Opinions/Position Paper:

Selection versus Transmission: Quantitative and Organismic Biology in Antibiotic Resistance

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ABSTRACT

We aimed to determine the importance of selection (mostly dependent on the anthropogenic use of antimicrobials) and transmission (mostly dependent on hygiene and sanitation) as drivers of the spread of antibiotic-resistant bacterial populations. The first obstacle to estimating the relative weight of both independent variables is the lack of detailed quantitative data concerning the number of bacterial cells, potentially either pathogenic or harmless, and bacterial species exposed to antimicrobial action in the microbiotas of specific environments. The second obstacle is the difficulty of considering the importance of the various parameters influencing antibiotic resistance across eco-biological levels that constitute an "organism-like" entity. As a consequence, advances are urgently required in quantitative biology and organismic biology of antimicrobial resistance. The absolute number of humans exposed to antibiotics and the absolute number of potentially pathogenic and commensal bacteria in their microbiomes should influence both the selection and transmission of resistant bacterial populations. The "whole Earth" microbiome, with astonishingly high numbers of bacterial cells and species, which are also exposed to anthropogenic antimicrobials in various biogeographical spaces, shape the antibiotic resistance landscape. These biogeographical spaces influence various intensities of selection and transmission of potentially pathogenic bacteria. While waiting for more precise data, biostatistics analysis and mathematical or computational modeling can provide proxies to compare the influence of selection and transmission in resistant bacteria. In European countries with lower sanitation levels, antibiotic consumption plays a major role in increasing antibiotic resistance; however, this is not the case in countries with high sanitation levels. Although both independent variables are linked, their relative influence on the level of antibiotic resistance varies according to the particular location. Therefore,

although interventions directed to decrease antibiotic resistance should be designed "à la carte," the global effects of antibiotic exposure and resistance on local sites cannot be underestimated.

Introduction

The classical approach to answering the question of why antibiotic-resistant microorganisms increase in frequency has been hospital-based, with the initial response based on selection. The more antibiotics that are used in an environment (independent variable), the more resistant organisms (dependent variable) that survive in comparison with the susceptible ones. However, we can easily conceive (and this has been observed in the field) that even in a location with low antibiotic use, antibiotic-resistant organisms might invade and propagate, particularly if conditions favor their transmission. Similarly, locations with high rates of antibiotic consumption might not result in high rates of antibiotic resistance if the conditions for transmission from individual to individual are limited; for instance, by extensive sanitation or by individual isolation. Any intervention attempting to correct the trend toward increased resistance should consider the local conditions; however, generalizations are frequently useless. Quantitation of the variable elements involved in selection and transmission of antibiotic-resistant microorganisms is in its infancy, and more studies should be performed (González-Candelas et al., 2011). In this regard, further quantitative biology research is needed to construct "precision" models adapted to the local conditions and to therefore foster useful interventions (Howard, 2014). We remain, however, "not so much concerned with the number of organisms, as such, as we are with another quantity" (Elsasser, 1964). Unfortunately, many of the parameters required to determine the precise "space and size of antibiotic resistance" remain poorly established (Martinez and Baquero, 2014). In this review, we suggest that progress in the quantitative biology of antibiotic resistance should be integrated into an organismic biology perspective. The concept of "organism" as an individual

entity composed of integrated functional parts (organ-like), was conceived by the anti-mechanistic philosopher John Scott Haldane in 1917 (Herring and Radick, 2019; Sturdy, 1988) and later applied by Ridley to general biology (see below). From this perspective, selection and transmission are probably the more general causal mechanisms explaining the effect we are targeting: the spread of antibiotic resistance in an "organism-like" entity constituted by the ensemble of bacterial and anthropogenic functions.

Selection

1. Antibiotic consumption is a major driver for selection

1.1. The absolute number of individual hosts exposed to antibiotics and the absolute number of antibiotic-exposed potential pathogens

Comparing rates of antibiotic consumption among countries is frequently based on the daily-defined-dose/1000 habitants per day, roughly reflecting the number of individuals exposed to antimicrobial treatment each day. However, the selective consequences of such exposure in a particular region depends on the absolute number of individuals exposed to antibiotics, or in other terms, the absolute number of bacteria of the various species located in these individuals' microbiota. Each 70 kg "reference" human carries approximately 3.8×10^{13} bacterial cells (Sender et al., 2016), an estimated ratio of 1.3 bacterial cells for every human cell in the body (Gilbert et al., 2018). In the same study, only in the gut, a rough estimate of 1000 bacterial species was proposed, with an average of 2000 genes per species, yielding approximately 2,000,000 genes, 100 times the number of approximately 20,000 human genes. This distinction has been poorly explored, because it depends on the knowledge of the relative density of the various bacterial

90 populations. Even if we reduce this search to the more frequent antibiotic-resistant and potentially
91 pathogenic ("antibiotic threat") organisms in the intestine (such as *Escherichia coli* or
92 *Enterococcus faecium*), the absolute density in the human or animal intestine is high and extremely
93 variable, typically below 1% of the total human microbiota. This figure is consistent with
94 quantitative polymerase chain reaction studies of bacteria adhered to gastrointestinal mucosa
95 (Huijsdens, 2002). This proportion can increase in pathological conditions (including
96 undernutrition), in which *E. coli* can increase by over 10^5 cells/ml in the upper gut, a volume
97 roughly equivalent to the human large intestine. Despite its potential interest, there is scarce data
98 on the total number of cells in the *E. coli* population (as an example) in human and animal
99 microbiomes. Similarly, although the estimated number of cells in local environments (including
100 sewage) remains poorly studied, it can be suggested that the number of cells/ml of many potentially
101 pathogenic bacterial species in sewage does not differ significantly from the number in the large
102 intestine in humans and animals (Silkie and Nelson, 2009). However, given that the absolute
103 volume of contaminated water is extremely large, the number of cells provided by sewage is
104 important for any estimation of the total number of potentially pathogenic individual bacterial cells
105 in the species. The total number of bacterial cells on Earth (most with an "intrinsic resistome" is
106 approximately 5.10^{30} (https://www.worldatlas.com/how-much-bacteria-is-on-earth.html),
107 constituting (after plants) the "heaviest" biomass on the planet, including approximately 70
108 gigatons of carbon (Bar-On et al., 2018). In terms of "species," or operational taxonomic units
109 (OTUs) assembling closely related prokaryotic genomes, it has been estimated that there are more
110 than 1 million (perhaps reaching 1.6 million) prokaryotic OTUs on the Earth (Louca et al., 2019).
111 The distribution of these OTUs is environment dependent. However, a classic fundamental topic
112 in ecology is the relationship between frequency (the proportion of samples where a particular

113 species appears) and population density (the number of individuals belonging to this species in a
114 particular space). In principle, in a given environment, the denser the population the greater the
115 frequency with which the species will appear, so that both parameters appear to be correlated (Dice,
116 1948; Fisher, 1928). However, there are sampling biases due to the random distribution of some
117 species, probably more in the minority ones. For instance, the absolute density (number) of
118 potentially pathogenic intestinal bacteria in a given environment is dependent on 1) the density of
119 these pathogens in the gut of species present in the environment, considering the volume of the
120 colonized intestine in each species; 2) the local density of individuals of the various species; 3) the
121 volume and periodicity of dropping fecal material; 4) the conditions for survival and growth of the
122 pathogenic bacteria in the soil or water contaminated with fecal material and other fluids of human
123 origin; and 5) the extension (volume) and physical structure of the contaminated environment. This
124 last point will be developed in the next section. What we want to highlight here is the unimaginable
125 number of global bacterial cells or species potentially exposed to anthropogenic antimicrobial
126 agents, and therefore the vast opportunities to evolve to antibiotic resistance. Such an evolutionary
127 trend could have consequences for human treatment of infections, but also for the equilibrium not
128 only of the microbiosphere, but of the entire biosphere (Baquero et al., 2021).

129 ## 1.2. The space of antibiotic selection

130 The space for antibiotic selection is the ensemble of bacterially colonized areas inside or outside
131 the host where antibiotics can exert a selective effect, resulting in a local increase in antibiotic-
132 resistant bacterial populations. This space is physically, chemically and biologically
133 heterogeneous, thus the selective events in which these heterogeneities associate necessarily differ
134 into subspaces.

1.2.1. Gradients and granularity in selective spaces

Physical differences that influence antibiotic activity include space compartmentalization, granularity (proportion of particles in the space), fluidity and viscosity, temperature differences and other physicochemical parameters. An important point is that these conditions determine the formation of more or less steep gradients of antibiotic concentrations, with various selective consequences. For bacteria, there are numerous possibilities for becoming antibiotic resistant. Many mutations allow the cells to resist small concentrations of antibiotics and to be selected by these concentrations. This selection increases the possibility of climbing up in the gradient and tolerating increasing antibiotic concentrations (Baquero and Negri, 1997). Very small antibiotic concentrations, far below the classic "minimal inhibitory concentration" used in susceptibility testing, are indeed very selective (Hughes and Andersson, 2012). Each subspace along the gradient where a particular concentration occurs might select for a particular resistant variant (Baquero et al., 1998; Negri et al., 2000). The space where low antibiotic concentrations occur is much larger (exponentially) than the space where the bacteria are exposed to high antibiotic concentrations; therefore, the absolute number of bacteria confronting a selective effect is considerably more abundant (Baquero and Coque, 2014).

Selection also benefits from the extension of environmental surfaces in the physical space where bacteria and antibiotics meet. Bacterial cells, as well as nutrient molecules, tend to accumulate on surfaces, particularly in particulate granular material in water and soil. This accumulation produces microbiotic particles where bacteria colonize the surface of physical granules (organic or inorganic), such as interbacterial aggregates, microfungal particles, protozoa, phytoplankton, zooplankton, biodetritus (such as plant remains), humus, mineral particles (clay, carbonates, silicates) and particles of anthropogenic origin, such as wastewater particles and microplastics

(Baquero et al., 2022). The density of bacterial populations in microbiotic particles depends on the size (i.e., diameter) of the basic particle and the environmental conditions allowing multi-layered bacterial multiplication. Antimicrobial agents also accumulate at the surface of these microbiotic particles, which can exert selection for antibiotic resistance.

1.2.2. Antibiotic eco-pharmacokinetics and eco-pharmacodynamics

The environmental variation in drug concentrations over time, and its biological effect on the components of ecosystems, are the essential parts of environmental pharma-ecology (Jjemba, 2019). There is a potentially fertile microecological field of research on the kinetics of the antibiotic-bacteria interaction and antibiotic resistance selection in coalescent microbiotic particles. On one hand, bacteria frequently form more or less stable micro-biofilms after surface attachment (Puri et al., 2022), which is eventually followed by the shedding of planktonic bacteria. On the other hand, potentially selective antibiotic molecules might adsorb or de-adsorb from microbiotic particles and could also be detoxified when absorbed by clay minerals (degradative reactions influenced by light, metals or pH), charcoal, cellulose and chitin. Also can be sequestered by living and dead cells or cell components or biodegraded by microbial populations. Antibiotics have heterogeneous detoxification kinetics, and therefore their selective power for antibiotic-resistant populations might differ (Baquero et al., 2022). Once again, there are a lack of quantitative biological data (number and type of microbiotic particles, antibiotic kinetics and dynamics influencing the selective power for particular resistant bacteria) to help us understand the antibiotic selective processes.

1.3. Does the increase in resistant populations replace the susceptible ones?

Even after a very long period of exposure—more than a century—to antimicrobial agents around the world, and considering the high density and high replication rate of bacterial populations, resistant populations of pathogenic bacteria have not, with a few exceptions, replaced the susceptible ones. Once more, the lack of reliable data on the frequency of resistance (at least for the pathogenic bacteria) in non-exposed humans makes it difficult to estimate the size of the "susceptible reservoir," a critical parameter to predict the possibility of interventions directed to the biorestoration of naturally susceptible organisms, at least in the Anthropocene Operating Space (Jorgensen et al., 2018). Fortunately, the environmental limits within which humanity can safely operate are limited, meaning that most antibiotic resistance genes in the microbiosphere are placed in non-pathogenic bacteria. Therefore, if antibiotics enter a particular environment (such as the intestine, or in water and soil environments), selection acts on the dominant non-pathogenic organisms, which can also protect the susceptible pathogens (for instance, the release of beta-lactamases by anaerobic bacteria). Most "antibiotic resistance genes" have not originated or evolved as genes to confer antibiotic resistance, but to serve other functions (the "intrinsic resistome"), antibiotic resistance being a "secondary phenotype." Some of these genes can indeed occasionally be transmitted to kin pathogens. Given that resistance genes are listed without criteria in most databases, rules need to be established for estimating the risks associated with genes that are present in metagenomic resistomes by evaluating the likelihood of their introduction into human pathogens, as well as the consequences of such events for the treatment of infections (Martínez et al., 2015). On the other hand, every microorganism on Earth is subjected to environmental changes resulting in stress. The expression of antibiotic resistance, and the carriage of mobile genetic elements carrying antibiotic resistance genes, supposes an extra cost for individual resistant bacteria so that susceptible bacteria might have a competitive advantage over

the resistant ones. Long-term (decades) evolutionary experiments with a single *E. coli* in the absence of antibiotics show the progressive dominance of variant strains that are more sensitive to various antibiotics than their common ancestor(s) (Card et al., 2019). A possible way to accelerate this process and help susceptible bacteria prevail is to increase the fitness cost of resistant populations in the environment, including the gut (Baquero et al., 2024). Unfortunately, although the resistance fitness cost can be compensated by genetic variation, such variation might alter long-term bacterial physiology. In fact, the historical contingency of compensatory variation is a critical point in predicting the dominance of resistant pathogenic organisms (Card, 2019).

2. Transmission in the spatial spread of antibiotic resistance

Antibiotic resistance is a major health problem because bacteria that have been selected by antibiotic exposure are transmitted across various environments, allowing host-to-host direct or indirect transmission (Baquero, 2018). A host population with low rates of antibiotic consumption, and therefore low selective forces for antibiotic resistance, can be invaded by resistant bacterial clones for reasons unrelated to antibiotic use. Typically, this is the case (linked to extensive globalization) in countries with low antibiotic consumption, either because of stringent antibiotic-use policies (frequent in high-income countries) or due to drug unavailability (low-income countries).

2.1. The causes of transmission

Transmission is frequently a consequence of selection, ultimately on the local selective reproduction of resistant cells. Only if a critical number of antibiotic-resistant cells accumulate in a given spatial site can transmission occur, propagating these cells to other spatial locations.

However, successful transmission from a source can only be achieved if the antibiotic-resistant cells can multiply in the receiving patch. This dynamic has been likened to information theory as requiring "emitters" and "receivers" (Baquero, 2018). Transmission, or emission, requires leaving the niche of the original population and seeking other places for similar niches to be colonized. In such a process, resistant bacteria most frequently are obliged to cross "death valleys" in the adaptive landscape, where replication is difficult or impossible; therefore, the population density decreases and consequently the transmission might be aborted. Therefore, a significant initial density (as in the case of plant seeds, or fish eggs) is required. If such density is not achieved, or if we increase the difficulties for survival in "death valley," the spread of resistance will be reduced. An important point is that natural "empty niches" to be colonized are rare or nonexistent. This lack of empty niches implies that antibiotic-resistant populations should "invade" areas (patches, in terms of metapopulation biology) containing high-carrying capacity niches that are already colonized, as occurs in the human or animal intestine. How resistant bacteria at very low population sizes can invade heavily colonized areas (established microbiotas) in a new host in the absence of selection is a fundamental area of research that has, so far, scarcely been investigated. There are some possible answers.

First, there could be a pre-colonization area allowing multiplication of the resistant population, either in the environment (e.g., contaminated food or water), in the host itself (e.g., mouth, upper intestine), or in medical devices (e.g., ventilators in the hospital's intensive care units). The hospital setting can be invaded by clones that have previously successfully spread in the community, associated or not with disease ("hidden epidemics"), reaching high numbers in hosts outside hospitals (Rodríguez et al., 2021). Certainly, the "absolute population size" of resistant organisms exponentially increases during epidemics, so that epidemic events feed its propagation.

Second, the antibiotic-resistant bacteria might be endowed with "attack mechanisms" to replace resident bacteria (frequently phylogenetically close), as in the case of the very spreadable *E. coli* phylogroup B2, in which several high-risk clones (such as 025b-ST131), carry antibiotic peptides (microcins) (Micenková et al., 2017). In their turn, resistant clones that have succeeded in the colonization process use their former attack mechanisms as defense mechanisms to protect their conquered niche from re-invasion in formerly established non-resistant clones. Another possibility derives from the changes in the microecology of the gut, resulting from pathogenic effects on the host. A resistant pathogenic organism in the intestine, even at low densities, might produce reactive changes in the host, altering intestinal signals as well as secretion of antibacterial substances of innate immunity and changing the populational composition of the healthy microbiota so that the new colonizer gains in relative fitness (Chowdhury et al., 2023). Also, if the resident community is already disturbed by principally antibiotic medical interventions, the colonization resistance capacity (due to the unavailability of nutrients for the incoming organisms) is diminished, favoring colonization by this antibiotic-resistant colonizer (Pérez-Cobas et al., 2023; Spragge et al., 2023).

Third, small quantities of antibiotic-resistant bacteria might invade areas previously colonized by susceptible populations following cumulative events of transmission. Continuous contact of hosts colonized with susceptible bacteria with other hosts carrying antibiotic-resistant populations leads to a final cumulative-competitive number of resistant organisms. That is the case of transmission within families in which one of the members is carrying a resistant clone (Valverde et al., 2008), or of the farmers and veterinarians colonized by antibiotic-resistant animal strains (Gao et al., 2024). A similar case is human individuals chronically exposed to water or food contaminated by antibiotic-resistant organisms in low-income countries. Interestingly, this exposure might also occur in high-income countries; intensive care units in hospitals might contain "built

environments" where antibiotic resistant clones might persist for long periods of time (Aracil-Gisbert et al., 2024).

Fourth, the success of the spread of antibiotic resistance is also due to a process of "conversion", in which a particular resistant clone is transmitted to a particular patch containing antibiotic susceptible strains, "converting" these strains into resistant ones by horizontal gene transmission, most frequently mediated by conjugative plasmids carrying antibiotic resistance genes (Castañeda-Barba et al., 2024). In the absence of antibiotic selection this process of emergence of new resistant organisms, most frequently among commensals (Dionisio et al., 2023), entirely depends on the spontaneous plasmid conjugation rate. Computational simulations indicate that only high rates of transmission (such as 10^{-3}) might have a small transient effect on the acquisition of resistance (Campos et al., 2020). However, this process of genetic transmission might be facilitated by conditions in which susceptible and resistant bacteria enter into contact, such as in microbiotic particles, those present in the gut, or in free environments (see 1.2.1.).

2.2. Transmission barriers

There are several barriers to reducing the spread of antibiotic resistance in human and animal environments.

First, appropriate general sanitation. If resistant organisms colonizing a host are prevented from having access to another host, transmission does not take place. In the case of the main pathogenic intestinal microorganism, inadequate access to water, sanitation and hygiene is a key component of the spread of resistance in lower- and middle-income countries (Walsh et al., 2023; Nadimpalli et al., 2018). Water and food contamination with resistant organisms facilitates human and animal colonization, and following vicious circle dynamics, such colonization is followed by

environmental contamination. In the hospital setting, barriers impeding cross-colonization between patients, involving health care workers (including hand-washing) and medical device decontamination or preventing access to colonized built environments (see 2.1), reduces the spread of antibiotic resistance.

Second, vaccination against antibiotic-resistant clones. By far, the most effective documented intervention in the fight against antibiotic resistance has been vaccination against antibiotic-resistant clones of *Streptococcus pneumoniae* or *Haemophilus influenzae*. Developments in this field, encompassing antibiotic resistant Gamma-Proteobacteria (mostly Enterobacteriaceae), or Bacillota (mostly *Staphylococcus*, *Enterococcus*) high-risk clones are in the pipeline (Frost et al., 2023). The efficacy of vaccines might differ when targeting other pathogens; however, even imperfect vaccines might be useful in decreasing antibiotic resistance (Joice and Lipsitch, 2013). In any case, a limitation of this type of intervention is derived from the fact that many antibiotic-resistant high-risk clones are also commensal antibiotic-susceptible clones, coexisting and coevolving with humans, and thus part of the "normal microbiota." If vaccination contributes to their clearance (Kubinak and Round, 2016), the consequences are difficult to predict. Note that the spread of antibiotic-susceptible clones is competing with the spread of resistant ones.

Third, boosting the selection of antibiotic-susceptible clones. The ideal "magic intervention" to reduce or eliminate antibiotic-resistant clones is to facilitate the selection of antibiotic-susceptible kin organisms. This biorestorative task can be approached in various ways. One is based on microbiota transplantation with feces of antibiotic resistance-free individuals (Woodworth et al., 2023). In general, ensuring a high biodiversity in the microbiota, resulting in a wealth of interbacterial interactions, should reduce selection for antibiotic resistance (Nair and Andersson, 2023). Another possibility (proposed, not explored) is taking advantage of the fitness costs

associated with the expression of antibiotic resistance, which might be additive (synergistic in some cases?) with the "natural stresses" of the bacterial cell during the passage or stay in the intestine. Boosting such stresses might favor antibiotic-susceptible clones (Baquero et al., 2024)

Organismic biology and antibiotic resistance

As stated earlier, the notion of organismic biology is probably on the grounds of the contemporary One Health approach. However, this concept was coined more than a century ago, in 1919, by the zoologist W.E. Ritter, following the track of John Scott Haldane; he proposed that "the organism in its totality is as essential to an explanation of its elements as its elements are to an explanation of the organism" (Ritter, 1919; Herring and Radick, 2019). Around the middle of the last century, the term "organismic biology" was contrasted with pure "mechanistic biology" (Nagel, 1961; Elsasser, 1964; Milam, 2010). An organism is an "individual" that can be composed of other "individuals" of lower hierarchical ranges. In evolutionary theory, every individual is a "unit of selection" (Baquero, 2011). For the case we are considering, we can conceive a bacterial clone of a given antibiotic-resistant pathogen as a biological individual, composed of many bacterial cells, some of them genetic variants of their ancestors, so that the clone is a "clonal complex" acting as a single individual.

The biological functions *constitute* the organism as a biological individual, and therefore functions are the effectors determining paths and trajectories of evolution (what reproduces, what evolves) (Baquero, 2021) and transmission (what is transmitted) (Baquero, 2017). These are the basic functions shaping a biological individual: reproduction and transmission, respectively representing the biological conquest of the time and space dimensions. Necessarily, these basic functions are

associated: only if an organism reproduces does transmission take place; however, transmission assures the exploration of new spaces where new reproductive bursts can occur, overcoming local environmental instabilities. In a sense, this appears to be a case of mutual causation, as in Lois Frankel's metaphor of the "King and Queen of Hearts," playing cards that lean against one another, forming a simple card house. If either moves, the other will fall (Frankel, 1986). To ensure continuous adaptation to environmental variation, the organism either *changes its structure* to be selected (as a genetic or a phenotypic variant) or *changes its location* in the space. In such a way, we can compare transmission with genetic variation. Both are basic organismal functions that justify their functional unity under the organismic biology perspective (Pepper and Herron, 2008). A schematic illustration of this is presented in Figure 1. As in the "King and Queen" cards metaphor, efficient interventions against either selection and transmission of antibiotic resistant organisms (or both) should collapse the house of antibiotic resistance.

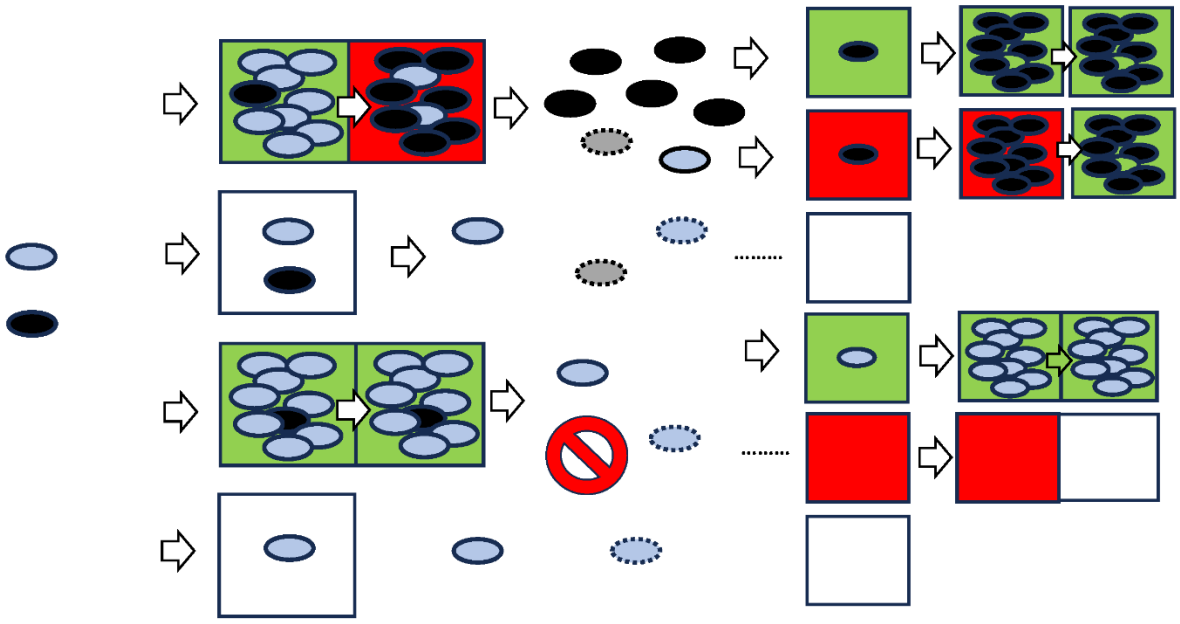

Figure 1. Selection and transmission. Square boxes represent ecological patches with different carrying capacities (conditions for bacterial exploitation): low (white), high (green, such as mammalian hosts, or sewage in warm-humid countries), or high but non-permissive (red, such as hosts or sewage with antimicrobial agents). White arrows are symbols for transmission, and the no-entry traffic sign represents high sanitation reducing transmission between patches. Light blue and black ovals, respectively, represent antibiotic susceptible (S) and resistant (R) bacteria. The **first row** depicts a patch highly colonized with S organisms with a minority of Rs. If this patch is in close contact with another one, this time under high antibiotic exposure, bacterial populations are transmitted and invade, but selection for Rs takes place. The high density of R populations assures a more efficient transmission in the inter-patch environment so that these Rs reach and invade other remote patches, either under the absence (green) or presence (red) of antibiotics. In the **second row,** S or R organisms enter into a low carrying capacity patch (white), so that reproduction is limited, and therefore organisms transmitted to remote patches, such as bacteria, die (discontinuous oval) during the transmission process or are too diluted to invade. **In the third row**, S-bacteria invade a patch with high carrying capacity, which transmits the same population to another neighbor patch. High densities of Ss reached in the patches might eventually overcome sanitation barriers, reaching new colonizable patches (green), thus expanding the S bacteria. Although they might not reach patches with antibiotics, if that were the case, they would become extinct. The possibility of reaching such spaces for R organisms is negligible with good sanitation. In the **fourth row,** high sanitation makes the transmission of organisms with low population densities almost impossible.

Let's now move upward. The concept of organismic biology expands the notion of "organism" to ensembles of individual entities. If bacterial cells compose the clonal complex "organism" or species, then ensembles of interacting organisms constitute the microbiota "organism." The notion of "intestinal microbiota as a human organ" had long ago been proposed (Baquero and Nombela, 2012). Can we conceive an ensemble of interacting microbiotas of human individuals (and health

workers?) and the microbiotas of the "built environment" from a hospital intensive care unit (ICU) as an organism, or just a particular ecosystem? It is certainly an ecosystem, with some organismic features, such as the permanence in time of many bacterial organisms for years despite the flux of patients, and its reproduction in analogous environments (such as a new ICU), which implies the effect of similar selective and transmission dynamics (Aracil-Gisbert et al., 2024). From an operational perspective, aiming to detect global changes in antibiotic resistance genes present in the ICU over time, we can consider an "ICU global intestinal microbiota" composed of all intestinal microbiota from patients attended during a given time. This consideration explores the evolution in time of antibiotic resistance by "pooling" procedures (mixing samples from the patients), to be used in metagenomic studies (Aracil-Gisbert et al., 2022).

Selection versus transmission: quantitative biology and modeling approaches

In the previous sections, we noted the need for more precise quantitative experimental data to understand the dynamics of antibiotic resistance. However, we also mentioned the overwhelming complexity of the task of defining the parameters shaping the various selective and transmission spaces (Martínez and Baquero, 2014). Most importantly, we are very short of knowing the critical issues to determine; for instance, the total number of bacterial cells of a given species or particular clones in a given population, the changes in the diversity of bacterial subpopulations or the size of the selective and transmission exposome (Wei et al, 2022). We need to know (or to realistically estimate), the absolute number of clinically relevant resistant bacterial populations, versus the absolute number of resistant populations rarely associated with infections or the absolute number

400 of individuals hosting resistant bacteria in a particular environment. Such an ambitious task should
401 be studied in well-described ecological systems and followed over time. We need to expand the
402 quantitative biology of antibiotic resistance based on a deeper analysis of the microbial
403 composition of our colonized habitat. Similarly, the quantitative effects of interventions, such as
404 specific restrictions on the use of particular antibiotics in a hospital to decrease antibiotic
405 resistance, are based on low-quality evidence (Chatzopolou and Reynolds, 2020). Another case is
406 the quantitative insufficiency of data on the transmission of antibiotic resistance from the
407 environment to humans, given that the abundance of resistant bacteria and antibiotic resistance
408 genes does not necessarily provide accurate risk assessment (Manaia, 2017).

409 We can argue that, as in the case of quantitative cell biology, quantitative environmental biology
410 should not only be oriented to obtain precise observational and experimental results but to test the
411 plausibility of testing theories using statistical, mathematical and computational models (Howard,
412 2014). An example of this approach is the application of membrane computing procedures to
413 predict the effect of changes in selection (antibiotic consumption) and transmission (host-to-host
414 cross-contamination with resistant organisms) (Campos et al., 2019). This computing methodology
415 (derived from natural computing) considers the elements of the system (such as susceptible and
416 resistant bacteria, antimicrobial agents, mobile genetic elements carrying antibiotic resistance and
417 infected or colonized hosts) as "objects" defined by virtual membranes. Each object can be
418 endowed with deterministic or stochastic rules by which they can replicate, propagate, dissolve
419 and be transmitted and selected when interacting with another "object". The application of this
420 model to the selection-transmission dynamics of antibiotic resistance indicates that in hospitalized
421 patients, reductions in antibiotic use are much more effective for preventing the rise of antibiotic
422 resistance in the intestinal microbiota than reductions in host-to-host transmission. A possible

interpretation is that high transmission rates *also* facilitate the spread of antibiotic-susceptible bacteria. If antibiotic consumption (selection) is high, resulting in high rates of antibiotic resistance, a decrease in transmission will be highly effective. For example, using publicly available datasets (Wolf et al., 2022; Versporten et al., 2021), Figure 2 illustrates the interaction between selection (antibiotic consumption) and transmission (sanitation, hygiene) in 5 European Regions (Mediterranean, North, West, East and Central Europe) countries, shaping the local frequency of third-generation cephalosporin resistance in *E. coli*. This figure reveals a dynamic and complex relationship regarding the drivers of antibiotic resistance. The extent of the association between increased antibiotic consumption and higher antibiotic resistance is influenced by the hygiene index of the countries composing a region (circles in the figure). Both variables were standardized to be compared. Regions with suboptimal hygiene indices experience a more pronounced rise in antibiotic resistance with increased consumption. Conversely, in regions with better hygiene indices, the impact of antibiotic consumption on resistance is mitigated.

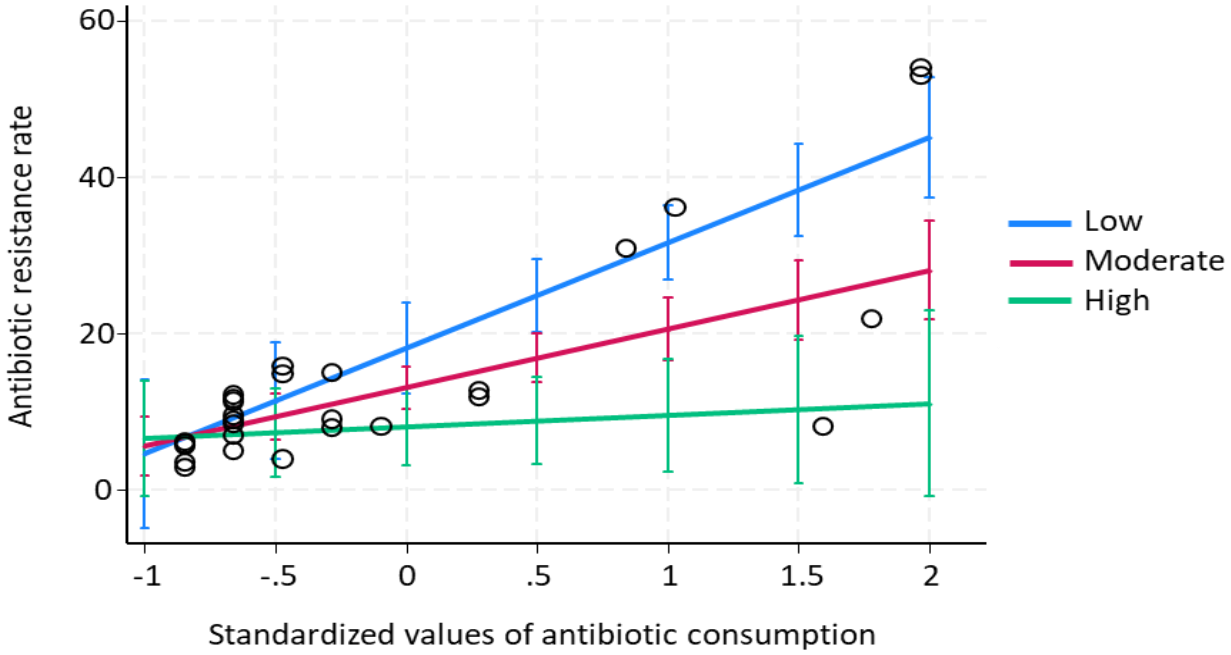

Figure 2. Antibiotic consumption versus sanitation. Influence of low, moderate and high levels of sanitation in various European countries on the effect of antibiotic consumption (third-generation cephalosporins) in *Escherichia coli* resistance to cefotaxime-ceftriaxone. In countries with low sanitation levels, antibiotic consumption plays a major role in increasing antibiotic resistance.

The biogeographical patterns of selection and transmission: the anthropogenic causation of resistance exposome

As discussed previously, both selection and transmission of antibiotic resistance are mutually synergistic in the emergence and spread of antibiotic resistance. The weight of such synergy depends on the intensity of each one of these variables in particular environments, and the time during which selection and transmission are exerting their effects in the microbiosphere, the "exposome" temporal dimension (Wei et al., 2022). The "cumulative history of antimicrobial use" over the last century (or more if heavy metal-based anti-infectives were considered) in a particular location could be critical to understanding the present scenarios (Coque et al., 2023). However, the current rates of antibiotic consumption and the rates of sanitation widely vary in different parts of the world, and therefore we could predict to a certain extent the main biogeographical areas where antibiotic resistance will emerge and spread. The main reason for the various combinations of selection and transmission is anthropogenic, encompassing economy and culture, which in turn are tightly associated. In other words, inequality is the main difficulty in designing interventions directed at limiting antibiotic resistance (Nadimpalli et al., 2021). As stated in a previous paragraph, areas with low antibiotic consumption (low selection) and high sanitation (low

transmission) have lower antibiotic resistance rates, followed by those with low consumption because of poor accessibility. However, the resistance burden in areas with medium-high consumption depends on the rate of sanitation (particularly water and soil fecal pollution); high antibiotic consumption and low sanitation provide the "perfect storm" for antibiotic resistance. As stated previously, these conditions depend on the economic background of the various areas, which influences and is influenced by the sociocultural landscape. For instance, the application of the Inglehart-Welzel World Cultural Map to the consumption of antibiotics reveals that countries with more "traditional" versus "secular" values and "survival" versus "self-expression" values tend to have higher rates of antibiotic consumption, except when accessibility to drugs is very limited (Dionisio et al., 2023). With this exception, low sanitation probably also correlates with "traditional" and "survival" cultural dimensions. As is clear, climatology influences the possibility of economic development of particular countries; in warmer-humid countries, the persistence of antibiotic resistance in the environment is probably longer (MacFadden et al., 2018; McGough et al., 2020). Concerns about the effect of global warming, increasing transmission of antibiotic resistant pathogens and the number of antibiotic-treatable infections (increasing selection) are well justified. These changes also influence the extensive international exchange of human and animal hosts, food, and also geological phenomena, such as oceanic currents (Zhang et al., 2012), contributing to the Earth's dispersion of antibiotic resistant populations. We can conclude that interventions directed to decrease antibiotic resistance should be designed "à la carte" (Rahbe et al., 2023), but the global effects of antibiotic exposure and resistance on local sites cannot be underestimated.

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