceptibility to all antimicrobial agents defines PDR. Given that, simple drug-resistance can be thought as the natural susceptible pattern of a wild-type microorganism. Proposed more recently, the Anthropocene Operating Space (AOS) of biocide susceptibility framework classifies microorganisms using the precautionary risk of planetary boundaries (Jørgensen et al., 2018). Planetary boundaries define and delimit key functions and tipping points using assessments of the impacts of human activities on systems (Steffen et al., 2015). Planetary boundaries focus on areas and processes of the system that determine the self-regulating capacity of the planet and where humans can safely operate. This concept incorporates tipping points or thresholds related to processes and reaching or crossing those can trigger non-linear abrupt changes in the functioning of the system, with risk of sudden and irreversible changes, thereby diminishing resilience from regional to global consequences (Steffen et al., 2015). The AOS assessed the state and governance priorities of biocide susceptibility at general level of Gram-positive and Gram-negative bacteria, using zones of increasing risk for current antimicrobial practices: 'safe', 'uncertain' and 'surpassed' (Jørgensen et al., 2018). No relevant resistance or presence of single biocide resistance at low frequencies and with many other available biocides falls into 'safety' whereas 'uncertainty' is entered when less desirable treatments must be applied due to multiple resistance or when single resistance is common but few alternatives are available. Therefore, when resistance is observed to all relevant therapies (pan-resistance) the surpassed zone is entered (Jørgensen et al., 2018).

As it is shown, multiple classifications exist for ranking resistance in terms of sizing the threat and urgency for taking action but global application of them is difficult as they apply heterogeneous and specific criteria. In our comprehensive study, well-known established classifications of AMR, non-linear dynamics of ecosystems involved in resistance and risk-assessment of current tipping points in treatability, based on updated literature search, at the level of priority pathogens have been integrated in a holistic framework for public health use. This framework called the Anthropocene Operating Space for Antimicrobial Resistance (AOS for AMR) can be used, alone or with other frameworks, in a 'One Health' context and across sectors to inform and to warn of the current situation and limitations where we can safely operate and maintain effective therapies. While advising towards global sustainable policies, from a worldwide perspective, the AOS for AMR details the current situation of 20 priority pathogens for global public health protection purposes.

2. Methodology

a. Identifying a set of priority organisms for assessment

Microorganisms at individual level were identified and assessed in this study for risk of tipping points in resistance associated with remaining efficacious antibiotics. This selection compares and combines some of the major important and well-established surveillance frameworks in human medicine on a global scale or on supranational or large national organizations (Table 2). However, not all regions and countries are equally represented or have robust surveillance

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systems. Low-middle-income countries (LMICs) in Asia, Africa and South-America often cope with multiple challenges, if they do have those systems (Ashley et al., 2018). The major surveillance system established worldwide is the Global Antimicrobial Resistance Surveillance System hosted by the World Health Organization (WHO) that gathers AMR data of 8 bacteria (WHO, 2017) (Table 2). Moreover, big supranational organizations (e.g. in Europe different programs inside The European Surveillance System) and national surveillance programmes of large countries (e.g. United States Centers for Disease Control and Prevention (US CDC)) were considered to identify and compare microorganisms commonly tracked (Table 2).

Apart from surveillance, new approaches or new drugs are urgently needed for pathogens identified by WHO in its list of pathogens for which new antibiotics are urgently needed and by US CDC in its estimations of cases/infections and deaths per year caused by resistant microorganisms (Table 3) (CDC_2019; WHO_2017).

Table 2: Microorganisms tracked in antimicrobial resistance surveillance programmes sponsored by health organizations worldwide. AGAR= Australian Group on Antimicrobial Resistance, AGSP= Australian Gonococcal Surveillance Programme, ARLN= CDC Antibiotic resistance Lab Network, AESOP= Australian Enterococcal Sepsis Outcome Program, ASSOP= Australian Staphylococcal Sepsis Outcome Program, CAESAR= Central Asian and Eastern European Surveillance of Antimicrobial Resistance, US CDC= Centers for Disease Control and Prevention in United States, EARS-Net= European Antimicrobial Resistance Surveillance Network, ECDC = European Centre for Disease and Control, ECDIS-Net= European Clostridium difficile Infection Network project, EURGen-Net= European Antimicrobial Resistance Genes Surveillance Network, Euro-GASP= European Gonococcal Antimicrobial Surveillance Programme, FWD-Net= European Food- and Waterborne Diseases and Zoonosis Network, GISP= Gonococcal Isolate Surveillance Project, GLASS= Global Antimicrobial Resistance Surveillance System, GNSOP= Gram Negative Sepsis Outcome Program, NARMS= National Antimicrobial Resistance Monitoring System for Enteric Bacteria in the US, TME= WHO Tuberculosis Monitoring and Evaluation platform, WHO= World Health Organization, GASP= WHO Gonococcal Antimicrobial Surveillance Programme, *= including also other *Enterobacteriaceae*, ¢= starting from 2020/2021, §= Shiga toxin producing *Escherichia coli* (STEC), §§ sponsored by the Australian Government- Department of Health, ¤= and European Food Safety Authority (EFSA).

		Sponsor or collaborative organizations of surveillance systems				
		Global	International		National	
	Microorganism	WHO	ECDC	WHO-RIVM-ESCMID	US CDC	AGAR
Gram Negative bacteria	<i>Klebsiella pneumoniae</i>	GLASS	EARS-Net /EURGen-Net*	CAESAR	ARLN*	GNSOP*
	<i>Acinetobacter spp.</i>	GLASS	EARS-Net /EURGen-Net ¢	CAESAR	ARLN	GNSOP
	<i>Pseudomonas aeruginosa</i>		EARS-Net	CAESAR		GNSOP
	<i>Escherichia coli</i>	GLASS	EARS-Net /EURGen-Net*§ /FWD-Net §ª	CAESAR	ARLN*/NARMS	GNSOP*
	<i>Neisseria gonorrhoeae</i>	GLASS/ GASP	Euro-GASP		ARLN/GISP	AGSP§§
	<i>Salmonella spp.</i>	GLASS	FWD-Net ¤	CAESAR	ARLN/NARMS	
	<i>Shigella spp.</i>	GLASS			NARMS	
	<i>Campylobacter</i>		FWD-Net ¤		NARMS	
Gram Positive bacteria	<i>Staphylococcus aureus</i>	GLASS	EARS-Net ¤	CAESAR		ASSOP
	<i>Streptococcus pneumoniae</i>	GLASS		CAESAR	ARLN	AESOP
	<i>Enterococcus spp.</i>		EARS-Net	CAESAR		
	<i>Clostridioides</i>		ECDIS-Net		ARLN	
Other bacteria	<i>Mycobacterium tuberculosis</i>	TME	Tuberculosis Disease Network		ARLN	
Fungi	<i>Candida spp.</i>				ARLN	

Table 3: Urgent threats that require new available antibiotics. US CDC= Centers for Disease Control and Prevention, CR= Carbapenem Resistant, C3G= Third generation Cephalosporin, FQ= Fluoroquinolone, ESBL= Extended Spectrum B-Lactamase, MDR= Multidrug Resistant, MRSA= Methicillin Resistant *Staphylococcus aureus*, NA = Not assessed, R= Resistant, VISA= Vancomycin- Intermediate *Staphylococcus aureus*, VRSA= Vancomycin Resistant *Staphylococcus aureus*, VRE= Vancomycin Resistant Enterococcus, WHO= World Health Organization, XDR= Extensively-drug Resistant, *=not assessed but considered critical.

Microorganism (s)		WHO		US CDC	
		Threat level	Resistance mechanism / profile	Threat level	Resistance mechanism / profile
Gram Negative bacteria	<i>Enterobacteriaceae</i>	Critical	CR	Critical	CR
	<i>Acinetobacter spp.</i>	Critical	CR	Serious	MDR/XDR

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	<i>Pseudomonas aeruginosa</i>	Critical	CR	Serious	MDR/XDR
	<i>Enterobacteriaceae</i>	Critical	ESBL	Serious	ESBL
	<i>Neisseria gonorrhoeae</i>	High	C3G R, FQ R	Critical	C3G R, FQ R
	<i>Salmonellae</i>	High	FQ R	Serious	FQ R
	<i>Shigella</i> spp.	Medium	FQ R	Serious	FQ R
	<i>Campylobacter</i> spp.	High	FQ R	Serious	FQ R
	<i>Helicobacter pylori</i>	High	Clarithromycin R	NA	NA
	<i>Haemophilus influenzae</i>	Medium	Ampicillin R	NA	NA
Gram Positive bacteria	<i>Clostridioides difficile</i>	NA	NA	Critical	NA
	<i>Staphylococcus aureus</i>	High	MRSA, VISA/VRSA	Serious	MRSA, VISA/VRSA
	<i>Enterococcus</i> spp	High	VRE	Serious	VRE
	<i>Streptococcus pneumoniae</i>	Medium	Penicillin R	Serious	Penicillin R
	<i>Streptococcus</i> Group A	NA	NA	Concerning	Erythromycin R
	<i>Streptococcus</i> Group B	NA	NA	Concerning	Clindamycin R
Other bacteria	<i>Mycobacterium tuberculosis</i>	NA*	NA	Serious	XDR
Fungi	<i>Candida auris</i>	NA	NA	Critical	NA
	<i>Candida</i> spp.	NA	NA	Serious	Fluconazole R

b. Operationalization, criteria and categories of the Anthropocene Operating Space for Antimicrobial Resistance (AOS for AMR)

To operationalize the framework at the level of individual pathogens, the commonly used MDR-XDR-PDR framework and the AOS framework were integrated (**Table 4**) (Magiorakos et al., 2012; Jørgensen et al., 2018).

Table 4: Operationalization of the Anthropocene Operating Space framework for Antimicrobial Resistance (AOS for AMR). AMR= antimicrobial resistance; AOS =Anthropocene Operating Space; MDR= Multidrug resistance; PDR=pandrug resistance; SDR= simple drug resistance; XDR=extensively-drug resistance.

FRAMEWORK		
MDR-XDR-PDR + AOS INTEGRATION		AOS for AMR
PDR	Surpassed zone	Surpassed zone: Therapy unavailable (resistance is observed to all relevant biocides)
XDR / MDR	Uncertain zone	Uncertain zone: Less desirable therapies or few alternatives (multiple biocide resistance is observed or single biocide resistance is common with few alternatives)
SDR	Safe zone	Safe zone: Therapy available (no relevant resistance / presence of single biocide resistance at low frequencies)

The final operationalization divided the uncertain zone into 3 areas ending up in five zones (**Table 5**) to better adapt the complexity of AMR not reflected in the initial categorization. The chosen criteria for this new organization (by importance) are: (i) Reported acquired resistance in literature; and (ii) threat level and priority for new drugs (**Table 3**). The first criteria implies that selected microorganisms tracked have already acquired mechanisms of resistance that have also been detected and described in literature. To be used for public health protection purposes, when acquired resistance at the level of MDR, XDR and PDR is well-described in literature the species is categorized according to this profile independently of the percentage of strains having this resistance pattern. Therefore, a literature search was done for each pathogen looking for PDR ('(pandrug or pan-drug) and resistance' or 'pan-resistance or panresistance'). Otherwise, the search was focused on the next level, XDR. If XDR was not described, finally the literature search was done looking for MDR. The second criteria emphasizes the importance of innovation in medicine to have available therapies to treat infections and to ensure clinical procedures that rely on antibiotics. Depending on the risk of treatability being compromised, final categories were: (i) surpassed zone, (ii) uncertain zone high risk area, (iii) uncertain zone medium risk, (iv) uncertain zone low risk; and (v) safe zone.

Table 5: Decision criteria for the Anthropocene Operating Space for Antimicrobial Resistance framework (assessment based on Table 3 and Table 4). AMR= antimicrobial resistance; AOS =Anthropocene Operating Space; MDR= Multidrug resistance; PDR=pandrug resistance; SDR= simple drug resistance; XDR=extensively drug resistance; R=resistance.

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CRITERIA		ASSESSMENT
HIGHEST R REPORTED	THREAT LEVEL, PRIORITY FOR NEW DRUGS	AOS for AMR
PDR	All cases	Surpassed zone
XDR	Critical	Surpassed zone
XDR	Serious or High	Uncertain zone: high risk
XDR	Concerning or Medium	Uncertain zone: medium risk
MDR	Critical	Uncertain zone: high risk
MDR	Serious or High	Uncertain zone: medium risk
MDR	Concerning or Medium	Uncertain zone: low risk
SDR	All cases	Safe zone

3. Results: risk assessment of tipping points in treatability for priority pathogens

Here we assess the current risk of tipping points in priority pathogens (**Table 2** and **3**) according to the operationalized AOS for AMR framework (**Table 5**). The final assessment is specified in **Table 6** and **Figure 1** with the latter showing the planetary boundary regions.

The first level of risk is the ‘surpassed zone’ which includes microorganisms whose treatability is already compromised because the tipping point has been surpassed. In the surpassed category there are 7 out of 20 pathogens assessed 6 Gram- negative bacteria (GNB) and 1 fungi being them: (I) *Acinetobacter* genus, (II) *Pseudomonas aeruginosa* (*P.aeruginosa*), (III) *Escherichia coli* (*E.coli*), (IV) *Klebsiella pneumoniae* (*K.pneumoniae*), (V) other *Enterobacteriaceae* (without *Salmonella* and *Shigella*) at community or hospital level, (VI) *Neisseria gonorrhoeae* (*N.gonorrhoeae*) at community level and (VII) the yeast *Candida auris* (*C.auris*) at hospital level.

The uncertain zone covers a range of increasing risk of treatability being compromised. It comprises 3 areas of risk (high, medium, low) and the rest of pathogens assessed (13 out of 20). All priority Gram-positive bacteria (GPB) pathogens are inside this area (6 out of 20).

The second level of the AOS for AMR is the uncertain high risk area which is just reaching the tipping point and where microorganisms are at high risk of surpassing it. It includes 5 pathogens out of the 13 inside uncertainty, and, 5 out of the 20 assessed. In this category we find (I) *Salmonella*, (II) *Mycobacterium tuberculosis* (TB) and the firsts GPB until now. (III) *Clostridioides difficile* (*C.difficile*), (IV) *Staphylococcus aureus* (*S.aureus*) and (V) the genus *Enterococcus*.

The third level includes 6 pathogens inside the uncertain zone medium risk implying that the tipping point can be reached by those pathogens. It is the most heterogeneous sub-zone with MDR and XDR pathogens and serious/high or concerning/medium priority for new drugs. It includes the fungal genus (I) *Candida* (except *C.auris* assessed inside the first level-surpassed); the GNB genera (II) *Shigella* and (III) *Campylobacter*, the species (IV) *Helicobacter pylori* (*H.pylori*), (V) *Haemophilus influenzae* (*H.influenzae*) and the GPB (VI) *Streptococcus pneumoniae* (*S.pneumoniae*).

The fourth level closes the uncertain area with low risk and it only includes GPB pathogens (2 out of 13). This fourth level implies availability of therapies but increasing resistance to key and critical antibiotics of microorganisms that have left the safe zone. (I) *Streptococcus* group A (GAS) and (II) *Streptococcus* group B (GBS) belong to this sub-zone.

The fifth level in riskiness or ‘safe zone’ is the wild-type susceptibility or intrinsic resistance of microorganisms that could fit in the safe area in **Figure 1** and probably it includes most microorganisms not mentioned in **Table 6**.

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Figure 1: Current global status of treatability in selected pathogens using the Anthropocene Operating Space for Antimicrobial Resistance framework. *Acinetoba*= *Acinetobacter* genus; *C.difficile*= *Clostridioides difficile*; *Campy*= *Campylobacter* genus; *Candida*= *Candida* genus except *Candida auris*; *C.auris*= *Candida auris*; *Enterobact*= *Enterobacteriaceae* family except *Escherichia coli*, *Klebsiella pneumoniae* and genera *Salmonella* and *Shigella*; *Enterococ*= *Enterococcus* genus; *E.coli*= *Escherichia coli*; *GAS*= *Streptococcus* Group A; *GBS*= *Streptococcus* Group B; *H.influen*= *Haemophilus influenzae*; *H.pylori*= *Helicobacter pylori*; *K.pneumo*= *Klebsiella pneumoniae*; *N.gono*= *Neisseria gonorrhoeae*; *P.aerugi*= *Pseudomonas aeruginosa*; *Salmonella*= *Salmonella* genus; *Shigella*= *Shigella* genus; *S.pneumo*= *Streptococcus pneumoniae*; *S.aureus*= *Staphylococcus aureus*; *TB*= *Mycobacterium tuberculosis*.

Table 6: Assessment of tipping points in treatability in selected pathogens using the Anthropocene Operating Space for Antimicrobial Resistance (AOS for AMR) framework based on Table 5. HR= high risk, LR= low risk MR= medium risk, MDR= Multidrug resistance; PDR=pandrug resistance; XDR=extensively-drug resistance. *= except *Escherichia coli*, *Klebsiella pneumoniae*, and genus *Salmonella* and *Shigella*.

	Microorganism(s)	AOS for AMR assessment	Reported resistance	Innovation need (Table 3)	References
Gram Negative bacteria	<i>Acinetobacter</i> spp.	Surpassed	PDR	Critical	(Rolain et al., 2013; Göttig et al., 2014; Nowak et al., 2017)
	<i>Pseudomonas aeruginosa</i>	Surpassed	PDR	Critical	(Khosravi and Mohammadian, 2016; Shokri et al., 2016)
	<i>Klebsiella pneumoniae</i>	Surpassed	PDR	Critical	(Avgoulea et al., 2018)
	<i>Escherichia coli</i>	Surpassed	PDR	Critical	(Kim et al., 2019)
	<i>Enterobacteriaceae</i> * (e.g. <i>Enterobacter</i> , <i>Citrobacter</i> , <i>Proteus</i> , <i>Morganella</i> , <i>Providencia</i> , <i>Serratia</i>)	Surpassed	PDR	Critical	(Gruber et al., 2014; Hernández-García et al., 2018)
	<i>Neisseria gonorrhoeae</i>	Surpassed	XDR	Critical	(Cámara et al., 2012; ECDC, 2018)
	<i>Salmonella</i> spp.	Uncertain: HR	XDR	Serious	(EFSA-ECDC, 2020)
	<i>Shigella</i> spp.	Uncertain: MR	MDR	Serious	(Puzari et al., 2018)
	<i>Campylobacter</i> spp.	Uncertain: MR	MDR	Serious	(Sproston et al., 2018; EFSA-ECDC, 2020)
	<i>Helicobacter pylori</i>	Uncertain: MR	MDR	High	(Boyanova et al., 2019)
Gram Positive bacteria	<i>Haemophilus influenzae</i>	Uncertain: MR	XDR	Medium	(Su et al., 2020)
	<i>Clostridioides difficile</i>	Uncertain: HR	MDR	Critical	(Peng et al., 2017)
	<i>Enterococcus</i> spp.	Uncertain: HR	XDR	Serious	(Said and Abdelmegeed, 2019)
	<i>Staphylococcus aureus</i>	Uncertain: HR	XDR	Serious	(Cabrera et al., 2020)

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	<i>Streptococcus pneumoniae</i>	Uncertain: MR	MDR	Serious	(Cillóniz et al., 2018)
	<i>Streptococcus</i> Group A	Uncertain: LR	MDR	Concerning	(Ferretti et al., 2016)
	<i>Streptococcus</i> Group B	Uncertain: LR	MDR	Concerning	(Moraleda et al., 2018)
Other	<i>Mycobacterium tuberculosis</i>	Uncertain: HR	XDR	Serious	(ECDC, 2019)
	<i>Candida spp.</i>	Uncertain: MR	MDR	Serious	(Arendrup and Patterson, 2017)
Fungi	<i>Candida auris</i>	Surpassed	PDR	Critical	(Lockhart et al., 2017; Ostrowsky et al., 2020)

4. Discussion

a. The practical species level and lower levels of public health concern

Many frameworks flag pathogens in different ways and with different objectives making their use difficult to apply across sectors. Hence, our study comprehends the most used and important AMR classifications assessing the current situation in treatability to describe a new framework -AOS for AMR- with global scale application at the level of species or genera. The ‘ESKAPE’ pathogens, whose name was a wink to the ability of bacteria to ‘escape’ antimicrobial exposure thanks to high abundance of mobile genetic elements and frequent genetic exchanges via HGT (Boucher et al., 2009), raised awareness of even lower levels of public health concern: mobile resistance genes and high risk clones.

On one hand, among the most worrisome mobile resistance genes, there are: (i) extended-spectrum β -lactamases (ESBLs), (ii) carbapenemases and (iii) mobile colistin resistance (*mcr*) genes. The first two encode for β -lactamase enzymes that lead to, at least, multi-drug resistance to the β -lactam class of antibiotics. ESBLs hydrolyse β -lactams excluding cephamycins and carbapenems (Ur Rahman et al., 2018) being CTX-M among the most widespread, both geographically and among human/animals (Cantón et al., 2012; Woerther et al., 2013). Carbapenemases confer resistance to carbapenems (last resort β -lactam with the broadest spectrum of action). Carbapenemases are classified in three groups with different distribution globally (van Duin and Doi, 2017): (i) Ambler Class A like *K.pneumoniae* carbapenemase (KPC), commonly found in the United States and in Mediterranean countries; (ii) Ambler Class B like New Delhi, Verona-integron and imipenem-resistant *Pseudomonas* metallo- β -lactamases (NDM, VIM and IMP, respectively) common in the Indian subcontinent and in some European countries; and (iii) Ambler Class D OXA-48-like carbapenemases (e.g. OXA-48, OXA-181, OXA-23), whose ability to mutate and expand their spectrum of activity is remarkable, are mainly found in Turkey and Middle-East. Nonetheless, travels to endemic regions and nosocomial outbreaks have faded away geographical barriers and all being reported worldwide (e.g. Hernández-García et al., 2019). The last highlighted mobile resistance genes, *mcr* genes, encode for colistin resistance, a last resort drug with severe side effects also used in veterinary medicine (Liu et al., 2016). Ten *mcr* genes (*mcr-1* to *mcr-10*) have been described (Wang et al., 2020). First detected in 2015 from pigs (*mcr-1*), *mcr* genes were soon widespread across the ‘One Health’ spectrum (Skov and Monnet, 2016). On the other hand, high risk clones are clone-clusters inside species whose identification relies on species-specific molecular typing techniques. High risk clones are extremely overrepresented among clinical isolates and they have enhanced global dissemination of mobile resistance genes (both intra- and interspecies) helped by selective pressure in hotspots (Mathers et al., 2015).

Although, mobile resistance genes and high risk clones are remarkably important in AMR, from a realistic view and practical usage, their identification requires time, technical personnel and specific facilities not available everywhere, especially in LMICs or small hospital labs. For global public health, the application of the AOS for AMR framework at the level of species or genera is much more suitable, practical and feasible because identification at this level is easier,

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cheaper and routinely done in most laboratories worldwide, including those countries with less income resources. Assessment of the most worrisome resistance concerns at species/genera level (**Table 6**), such as HGT and high risk clones, and non-linear dynamics (**Table 1**) have been considered to contextualize the AOS for AMR. However, defining every resistance mechanism, for every antimicrobial and pathogen is beyond of the scope of this framework. Overall, our assessment points out that GNB (whose cell wall differs from GPB or mycobacteria) are the most remarkable exceeding our limits to safely maintain treatability accounting for 11 out of the 20 pathogens assessed, and 6 having already crossed the tipping point. Moreover, our assessment concludes that XDR and PDR infections caused by pathogens in the surpassed zone or inside the uncertain high-risk zone represent a huge risk for sustaining available therapies. Those lack of options in treatability involve contact prevention-isolation measures, higher lengths of stay in hospitals or much more expensive associated costs impacting significantly on mortality and morbidity (Kousouli et al., 2019).

b. AOS for AMR: current state, drivers and resilience for sustained treatability

Defining AMR is not easy and it is difficult to categorize microorganisms that, if not fully resistant, need much higher doses of antibiotics to be effective with a risk of more severe side effects. This can also be seen as a sign of the decreasing set of options that prescribers have to treat infections. And with the growth in use of second-line or last resort antibiotics (for MDR and XDR infections often dosed intravenous or intramuscular needing trained professionals and hampering accessibility. Protected drugs, combination of drugs or drugs still on trial (for PDR infections) often have undesirable side effects leading to higher mortality rates (Aslam et al., 2018; Klein et al., 2018; Karaikos et al., 2019; Tsala et al., 2019). The AOS for AMR can make more understandable to everyone, even citizenship, that MDR or XDR pathogens can also be jeopardizing treatability. They send a false sense of ‘security’ because they still have treatment available but they might be on the edge of crossing the tipping point (e.g. if XDR turns easily to PDR). As this framework is aimed to be applied for priority pathogens at level of species or genera, it is interesting to point out that XDR of problematic pathogens can be categorized within the ‘uncertain zone’ per definition but when strains can overstep to the ‘surpassed zone’, those XDR strains can be considered at the level of PDR in treatability (e.g. *Acinetobacter* susceptible only to the last resort antibiotic colistin and with high probability to develop resistance (Mustapha et al., 2018; Trebosc et al., 2019)). The AOS for AMR categories can be a useful concept for health and non-health professionals, the latter less familiar with antimicrobials categories and implications of different use.

Considering the specific features of all mentioned classifications, there is one big similarity within them: the aim to optimize monitoring and global epidemiological surveillance while pointing out risks of increasing AMR worldwide. Resistance rates may be under- or overestimated due to lack of surveillance data world-wise although reported mechanisms may be accurate. Surveillance systems in human health have limited resources and low coverage in LMICs, especially in regions inside Africa, Asia and South America, because resistance diagnostics are cornered to research centres, universities or pharma industry and they face challenges such low coverage, selective sampling and underfunding (Ashley et al., 2018). However, the application of our framework in countries with incipient or low coverage surveillance is not an impediment. Finding a pathogen with an unreported MDR, XDR or PDR profile can categorize the pathogen inside the framework or in a higher level and warn about

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resistance, not in an alarming but in a guarding way to inform rapidly and globally. If AMR surveillance in human healthcare has low coverage in LMICs, the challenge of AMR surveillance in animals is even harder and, if exists, it is based on point-prevalence surveys (Van Boeckel et al., 2019). Interestingly, AMR surveillance in animals has not stood out as strongly as in humans in LMICs, although the majority of the antimicrobials (up to 73%) are used in husbandry consequence of the worldwide growing demand for animal protein (Van Boeckel et al., 2019). Correlation between antibiotic usage and resistance seems obvious, being the most used antimicrobials in farming (tetracyclines, sulphonamides and penicillins) the ones with highest resistance rates among animal isolates in LMICs (Van Boeckel et al., 2019) but also observed in several contexts in our assessment such macrolides use and macrolide resistance in *H.pylori* or *Streptococcus* (Ferretti et al., 2016; Boyanova et al., 2019). While interplay for survival, competence and resistance against stressors naturally occurs in microbial communities, since the discovery of antibiotics, anthropogenic disturbances have been the major driver for AMR evolution (Jørgensen et al., 2020), especially selection pressure consequence of antimicrobial use. Supporting this claim, resistance has also emerged from different locations simultaneously, such as the case of the yeast *C.auris*, probably consequence of our misuse of antimicrobials during decades (Forsberg et al., 2019)..

Several efforts are done to reduce antimicrobial use but not even complete antimicrobial withdrawal is a silver bullet. Despite absence of antibiotics, once resistance is acquired, it may not be reversed. For example, fluoroquinolones were widely used in husbandry production since the 1980's, but resistance rates led to: (i) restrictions in the European Union (2003 and 2006) and the United States (2005) and (ii) surveillance programs among foodborne pathogens (Sproston et al., 2018). But, AMR data has barely declined trends of fluoroquinolone resistance in *Campylobacter* isolates from humans (EFSA-ECDC, 2020). Resistance mutations explain their maintenance in an environment with antibiotics but, in the absence of selective pressure, low fitness cost can lead to persistence and expansion due to clonal division. This is also the case of *N.gonorrhoeae* whose biological fitness does not seem affected by resistance traits, therefore fixing the resistance even when no antibiotic selection pressure is applied (Alirol et al., 2017). Even if those mutations have high fitness cost, in the absence of antibiotic, selection of compensatory mutations can reduce this cost which implies some degree of resistance loss ending with mixed populations of cells like in heteroresistance. Moreover, resistance can have advantages in transmission (biofilm formation in aerobic conditions) and/or pathogenicity (virulence through invasive phenotypes), facts that may help also to resistance stabilization (Ferretti et al., 2016; Whelan et al., 2019). Those aperiodic dynamics for resistance fixation make the framework useful for describing the surpassed or uncertain area in which non-linear dynamics play a role that cannot be foreseen. *Campylobacter*, *N.gonorrhoeae* or *Streptococcus* are examples of resistance fixation within assessed pathogens. Pathogens in the surpassed area have crossed the tipping point. But in the uncertain area, although we may still be inside the planetary boundary, we lack of knowledge to predict the extent and consequences of resistance once acquired.

Following this line, the AOS for AMR also has the aim of warning sternly about the importance of treatment sustainability advising to approach this challenge with a broader view. Because there are several pieces affecting the social-ecological system (SES), including our actions as society, influencing on AMR. The SES is a complex adaptive system strongly driven by anthropogenic ecoevolutionary forces (Jørgensen et al., 2020) but all system connections, how and how much each one interact with each other is poorly understood yet. From the ecological perspective, drivers for AMR evolution also influenced by human activity are, for example,

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co- selection for resistance lead by stressors (e.g. chlorhexidine) or heavy metals (Gullberg et al., 2014; Jørgensen et al., 2018; Hashemi et al., 2019). Antibiotics are not specific and also affect beneficial microorganisms. Selection pressure is exerted in the whole microbiome unbalancing systems especially when they are affected for long periods. From the social perspective, behaviour plays an important role in driving AMR with (i) Direct actions, for example, safe-sex promotion/awareness can prevent infections (and antibiotic use) enhancing better societal outcomes; or with (ii) Indirect actions, for example, antivaccine movements whose consequences are far-reaching. The SES is also impacted by historical and societal features like: (i) access difficulty to antimicrobials; (ii) the structure of the health system; (iii) support of institutions in surveillance programmes; (iv) awareness of the population; or (v) investments in research and innovation. The latter is basically supported by public institutions, often with scarce funding depending on grants and with small possibilities to go through the expensive last phases of clinical development. Among new strategies in research we can find: (i) new antibiotics (Imai et al., 2019); (ii) new vaccines for community infections (*N.gonorrhoeae*, *Shigella*, GBS or *H.influenzae*); (iii) new methods in clinical microbiology like whole genome sequencing as powerful tool to study the global resistome and improve surveillance (Rolain et al., 2013; Cuypers et al., 2018); (iv) new designs for point-of-care rapid diagnostics (Cruz et al., 2019) or (v) different novel approaches in interventional science (AMResilience (<https://amr-resilience.gtglab.net/>)). Meanwhile society awaits for innovation, the AOS for AMR gives the grounds to alert about the situation if those new approaches take time. This is key as there are many hopes in new drugs or diagnostics but they may be finally on the market several years from now, and even if they are now out, therapy safety and sustainability may be still in danger.

However, a big change on how address this complex challenge is needed or not even with new approaches we will succeed. Basically, until now, we as society have respond to disturbances but we have not addressed the roots. Disturbances have been rapidly overcome because resistance implies to some extent a fitness cost and because species have a proportional balance in the biome. But, our system disruption is serious and maintained for decades jeopardizing now treatability and the whole health system. This is especially seen with the 7 pathogens inside the surpassed category which have left the safe area. Those pathogens have few high risk clones overtaking the majority of infections in healthcare settings and they account the vast majority of therapeutic dilemmas microbiologists are dealing with trying to respond as best as they can. AMR of species of epidemiological significance within the nosocomial system are often on the spot, whereas AMR in the microbial community is less discussed but it may be affected. With this first assessment of the framework we also emphasize to focus on pathogens that are not always in the spot light. GAS and GBS have already entered the uncertainty area, and 6 pathogens, usually found at community level, are in the medium risk (*Shigella*, *Campylobacter*, *H.pylori*, *H.influenzae*, the GPB *S.pneumoniae* and the fungi *Candida*). Moreover, promotion of heterogeneity and susceptibility of microorganisms in microbial communities is discussed to even a lesser extent. The AOS for AMR has also as objective to promote a big mind-set change going towards treatment sustainability and preservation of antimicrobial effectiveness. We do need new antibiotics, antimicrobials and drugs to have therapeutic options for resistant pathogens, but what we do need the most is acknowledging that actions in society also affect this challenge in the Anthropocene. The AOS for AMR identifies the context of treatability and AMR at a global scale for 20 pathogens but further studies will need to provide the ways in which we can remain in the safe zone.

c. Advantages and limitations

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The AOS for AMR points out the increasing risk of resistance and available therapy for 20 priority pathogens. Some have crossed the tipping point for treatability (7) and the rest can surpass it soon (13). This framework relies on two of important parameters at the same time: the clinical epidemiology state and the ecological sustainable goal of maintaining treatability. It can be used across sectors gathering current and updated AMR information for global public health protection. Some of the biggest strengths of this classification is that can be feasibly applied on a bigger scale with little or without economic investment at the level of species or genera even in countries with less economic resources. It can be quickly updated, and it is easily understandable for actors involved in AMR and not only for health professionals. Also, it introduces the concept of planetary boundaries in AMR at species or genera resolution and it encourages to preserve antimicrobials and to build resilience in our health system.

However, our framework has some limitations too. Not all important pathogens are currently assessed in the framework. Only 20 priority pathogens have been assessed, although the list of assessed pathogens including protozoa and virus can be extended in the future. In addition, it can be used but it is not practical in smaller scales (e.g. hospital reports of patients) and in that case the current MDR-XDR-PDR can be more suitable. Another limitation is the risk of misinterpretation when it comes to resistance patterns. This is not a framework thought to generalize about resistance profiles but to be used for health protection purposes. In that sense, not all strains of pathogens assessed in the surpassed zone have a PDR profile but this profile has been found, in more or less proportion in the species, and we must be careful applying precautionary principles.

To our knowledge, the AOS for AMR framework is the first one that can be used between and across different sectors such health professionals, ecologists or policy makers and it warns also society in a dual way: (i) our current epidemiological and treatability situation of bacterial and some fungal infectious diseases; and (ii) advice for considering the SES context to address this global challenge and to maintain the planetary boundary promoting actively awareness and resilience of the health system rather than answering to its disturbances.

d. Current context

AMR is a dynamic process and resistance can emerge in species that were not worrisome in previous years. This fact may lead to enlarge surveillance programs with those candidates (e.g. *Mycoplasma genitalium*, *Stenotrophomonas maltophilia* or *Bordetella pertussis*). Other AMR public health threats followed-up in detail, but not covered in this study, can be assessed with this framework; e.g. HIV-AIDS, especially when the first PDR HIV virus has been reported (Puertas et al., 2020). Resilience in healthcare systems is important, especially when running out of options. And, in that way, the new coronavirus disease 2019 (COVID-19) pandemic has jeopardized our health system showing the problems of untreatable infectious diseases bringing to light the remaining strategies to contain them which are difficult and costly involving prevention, contact precaution and isolation of carriers in different settings. Some non-linear dynamics pointed before can also apply to COVID-19 and other infectious diseases such long-distance transmission. In this novel situation, precautionary principles apply and patients may receive antibiotics that can end up being unnecessary. Suspected hospitalized COVID-19 patients are often treated with antibiotic when only in a minority may be appropriate (Antimicrobial resistance in the age of COVID-19., 2020). Effective stewardship and antibiotic limitation during the pandemic is priority as increased and prolonged use of antibiotics can

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enforce a time-bomb for AMR. Food for thought is that AMR microorganisms can jeopardize the situation in no time especially in healthcare associated untreatable infections.

e. Conclusions

To conclude, this novel framework assessed 12 out of 20 pathogens in a high compromised situation regarding antimicrobial effectiveness and therapy sustainability: 7 assessed in the surpassed and 5 in the uncertain high risk zones, respectively. The AOS for AMR can be implemented without major efforts worldwide and must be taken as a global risk-assessment of acquired resistance and therapy available at the practical level of species framing threats we are already dealing with, here and now, not in the future. Global coordinated and interdisciplinary action using a common framework for a better communication is the best option that we have in this complex adaptive system. The challenge of AMR needs interdisciplinary frameworks, like this one, as common ground for communication and collaboration between different actors and stakeholders while surveillance and research of infectious diseases must still be milestones. Facing the truth, mortality, morbidity and costs are predictably going to increase as options for treating these priority pathogens are scarce, when available, because we have already surpassed our limits in a concerning number of cases but it is in our hands to minimize the increase of this gradient strengthening efforts from different perspectives.

5. Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

6. Authors' Contribution

PSJ initiated the framework and all authors (TG, CH and PSJ) drafted a schematic model. TG wrote the manuscript including tables and figure. TG and CH did a narrative review of the literature on AMR. All authors (TG, CH and PSJ) provided comments and suggestions on the final manuscript.

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