UNTANGLING ANTIMICROBIAL RESISTANCE (AMR)

The legacy of an unhealthy development model

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UNTANGLING ANTIMICROBIAL RESISTANCE (AMR), THE LEGACY OF AN UNHEALTHY DEVELOPMENT MODEL

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FOREWORDS

Antimicrobial resistance (AMR) possibly represents the greatest global crisis in public health today, and yet - as we shall try to illustrate - the phenomenon stretches well beyond the health domain. AMR is closely associated with some of the human disruptions enshrining globalization and the unfolding era of Anthropocene, being reproduced and transmitted as vectors of disease: the environmental crisis and climate change. Already, AMR is estimated to lead to 5 million deaths every year[1] and will claim 50 million lives in the coming decades. If "COVID-19 has revealed and exacerbated fundamental weaknesses in pandemic preparedness and response at both national and global levels [...] These same weaknesses are also true of the global response to AMR", declared the Director General of the World Health Organization (WHO), Dr Tedros Adhanom Gebreyesus, in early 2022. In fact, the risks entailed in AMR make the COVID-19 pandemic a rather amenable crisis in comparison.

AMR has become an extremely concerning scenario not so much due to the transfer of bacteria and genes - a natural and necessary biological process between humans and animals inhabiting the same environment[2] - but rather with the fact that it has literally gone out of control, altered by anthropogenic interventions. A vast majority of chemical products used in industrial agriculture and animal husbandry cycles, in aquaculture, the flower industry, and in industrial processes leading to plastic and heavy-metal pollution end up in the wild unchecked, unseen, leading to antimicrobial resistance. Human impact on the microbial world is a phenomenon that has potentially reached the catastrophic level, bringing us back to a 19th century pre-antibiotic era, when most diseases could not be treated. In 2015, the WHO Director General warned the world that AMR risked leading to "the end of modern medicine as we know it"[3]. In many parts of the planet, the functionality of healthcare systems hinges on the availability of effective antibiotics for bacterial infections. Surgeries, cancer treatment, organ transplantation, and community-acquired infections could be fatal once again without effective antibiotics and some of the gains in childhood survival due to availability of effective antibiotics for respiratory infections would also be washed away. This would result in millions of additional lives lost annually.

Having said that, the AMR discussion needs to be placed in the proper context. We wish to assert our firm distance from the increasing anti-bacterial narrative that has come with modernity. Like the famous microbiologist Dr Jacques Acar, who used to claim being

1 World Health Organization (2022). WHO Director-General's Remarks at the Commonwealth Heads of Government Meeting side event on antimicrobial resistance. WHO, 23 June 2022, https://www.who.int/director-general/speeches/detail/who-director-general-s-speech-for-chogm-2022-side-event---23-june-2022.

2 Gillings M.R., Paulsen I.T., (2014). Microbiology of the Anthropocene. Anthropocene, ScienceDirect, Volume 5, March 2014, pp. 1-8. https://www.sciencedirect.com/science/article/pii/S2213305414000319#tbl0005

3 https://www.reuters.com/article/us-health-antibiotics-who-idUSKCN0T50X720151116

"the friend of bacteria"[4], the authors of this paper do not intend in any way to contribute to strengthening the notion that bacteria are our enemies and that we need to protect ourselves from them. This is in open contradiction with the reality of the human body and its microbiome: without bacteria we would not exist. Most conservative estimates suggest a 1:1 ratio between human and bacterial cells[5], but the majority of scientists believes it is actually higher in favor of bacteria, not to mention the 8percent of viral DNA that humans carry[6]. It is therefore urgent to break the isolationist view of the human body and embrace its reality as a micro-universe where human cells live in symbiotic relations with other organisms in an open relation with the broader ecological system. It is precisely such a biocentric (rather than anthropocentric) notion of the human body that, among other beneficial outcomes, opens the way to a true understanding of One Health[7]. Conventional medicine is beginning to wake-up to the idea that our physiology depends as much on the metabolites of human cells as it depends on the metabolites of bacterial cells. This means that we cannot win the fight against AMR with a defensive strategy. In fact, it is this defensive antimicrobial obsession that has contributed to generating the selective pressure triggering AMR in the first place.

Over the past decades, institutions have gathered with increasing frequency to discuss and plan against the threats related to antimicrobial resistance. What has been done so far? Has the policy response been up to the mounting challenge? Unfortunately not. The international community seems to be heading to a nightmare scenario mentioned above, in the grip of a fragmented antimicrobial resistance governance that is looking at piece-meal diagnoses, avoiding the root causes of the problem, and proposing insufficient solutions. As a priority, most institutions have focused on the development of new antibiotics and possibly vaccines through public investment programs, to fill the current gaps. The last drugs with novel mechanisms of actions were developed in the 80's. Since then, it has been estimated that 17 percent of infections - and up to 40 percent or more in Brazil, India, or Russia - no longer respond to antibiotics. Novel drugs become useless in ever-shortening spans of time.

Yet, until the political economy of AMR remains ignored, superficially understood and not addressed in all its complex implications, the development of new drugs seems secondary and will not help eradicate the widespread resistance. In fact, "bringing a new antibiotic on the market, without first strengthening Infection Prevention and Control, would be like pouring fuel on the fire", Dr Dominique Monnet, AMR Lead at the European

4 Cambau E., Gutmann L., et al., (2020). Jacques F. Acar (1931-2020). In Clin Microbiol Infect, 2020 Sep; 26(9): 1261–1263, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7287428/.

5 Sender R., Fuchs S., et al., (2016). Revised estimates for the number of human and bacteria cells in the body. In PLOS Biology, 6th January 2016, https://journals.plos.org/plosbiology/article?id=10.1371/journal.pbio.1002533.

6 It is common knowledge that bacterial cells outnumber human cells by a ratio of 10:1, as widely cited in scientific literature. However, this estimate has been critically re-examined (see reference above), and that is why we talk here about "most conservative estimates".

7 Alas M., (2020). Antimicrobial Resistance: Examining the Environment as Part of the One Health Approach. The South Centre, Research Paper 104, March 2020, https://www.southcentre.int/wp-content/uploads/2020/03/RP-104.pdf.

Center for Disease Control (ECDC) stated in 2017[8]. While insistence on pharmaceutical solutions and on novel antibiotics' research is gaining ground, the paradox of AMR is that the best defense might actually be one that embraces new positive symbiotic relations with the bacterial world. It is only other bacteria – other than the resistant ones – that can help restore balance and, through mechanisms of competitive inhibition, limit the expansion of resistant populations. But this will never happen if we continue to think about bacteria as our enemies.

The prevalence of AMR worldwide has constantly increased and it is indeed a telling irony that public health premises like hospitals and healthcare centers should have become the hotspots of highest contamination. One of the greatest threats is the widespread ignorance of this syndemic, pre-existing the arrival of Covid-19. At the same time, there is a need for policymakers to completely reconsider the political narrative underlying antimicrobial resistance, and to reverse the ill-devised economic development that favors the environmental dissemination of resistant organisms and genes, and their impacts on biodiversity and human health. The world needs to address the structural determinants of this crisis and transformative policies are needed now.

8 Meeting of the Drive AB initiative, Brussels, September 2017. Dr Monnet's quote was extracted by Garance Upham, attending the meeting. For info on Drive-AB: http://drive-ab.eu/events/drive-ab-project-events/drive-ab-final-conference/. Unfortunately, Dr. Monnet's public remarks were not included in the official report of the meeting.

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List of abbreviations

AB	Antibiotics
ABS	Antibiotic stewardship
AMR	Antimicrobial Resistance
ARG	Antibiotic Resistant Gene
CAFO	Concentrated Animal Feeding Operation
DNA	DeoxyriboNucleic Acid
EC	European Commission
ECDC	European Centre for Disease Control
FAO	Food and Agricultural Organization at the United Nations
GLG	Global Leaders Group on Antimicrobial Resistance
GMO	Genetically Modified Organism
HAI	Hospital Acquired Infections
HICs	High Income Countries
HIV	Human Immunodeficiency Virus
HGT	Horizontal Gene Transfer
IPC	Infection Prevention and Control
IPCC	Intergovernmental Panel on Climate Change
IPEA	Independent Panel on Evidence for Action
LMICs	Low and Middle Income Countries
MDR	Multidrug Resistant
NAP	National Action Plan
UNEA	United Nations Environment Assembly
UNEP	United Nations Environmental Program
WAHO	World Animal Health Organization (previously World Organization for Animal Health, OIE)
WHA	World Health Assembly
WHO	World Health Organization
WWTP	Wastewater Treatment Plant

1. ANTIMICROBIAL RESISTANCE (AMR): DEFINITION AND SPREADING MECHANISMS

1.1 A natural phenomenon? Debunking antimicrobial resistance

Resistance by bacteria and other microbes to antibiotics and other medicines is often referred to as a "naturally occurring mechanism"[9] by which microorganisms evolve to become resistant to the antimicrobial medicines[10]. This statement deserves more accuracy. Bacteria can acquire antibiotic-resistance through multiple mechanisms, which will be detailed in this section. Sometimes, resistant bacteria have a competitive advantage against non-resistant ones. They can gain or lose antibiotic-resistance. This dynamic process therefore depends on externalities and also on the biodiversity-related competition in a given environment.

Therefore, we need a more precise representation when confronted with the multiplicity of human actions that have made AMR emerge and spread beyond natural trends. The rate of resistance is constantly accelerating and its scope is extended by a widening diversity of anthropogenic factors. Antimicrobial resistance is primarily generated by industrial pollution, urbanization, by the injudicious use of the commonly available antibiotics in animal husbandry and aquaculture, by pesticides and other chemicals massively used in global agriculture, and by the presence of metal residues. These chemicals have created a frightening selection pressure for bacteria, leading to a loss of biodiversity which favors the emergence of resistant pathogens. The footprint of waste generated stimulate the drug resistance in the environment, with prospective resistome-spill over to humans and animals[11]. Armed conflicts are also drivers of AMR, as seen in the wake of the American invasion of Iraq in 2003[12]. The environmental devastation deriving from all these circumstances enables the many species of "bacteria", "viruses", "fungi" and "parasites" to flourish and become resistant.

One striking aspect of the current state of AMR research is that we know only about 1 percent of the diversity of bacteria, viruses and parasites. And we know there can be up

9 World Health Organization, Policy Brief 39, Web ISSN 1997-8073, https://apps.who.int/iris/bitstream/handle/10665/339629/Policy-brief-39-1997-8073-eng.pdf

10 REACT. How did we end up here?. https://www.reactgroup.org/toolbox/understand/how-did-we-end-up-here/

11 Oyekale A. S., and Oyekale T. O., (2017). Healthcare Waste Management Practices and Safety Indicators in Nigeria. *BMC Public Health* 17, 1–13. doi:10.1186/s12889-017-4794-6.

12 Haraoui L.P., Sparrow A., et al. (2019). Armed conflicts and antimicrobial resistance: A deadly convergence. In Global Health Security, AMR Control, 2019, pp. 69-73, http://resistancecontrol.info/wp-content/uploads/2019/05/Haraoui.pdf.

to 1 billion viruses and up to 10 million bacteria per gram of soil. This diversity acts as a huge reservoir pool for antibiotic resistant genes (ARG), adding to the probability of their emergence and spread under environmental stress, including that caused by human activity[13]. In 2017, the third United Nations Environment Assembly (UNEA-3) requested a report on the environmental impacts of AMR and the causes of the development and spread of resistance in the environment, including the gaps in understanding those impacts and causes. In 2022, finally, the United Nations Environment Program (UNEP) was brought in the tripartite AMR One Health management in the United Nations. Will this new development bring a better chance to lead AMR policies in the right direction?

BOX 1.

WHY DO WE SPEAK ABOUT ANTIMICROBIAL RESISTANCE?

Antimicrobial resistance happens when germs develop the ability to defeat the drugs designed to kill them. That means the germs are not killed and continue to grow. **The United Nations has identified such microbes according to the following taxonomy[14]:**

Bacteria: Pathogens from the bacterial families become resistant to antibiotics used in day-to-day medicine. AMR Tuberculosis is a looming pandemic (airborne, like the viral COVID-19), Escherishia coli, Listeria, Salmonella, and many others are common pathogens of our food chains.

Fungi: Pathogens from the fungus families resistant to fungicide drugs. Such as the deadly Aspergillus fumigatus.

Viruses: Pathogens from the viral families are increasingly reported as being no longer affected by antiviral drugs. This is the case for example of HIV infections no longer responding to treatments, especially for patients living with TB and HIV fueling each other.

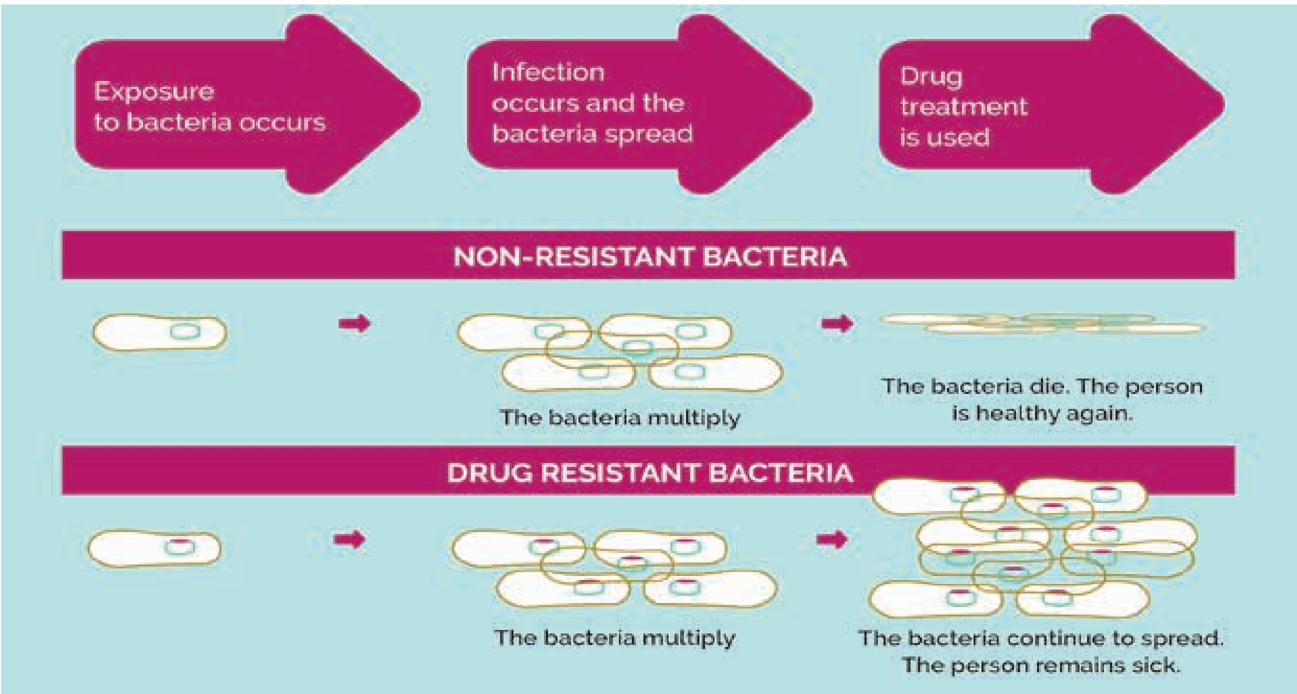
Parasites: Parasites are not normally embraced in the definition of "microbes", but are included in the definition of AMR when becoming unresponsive (resistant) to antiparasitic drugs, such as antimalarial therapies, or the treatment for other parasitic diseases. Indeed, intestinal parasites are normally treated and/or controlled by drugs that are extensively used in animal health, and which have developed resistance for their animal use targets.

13 Baquero F., Tedim A.P, and Coque T.M., (2013). Antibiotic resistance shaping multi-level population biology of bacteria. *Frontiers in Microbiology*, 4:15, 6 March 2013, https://www.frontiersin.org/articles/10.3389/fmicb.2013.00015/full.

14 https://www.who.int/news-room/fact-sheets/detail/antimicrobial-resistance

1.2 The mechanisms of AMR emergence

In 2017, the WHO published the first-ever list of antibiotic-resistant priority pathogens, describing a catalog of twelve bacterial families posing the greatest threat to human health due to their resistance[15]. In natural biological processes, antimicrobial resistance emerges through a variety of mechanisms[16]:

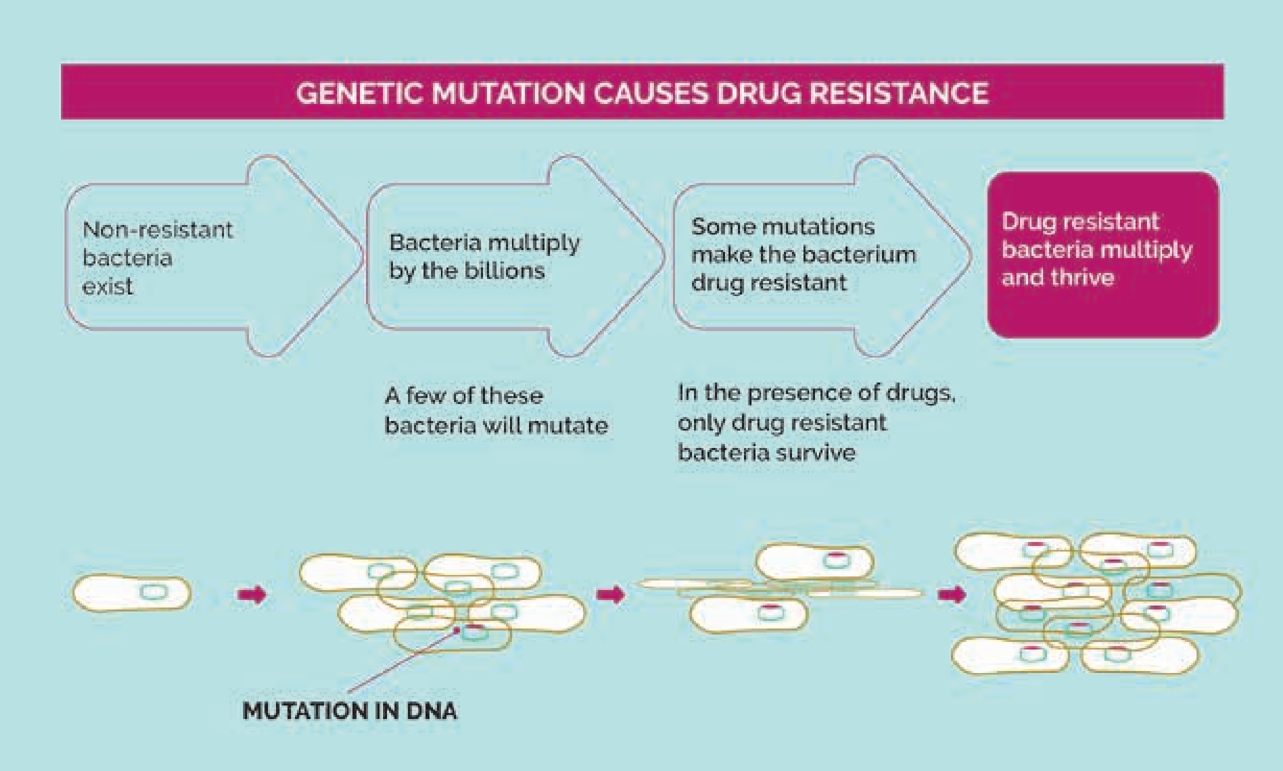


1. SELECTIVE PRESSURE

In the presence of an antimicrobial, microbes are either killed or, if they carry resistance genes, they survive. These survivors replicate, and their progeny quickly becomes the dominant type throughout the microbial population, allowing for resistant organisms to grow and colonize the environment. It is often thought that the selective pressure caused by antibacterial medicines is the main factor for the emergence of AMR genes. But in addition to antibiotic drugs and antiviral compounds, as we have said already, AMR is fuelled by herbicides, fungicides, parasiticides, disinfectant chemicals, by metals (cobalt, aluminum, uranium, silicium, etc.) and microplastics. They are shown to act as co-selecting compounds.

15 https://www.who.int/news/item/27-02-2017-who-publishes-list-of-bacteria-for-which-new-antibiotics-are-urgently-needed

16 Descriptions and illustrations here are borrowed from the National Institute of Allergy and Infectious Diseases (NIH), https://www.niaid.nih.gov/research/antimicrobial-resistance-causes.

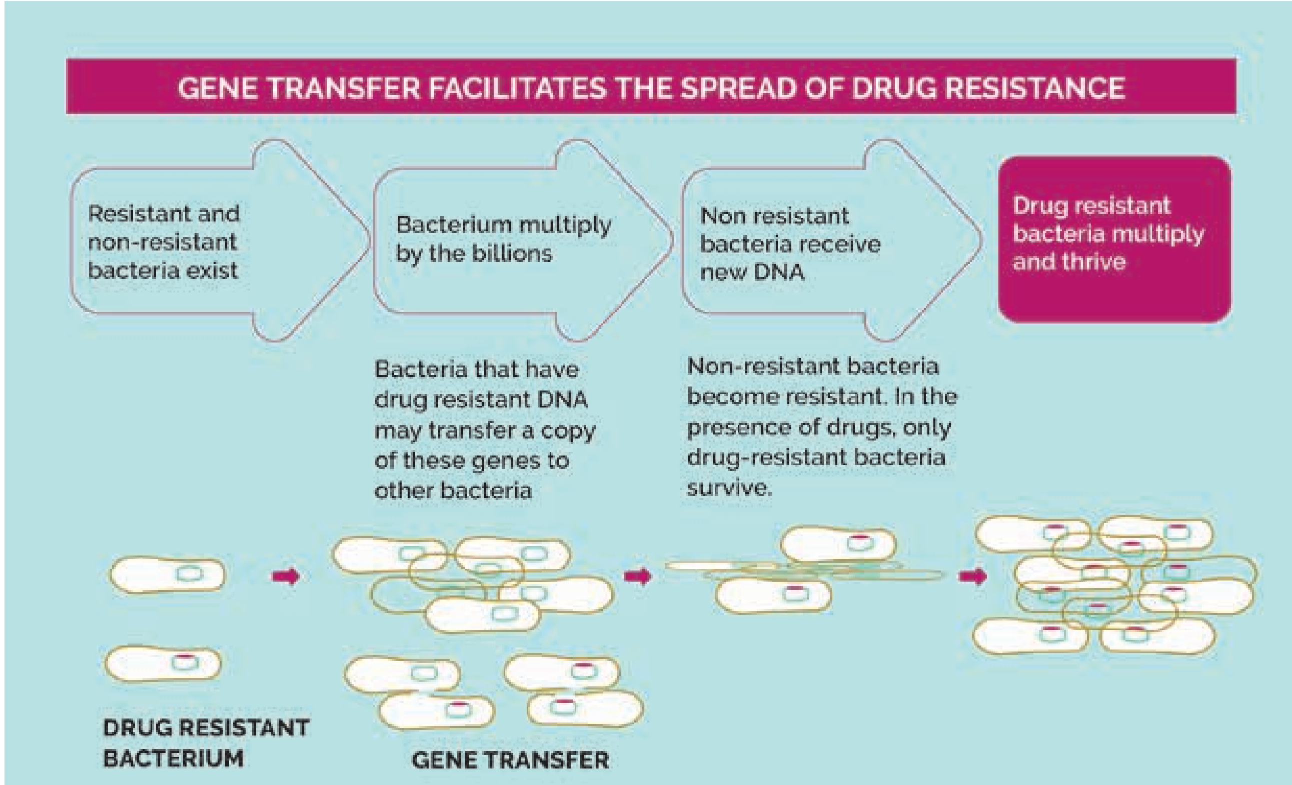


2. MUTATION

Most microbes reproduce by dividing every few hours, allowing them to evolve rapidly and adapt quickly to new environmental conditions. During replication, mutations arise and some of these mutations may help an individual microbe survive exposure to an antimicrobial.

Mutations arise in a stochastic manner, i.e. with a random probability in distribution and patterns, and research has shown that this can happen in the absence of any antimicrobial molecule.

Pharmaceutical drugs, pesticides, copper, zinc, and other co-products strongly favor mutations to be fixed in the population. In this regard, the use of Low and Middle Income countries (LMICs) by High Income Countries (HIC) for dumping grounds for their industrial waste products is no less than a scandalous practice.



3. GENE TRANSFER

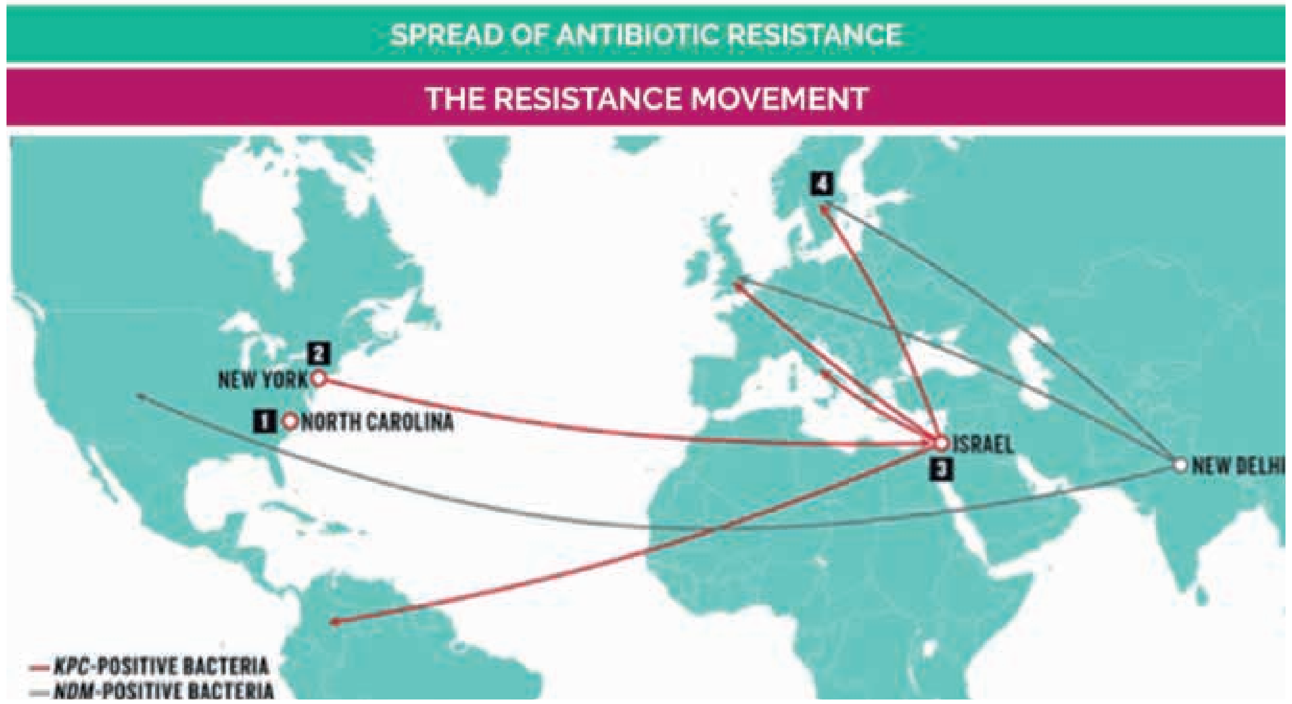
Microbes also may get genes from each other, including genes that make the microbe drug resistant, through a process that is referred to as Horizontal Gene Transfer (HGT). Bacteria multiply by the billions.

Bacteria that have drug-resistant DNA may travel on genetic vectors such as plasmids and phages, which can be disseminated in air and water, and transfer a copy of these genes to other bacteria.

Non-resistant bacteria receive the new DNA and become resistant to drugs. In the presence of drugs, only drug-resistant bacteria survive. The drug-resistant bacteria multiply and thrive.

1.3 *AMR spread mechanisms now recognized*

After 20 years of scientific publications on the causes underlying the spread mechanisms of AMR, the issue is beginning to be acknowledged. AMR comes from the environment around us. In one recent overview for policymakers, UNEP makes it clear from the start that "many human activities create pollution which promotes the emergence of AMR in the environment. AMR in the environment can cause animal or plant diseases or soil biodiversity loss that can lead to further use of antimicrobials (a negative feedback from initial use) that only increases the selective pressure further"[17]. While the report recognizes that the environmental impacts of AMR, and the causes of the development and spread of resistance in the environment are complex, "there is evidence that both biological and chemical pollutants, which enter the environment, can fundamentally influence and change what is happening in the environment, especially AMR development, transmission and spread. Human activity and increasing populations are damaging the natural microbial world – the very foundation of global ecology"[18]. In other words, the bacterial and fungal families we have mentioned earlier, which include thousands of different species, are likely to develop a genetic code for drug resistance as a main result of overuse of antibiotics, herbicides and fungicides in agriculture and their industrial systems.



1 - 2000: Analysis of a 1996 sample from North Carolinian hospital finds infectious Klebsiella pneumoniae carrying a genie called KPC that confers resistance to carbapenems.

2 - 2003: KPC-positive bacteria are found spreading rapidly through hospitals across new York City. By 2007, 21% of clebsiella in the city carry the resistance gene.

3 - 2005: KPC-positive make their way from New York to several other countries, including Israel. From Israel, the bacteria travel to Italy, Colombia, the United Kingdom and Sweden.

4 - 2008: Dctors in Sweden find a new carbapenem-resistance gene, NDM. Traced back to India, NDM-positive bacteria have moved quickly.

17 United Nations Environment Programme (2022). Environmental Dimensions of Antimicrobial Resistance: Summary for Policymakers, UNEP 2022, https://wedocs.unep.org/bitstream/handle/20.500.11822/38373/antimicrobial_R.pdf

18 *Ibidem.*

Indeed, all these synthetic chemicals affect bacteria and fungi, leading to a higher probability of developing AMR. The more frequent the discharge of chemicals in the environment, even in low doses, the more likely drug-resistant bacteria or fungi will be selected. The list of biological phenomena that contribute to increasing AMR is likely to increase with upcoming research in the next decade. For example, recent studies point toward the possible influence of plastic, and other human-derived polymers, in developing conditions such as biofilm, that are favorable to genetic mutations[19]. Hence, microplastics are environmental pollutants that potentially have a positive synergistic effect on the development, persistence, transportation, and ecology of antibiotic resistant bacteria in the environment[20 21]. With frequent discharge of chemicals, the AMR resistant genes are more likely to appear in the organism population.

Last but not least, few understand that the small organisms we are talking about, and vectors such as plasmids, can be transported and propagated in the environment over long distances. The impact of international travel on transmission cannot be underestimated, in this regard. The NDM-1 antibiotic resistance gene (New Delhi Metallo-beta-lactamase-1), identified first in late 2009 in New Delhi, was a warning shot. From India, the bacteria spread fast: infected patients appeared in the UK in early 2010, then spread worldwide in mid-2010.

Similarly, other genes are found to travel worldwide[22], with the same kinetic that has spread the SARS-CoV-2 coronavirus and human behavior has been pointed out, to some extent, as a risk factor for the spread of AMR[23 24]. Avoiding the rise of AMR therefore requires preventive actions, surveillance, and proactive implementation research. It is essential to recognise that AMR is a text-book case of systemic challenges tightly linked to the human perturbations of an economic development model that degrades ecosystems and the environment around us. What we do to the planet comes back to us, not always in a way we would expect, and with vast health implications.

19 Kırmusaoğlu, S. (2016). Staphylococcal biofilms: Pathogenicity, mechanism and regulation of biofilm formation by quorum sensing system and antibiotic resistance mechanisms of biofilm embedded microorganisms. *Microbial biofilms: importance and applications. IntechOpen*, 189-209.https://pdfs.semanticscholar.org/5449/24498b2114cc1cf6590686592a1370da6e66.pdf

20 Bartkova S., Kahru A., et al., (2021). Techniques Used for Analyzing Microplastics, Antimicrobial Resistance and Microbial Community Composition: A Mini Review. *Frontiers in Microbiology,* 26th March 2021, https://www.frontiersin.org/articles/10.3389/fmicb.2021.603967/full.

21 Metcalf R., et al., (2022). Sewage-associated plastic waste washed up on beaches can act as a reservoir for faecal bacteria, potential human pathogens, and genes for antimicrobial resistance. *Marine Pollution Bulletin* 180 (2022): 113766.https://www.sciencedirect.com/science/article/pii/S0025326X22004489

22 Kieffer N, Ebmeyer S, Larsson DGJ. (2021). Evidence for *Pseudoxanthomonas mexicana* as the recent origin of the *blaAIM-1* carbapenemase gene. International Journal of Antimicrobial Agents. https://doi.org/10.1016/j.ijantimicag.2022.106571

23 Rodríguez-Molina D., Berglund F., Blaak H, et al.,(2022). International travel as a risk factor for carriage of extended-spectrum -lactamase-producing *Escherichia coli* in a large sample of European individuals - The AWARE Study. *International Journal of Environmental Research and Public Health,* 14th April 2022, https://www.mdpi.com/1660-4601/19/8/4758.

24 Burman E, Bengtsson-Palme J (2021). Microbial community interactions are sensitive to small differences in temperature. Frontiers in Microbiology, 12, 672910. http://dx.doi.org/10.3389/fmicb.2021.672910

2. THE PARALLEL LIVES OF CLIMATE CHANGE AND ANTIMICROBIAL RESISTANCE

Fifty years after the breakthrough United Nations Conference on the Environment in Stockholm[25], humanity is starkly confronted with the myriad effects of climate change on human health. The latest report of the Intergovernmental Panel on Climate Change (IPCC) is a grim reminder that if the world wants to limit global warming to 1.5˚C (2.7˚F), we need to make a serious U-turn and we are running out of time: the situation is becoming increasingly dire as the pace of anthropogenic climate change accelerates. Examples of its widely visible effects include heat-related mortality, desertification, food insecurity and reduced crop yields, hunger and increased suitability for infectious diseases transmission, rising sea levels, cancer morbidity, mortality from increasingly severe wildfires, and the multiple health effects resulting from other extreme weather events such as floods and droughts.[26]

One relatively underreported, and yet extremely relevant, intersection between climate change and health has to do with the mounting spread of infections, including antibiotic-resistant infections, worldwide. With the changed climate, the situation of antimicrobial resistance will be pushed closer to a breaking point. It is clear that the anthropogenic impact on the environment is the main source of climate change and AMR genes. The current global food system, for example, is a major contributor to global warming, responsible of 21-37 percent of annual emissions[27] as well as being a major trigger of AMR.

Scientific evidence demonstrates that heat is closely associated with bacterial processes and infections[28]. Horizontal gene transfer, a key mechanism for the acquisition of antimicrobial resistance, is propelled by increasing temperatures. Moreover, increases in temperature generally increment bacterial growth rates[29]. With global warming, the atmosphere's capacity to retain water grows exponentially, resulting in more frequent and intense precipitations that often lead to flooding, flood-related infections, displacement

25 https://sdg.iisd.org/news/stockholm50-legacies-of-1972-conference-and-challenges-ahead/

26 Watts N., Amann M., Arnell N., et al., (2020). The 2020 report of The Lancet countdown on health and climate change: responding to converging crises. Lancet 2020; 397: 129–170, https://www.sciencedirect.com/science/article/abs/pii/S014067362032290X.

27 Mbow C., Rosenzweig C., et al., (2019). Food Security. In *Climate Change Land: An IPCC Special Report on Climate Change, Desertification, Land Degredation, Sustainable Land Management, Food Security, Greenhouse Gas Fluxes in Terrestrial Ecosystems*,Retrieved from https://policycommons.net/artifacts/458644/food-security/1431487/.

28 Burnham J., (2021). Climate change and antibiotic resistance: A deadly combination.*Therapeutic Advances in Infectious Diseases,* 2021, Vol. 8:1-7. https://journals.sagepub.com/doi/pdf/10.1177/2049936121991374.

29 Pietikäinen J., Pettersson M., Bååth E., (2005). Comparison of temperature effects on soil respiration and bacterial and fungal growth rates. *FEMS Microbiol Ecol* 2005; 52: 49–58. https://academic.oup.com/femsec/article/52/1/49/483427?login=true.

of population including creation of climate refugees and human overcrowding. We are witnessing these phenomena with increasing frequency.

While overcrowding is itself associated with higher infection rates,[30] flooding can lead to the spread of waterborne infections due to the overflowing of contaminated waters by livestock or from sewage lines, a known reservoir for antibiotic-resistance genes.[31] More intense rainfalls are bound to result in an increase of overflows and higher levels of pollution in waters. Swelling agricultural runoffs will escalate bacterial blooms and high concentrations of bacteria will expand opportunities for the transfer of resistant genes. Flooding can also disseminate pollutants, heavy metals from industrial manufacturing and plastics in the environment, which are known to enhance AMR[32] [33] .

Extreme weather events can also enhance bacterial resistance for the opposite reason, i.e. water scarcity. Droughts inevitably lead to the combination of decreased sanitation and higher densities of populations are forced to share the same scanty water sources. In these circumstances, waterborne infections are primed for explosive outbreaks. In addition, droughts result in the elimination of mosquito predators, allowing parasitic vectors to multiply unhindered in residual sites in stagnant waters[34].

The 2020 Lancet Countdown Report makes it clear that bacterial and parasitic infections are impacted by climate change. Vector habitats expand due to ecosystems' transformation[35] and high temperatures enhance vector activities[36]. Climate change has already resulted in the spread of malaria to places previously not endemic[37], whereas

30 Cardoso, MR, Cousens, SN, de Góes Siqueira, LF, et al., (2004). Crowding: risk factor or protective factor for lower respiratory disease in young children?. *BMC Public Health* 2004; 4: 19. Also, in this regard, Blakiston MR., Freeman JT., (2020). Population-level exposures associated with MRSA and ESBL-E. coli infection across district health boards in Aotearoa New Zealand: an ecological study. *N Z Med J* 2020; 133: 62–69. https://journal.nzma.org.nz/journal-articles/population-level-exposures-associated-with-mrsa-and-esbl-e-coli-infection-across-district-health-boards-in-aotearoa-new-zealand-an-ecological-study.

31 Karkman A., Do T.T., et al., (2018). Antibiotic-resistance genes in waste water. *Trends in Microbiology,* Volume 26, Issue 3, March 2018, pages 220–228, https://www.sciencedirect.com/science/article/abs/pii/S0966842X1730210X

32 Gupta S., Graham D.W., et al., (2022). Effects of heavy metals pollution on the co-selection of metal and antibiotic resistance in urban rivers in UK and India. *Environmental Pollution,* Volume 306, 1st August 2022, 119326.https://www.sciencedirect.com/science/article/abs/pii/S0269749122005401?dgcid=coauthor

33 https://www.medicalnewstoday.com/articles/microplastic-waste-creates-hotspots-of-antibiotic-resistant-bacteria#Increases-in-3-resistance-genes.

34 Chase J.M., Knight T.M.,(2003). Drought-induced mosquito outbreaks in wetlands. *Ecology Letters,* 30th September 2003; 6: 1017–1024, https://onlinelibrary.wiley.com/doi/abs/10.1046/j.1461-0248.2003.00533.x

35 Watts N., Amman M., et al.,(2020). The 2020 report of *The Lancet* Countdown on health and climate change: responding to converging crises. *The Lancet,* Volume 397, Issue 10269, P. 129-170, 9th January 2021. https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)32290-X/fulltext.

36 Estallo E.L., Ludueña-Almeida F.F., et al., (2015). Weather variability associated with Aedes (stegomyia) aegypti (Dengue vector) oviposition dynamics in Northwestern Argentina. *PLoS One* 2015; 10:027820, https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0127820.

37 Lafferty K.D.,(2009). The ecology of climate change and infectious diseases. *Ecology,* 2009; 90: 888–900, https://esajournals.onlinelibrary.wiley.com/doi/10.1890/08-0079.1.

the dire social dimension of climate change already reflect the serious consequences on tuberculosis and its antibiotic-resistant spread[38].

While the growing interest in areas such as One Health has helped bridge key topics of AMR, climate change, and environmental research, the majority of studies are still limited to the silo of each individual issue[39]. The environmental dimension of AMR, clearly established in a large number of publications and scientific papers[40] [41], has not yet been acknowledged by institutions worldwide to a large extent. One Health is widely used as a mere buzzword for containment. It remains poorly defined and understood, including in policy terms.

38 Burnham J., (2021). Climate change and antibiotic resistance: A deadly combination.*Therapeutic Advances in Infectious Diseases,* 2021, Vol. 8:1-7. https://journals.sagepub.com/doi/pdf/10.1177/2049936121991374.

39 WHO (2014). Antimicrobial resistance: global report on surveillance. World Health Organization, Geneva, Switzerland, 2014.

40 De Roda Husman A-M, Larsson DGJ (2016). Risk assessment and risk management of antimicrobial resistance in the environment. AMR control 2016. Pages 104-107. Global Health Dynamics, UK. link: http://resistancecontrol.info/2016/amr-in-food-water-and-the-environment/risk-assessment-and-risk-management-of-antimicrobial-resistance-in-the-environment/

41 Bengtsson-Palme J., Larsson DGJ (2016). Why limit antibiotic pollution? The role of environmental selection in antibiotic resistance development. APUA Newsletter, 34(2), 6-9. link: https://microbiology.se/2016/10/05/published-opinion-piece-why-limit-antibiotic-pollution/

BOX 2.

ONE HEALTH

Coined by the Wildlife Conservationist Society in 2004[42], the concept of One Health refers to the recognition that all living beings - humans, animals and plants - by sharing the same environment, have profound and intrinsic health interconnections. The One Health concept has recently made its way to center stage in international and multilateral debates due to the COVID-19 pandemic event and its supposed zoonotic origins.

One Health defines the nexus across the fields of human, veterinary and environmental health bringing the need for new categories and interlinkages on critical areas like food systems, zoonoses, wildlife trade, biodiversity loss, microbiome diversity, and antibiotic resistance. Its goal is to address the causes of ill-health instead of limiting action to merely treating symptoms. The One Health concept is oriented to developing the nexus narrative and shaping policies that may produce positive impacts on the diversity of sectors and fields. In 2021, the One Health narrative landed in several international circles, including the WHO negotiations for a new binding instrument for pandemic prevention, preparedness and response,[43] and at the G20.

In international circles, the discussion on One Health as an approach to global health almost exclusively concentrates on improving surveillance and intersectional communication and collaboration through research and policy, mainly in the context of crisis management and health security.

According to the WHO definition, "One Health is an approach to designing and implementing programmes, policies, legislation and research in which multiple sectors communicate and work together to achieve better public health outcomes"[44].

However in reality, it is a much deeper approach which describes the health of humans as interdependent with the health of animals, plants and other living systems and vice versa.

While climate change is occuring everywhere on the planet, it is marginalized groups and people living in poverty that have contributed the least to global emissions, but bear the largest brunt and have the least capacity to protect themselves from the consequences of extreme events. In this complex "climate apartheid scenario"[45], where the wealthy can afford to buy their way out of rising heat and hunger while the rest of the world is left to suffer, the syndemic and social justice dimension of climate change and antimicrobial resistance needs to be recognized and addressed urgently.

42 Paul J., Gibbs E., (2014). The Evolution of One Health: a decade of progress and challenges for the future. *Veterinary Record*. (4):174 85–91. https://pubmed.ncbi.nlm.nih.gov/24464377/

43 https://apps.who.int/gb/COVID-19/pdf_files/2021/18_03/Item2.pdf

44 https://www.who.int/news-room/questions-and-answers/item/one-health.

45 https://www.ohchr.org/en/documents/thematic-reports/ahrc4139-climate-change-extreme-poverty-and-human-rights-report

3. FOOD SYSTEMS & THE AMR SPILLOVER

In a globalized world where corporate-led food supply chains are rooted in an planetary destructive system of industrial agriculture, food-producing environments, namely all environments where food of animal or non-animal origin is produced and/or processed, have become key drivers of antimicrobial resistance. This happens at the primary level (e.g. animal farms, fruits and vegetables cultivation fields, etc.) and at the secondary level (e.g. slaughterhouses, post-harvest processing plants, food processing, etc.). This phenomenon is spreading all over the world. That is why food and agriculture are one of the most important - if not *the* most important - landing pad for immediate action on AMR to address the environmental dimension of the problem.

The role played by natural and food producing environments in the emergence, selection, dissemination and transmission of AMR has received lesser interest than the direct selection and transmission within and between humans and animals. But scientific and empirical evidence demonstrates that food producing environments are increasingly contaminated by antimicrobial-resistant bacteria[46] (including mobile genetic elements) that derive from different environmental sources, such as:

- effluents from terrestrial/aquatic food-producing animals;
- effluents and other residues from post-harvest food plants (e.g. slaughterhouses and food processing plants);
- effluents from urban waste-water treatment plants;
- crop production and horticulture (due to direct use of antimicrobials).

Once antimicrobial-resistant bacteria contaminate food-producing environments, they can further spread throughout food systems through several routes posing a threat for public health and the environment - an example is the runoff of farmed animal manure during flooding events that are increasing worldwide due to the climate crisis[47]. When antibiotic resistance becomes the norm, as we have started to see, it is a clear indication that humankind has decided to wage a war against the environment it lives in, the animals it feeds on, the soil, the plants and the waters that humans depend on for their living. As we note the prevalent AMR narrative - at events that have mushroomed since the world has woken up to the global rise of antimicrobial-resistant organisms - points instead to the inappropriate use of antibiotics (frivolous drug-administering, inadequate dosing,

46 Koutsoumanis K., Allende A., et al., (2021). Role played by the environment in the emergence and spread of antimicrobial resistance (AMR) through the food chain. *EFSA Journal*, 2021, 6651, EFSA Panel on Biological Hazards (BIOHAZ). https://efsa.onlinelibrary.wiley.com/doi/pdf/10.2903/j.efsa.2021.6651. See also: NCCEH (2022). Antimicrobial resistance in the food chain. National Collaborating Centre for Environmental Health, 10th February 2022, https://ncceh.ca/environmental-health-in-canada/health-agency-projects/antimicrobial-resistance-food-chain.

47 Richardson J., (2021). Antimicrobial Resistant Bacteria Within Surface Water Bodies. In *University of Nebraska Lincoln Water*, Institute of Agriculture and Natural Resources, 22nd February 2021, https://water.unl.edu/article/animal-manure-management/antimicrobial-resistant-bacteria-within-surface-water-bodies.

poor adherence to treatment guidelines) as the practices that contribute to the increase of resistance[48]. The reality is far more complex, unfortunately.

In today's hygiene society, where biosecurity seems to have become an ideology, food safety regulations turns a blind eye towards the massive antimicrobial pollution in the environment, including food producing environments, but instead focus on residuals of antimicrobials only in animal based foods (milk, meat, etc.). These regulations contribute to the medicalized approach to food that leads to the forced separation between human health and planetary health. But food systems and agriculture are a primary entry point for immediate action against AMR. Highly industrialized food production, particularly the livestock sector, has become dependent on the use of antimicrobials to keep afloat its unsustainable model of productive stress, high animal concentration in reduced spaces and livestock monoculture through genetic selection. The commodification of nature and its living beings, prevalent in the industrialized food systems, and built on the overuse of antibiotics outside of the field of human medicine, is a key arena to address if we are to handle the problem beyond its ill-defined causes.

3.1 Husbandry and AMR: the tragedy of Concentrated Animal Feeding Operations

The official US Department of Agriculture stated that over 80 percent of US antibiotic consumption is used by the meat industry, primarily as growth promoters – an antibiotic makes the animal grow faster with more fat on less food. Globally, it is estimated that 70 percent of these antibiotics are used for humans[49]. There are at least 30 different antibiotics that are commonly used in agriculture and livestock, among which macrolides, penicillins and tetracyclines are the major ones[50].

The industrialization of meat production has ushered widespread bacterial resistance. In animal husbandry alone, the average yearly consumption of antibiotics has been estimated as 172 mg/kg in pigs, 148 mg/kg in chicken, and 45 mg/kg in cattle worldwide[51]. Non antibiotic products, such as metals like copper and zinc are also used, from the USA to rural Africa, which too induce AMR in bacteria[52]. There is a tension between the food security frameworks related to agro-industrialization, with their focus on standardizing farm productions and marketing activities, and on the other hand the need to prevent emerging diseases with pandemic potential. Food safety regulations end up creating a boomerang effect, as they are often used to raise standards beyond real necessity, thereby encouraging scaling up of even more industrialized food production at the expense of small scale animal farmers.

Dealing with AMR in the environment entails primarily addressing the sector of husbandry and its Concentrated Animal Feeding Operations (CAFOs) practices[53]. Livestock are now the main factor causing water pollution in China for example (pig and poultry waste from CAFOs)[54]. Our goal is not to provide an exhaustive review of CAFOs, but to report on some practices that specifically relate to AMR and health issues.

Animal concentration, welfare and AMR are linked together, yet livestock production has become increasingly dominated by CAFOs, beginning in the United States and progressively in other parts of the world[55]. Most poultry was raised in CAFOs starting in the 1950s, and most cattle and pigs by the 1970s and 1980s[56]. By the mid-2000s, CAFOs dominated livestock and poultry production in the United States, and the scope of its market share continues to steadily increase.

In 1966, it took 1 million farms to house 57 million pigs; by 2001, it took only 80,000 farms to house the same number [57] [58]. Another example: over 70 years - post WWII to

48 Ibrahim O.M., Polk R.E., (2014). Antimicrobial use metrics and benchmarking to improve stewardship outcomes: methodology, opportunities and challenges. *Infect Dis Clin North Am*. 2014 Jun;28(2):195-214. doi: 10.1016/j.idc.2014.01.006. PMID: 24857388. https://pubmed.ncbi.nlm.nih.gov/24857388/

49 Martin J.M., Thottathil S. et al., (2015). Antibiotics Overuse in Animal Agriculture: A Call to Action for Health Care Providers. *American journal of public health* vol. 105,12 (2015): 2409-10, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4638249/

50 Mann A., Nehra K., et al., (2021). Antibiotic resistance in agriculture: Perspectives on upcoming strategies to overcome upsurge in resistance. *Microbial Sciences,* Vol.2, December 2021, 100030, https://www.sciencedirect.com/science/article/pii/S2666517421000110.

51 *Ibidem.*

52 Yazdankhan S., Skjeve E., et al.,(2018). Antimicrobial resistance due to the content of potentially toxic metals in soil and fertilizing products. Microbial Ecology in Health and Disease, 2018 (29)1, published online 11th December 2018, doi: 10.1080/16512235.2018.1548248.

53 The U.S. Environmental Protection Agency (EPA) defines CAFO any Animal Feeding Operation (AFO) with more than 1000 animal units (an animal unit is defined as an animal equivalent of 1000 pounds live weight and equates to 1000 head of beef cattle, 700 dairy cows, 2500 swine weighing more than 55 lbs, 125 thousand broiler chickens, or 82 thousand laying hens or pullets) confined on site for more than 45 days during the year. Any size AFO that discharges manure or wastewater into a natural or man-made ditch, stream or other waterway is defined as a CAFO, regardless of size. https://www.nrcs.usda.gov/wps/portal/nrcs/main/national/plantsanimals/livestock/afo/.

54 Zhang L., (2021). China and the UN Food System Summit: Silenced Disputes and Ambivalence of Food Safety, Sovereignty, Justice, and Resilience. In *Development* 64, 303–307 (2021). https://doi.org/10.1057/s41301-021-00323-y.

55 Imhoff D., Tompkins D., Carra R.,(2010). CAFO: The Tragedy of Industrial Animal Factories. Earth Aware Editions, Devon, UK, 2010.

56 Burkholder J., Libra B., Weyer P.,Heathcote, S. et al., (2006). Impacts of Waste from Concentrated Animal Feeding Operations on Water Quality. *Environmental Health Perspectives*. 115 (2): 308–312. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1817674/

57 Walker P., et al. (2005). Public health implications of meat production and consumption. *Public Health Nutrition*. 8 (4): 348–356. https://www.cambridge.org/core/services/aop-cambridge-core/content/view/B22CB5C2097A13C6745A94B6D6B81284/S1368980005000492a.pdf/public-health-implications-of-meat-production-and-consumption.pdf

58 MacDonald, J., McBride W. (2009). The transformation of U.S. livestock agriculture: Scale, efficiency and risks. Economic Information Bulletin, No. EIB-43, January 2009, United States Department of Agriculture, archive.org/web/20120629041358/http://www.ershttps://web.a

today - Japan's meat industry went from 7,570,000[59] livestock farms units in 1955 down to 70,670 units in 2018[60]. Meanwhile, the Japanese population increased by 40 percent over the same period. One can then imagine how animal concentration has evolved in the meat industry farms, where animals are considered property goods, as dematerialized as stocks in Wall Street.

Currently, the European Commission (EC) advocates a limit of 33kg of chicken per square meter - which is nevertheless unacceptable. In the Netherlands, the livestock industry reaches 42.25kg on average. These numbers show how our farming systems are dependent on drugs to limit infection risks. At such extreme concentration, with the filth and the stress, the animal would not survive to maturity without antibiotics. Not surprisingly, chicken is considered as the first source of AMR pathogens in the food chain, a growing threat to human health and the environment. The chickenizing of farms and food is powerfully described in Ellen Silbergeld groundbreaking retrospective[61]. Silbergeld portrays how the systematic confinement of increasing numbers of birds throughout their short life cycles was soon replicated for other animals like swine and then ruminants, with a vertical integration and concentration of marketing strategies. In other words, the practices at CAFOs that initiated with chickens were promptly seized and extended as the business opportunity to develop and then dominate industrial production of animals for human food. The negative externalities, emerging with time and scale, got neglected in the face of the huge market innovation. The process, which included concentrated feed and antibiotics to enhance growth, soon exposed food sector workers and consumers to rapidly co-evolving microbes resistant to existing antibiotics[62].

It also in turn exposed the veterinary profession, which found itself at the heart of a controversy. Veterinarians soon got involved in the pervasive administering and misuse of antibiotics, associated with an array of incentives that pharmaceutical companies promoted to farmers and veterinarians alike: an overprescription trend driven by economic motives, in a clear conflict of interest with relevant industrial sectors[63]. Today, the booming veterinary drug market is most probably a leading factor in fuelling antimicrobial resistance that is making common antibiotics and antiviral agents progressively more ineffective – and also driving pandemic risks[64]. To note, there is no systematic monitoring of drugs

59 Germond Arno, from numbers published by Yamamoto K (1973)., assistant at the Ministry of Agriculture and Forestry, Tokyo, Japan. The number includes farm units for Milk cows, Beef Cattle, Pigs, Hens and chicken, and exclude breeding sites. https://www.jircas.go.jp/sites/default/files/publication/tars/tars7-_99-103.pdf

60 Germond A., from an analysis based on 2018 February data released by the Ministry of Agriculture, Forestry and Fisheries, Japan. The number includes farm units for Milk cows, Beef Cattle, Pigs, Hens and chicken, and exclude breeding sites. https://www.stat.go.jp/

61 https://foodanthro.com/2016/12/09/review-chickenizing-farms-and-food/.

62 Founou L.L., Founou R.C., (2021). Antimicrobial resistance in the farm-to-plate continuum: more than a food safety issue. *Future Science OA,* 2021 Jun; 7(5): FSO692, https://www.future-science.com/doi/10.2144/fsoa-2020-0189.

63 https://www.npr.org/sections/thesalt/2013/11/01/240278912/are-farm-veterinarians-pushing-too-many-antibiotics.

64 Fletcher E.R., (2022). Breeding Superbugs – Veterinary Drugs, More than Human Ones, Drive AMR. in *Health Policy Watch,* 4th May 2022, https://healthpolicy-watch.news/breeding-superbugs-veterinary-drug-amr/.

sold and used on animals (as well as humans) by the UN and multilateral organizations in charge. Despite commitments to handle pandemic risks and AMR together, it is unlikely that such surveillance will start anytime soon.

In 1994, the government of Denmark decided to address this conflict of interest and revolutionized livestock management by taking away incentives to veterinarians[65], who were drastically stopped from earning profits on such sales. The next year, antibiotic use dropped by almost 25 percent66. In most cases, halting the nontherapeutic use of antibiotics in livestock led to a significant decrease in resistant microbes in animals and meat within a year or two. The efficiency in animal farming increased as newborns were allowed to stay with their mothers for a much longer period, which enhanced their immune system naturally - young animals separated from their mothers are more susceptible to infections. Since then, Denmark has passed other regulations limiting antibiotic use in agriculture.

A growing sentiment for more rational husbandry and a much more responsible animal-friendly type of farming is spreading; this mood is exemplified in the EU's "Farm to Fork" strategy and in the proposition to reduce overall EU sales of antimicrobials by 50 percent for farmed animals and in aquaculture by the year 2030[67] - a welcome initiative, opposed by several corporates[68]. However, the EU food strategy, framed in an ecomodernist assumption that more technology can address the externalities of current practices, continues to assume that food and agriculture constitute a global industry, and that animals and plants represent commodities subject to global market competition. How to make agribusiness look more compatible with sustainability criteria seems to be the only challenge they see. The fact is that improving the lives of the 400,000,000 farmed animals every year is not nearly enough.

After the COVID-19 pandemic, the tension between the modernization of the livestock industry and agri-food markets and the need to prevent emerging diseases with pandemic potential has grown significantly. The fact that pandemic influenza, SARS, and COVID-19 have emerged from increased exposures in the human-animal interface have placed wild animals and wet markets in the spotlight[69]. Resorting to even higher regulatory standards in the name of biosafety and disease prevention renders the situation

65 Levy S., (2014). Reduced Antibiotic Use in Livestock: How Denmark Tackled Resistance. In *Environmental Health Perspectives*, 2014 Jun; 122(6): A160–A165. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4050507/. In this regard, also, Jacobs A., (2019). Denmark Raises Antibiotic-Free Pigs. Why Can't the U.S.?. In *The New York Times*, 6th December 2019, https://www.nytimes.com/2019/12/06/health/pigs-antibiotics-denmark.html.

66 In 1994, the Danish government also banned sales of one important antibiotic, avoparcin, which may account for part of the decline in the use of antibiotics in animal farming. By 1999, all nontherapeutic use of antibiotics in pigs was outlawed—a huge change in a nation that is the world's leading exporter of pork.

67 European Commission (2020). Farm to Fork Strategy: For a fair, healthy and environmentally-friendly food system. EU, Brussels, 2020 https://ec.europa.eu/food/horizontal-topics/farm-fork-strategy_en.

68 Corporate Europe Observatory (2022). Agribusiness lobby against EU Farm to Fork strategy amplified by the Ukraine war. Corporate Europe Observatory (CEO), 17th March 2022, https://corporateeurope.org/en/2022/03/loud-lobby-silent-spring.

69 Zhang L., (2021). China and the UN Food System Summit: Silenced Disputes and Ambivalence of Food Safety, Sovereignty, Justice, and Resilience. In *Development* 64, 303–307 (2021). https://doi.org/10.1057/s41301-021-00323-y.

impossible for small scale animal farmers, leading to their further marginalization.

On the other hand the global scientific community and economic institutions like the World Bank are strong allies of biosecurity in animal production, that is why they are staunch supporters of industrializing this sector and replacing wet markets with supermarkets. This supermarketisation policy, at the detriment of traditional retail outlets like wet markets, is particularly vibrant is Asia[70]. In reality, the industrialization of pork and poultry production shows that the large-scale concentration of genetically homogenous animals is the main factor creating conditions for the acceleration of virus mutations that can spill over and cause epidemics among humans. It is the replacement of small-scale and decentralized livestock production by large-scale CAFOs that increases the risk and impact of epidemics among animals and humans alike. The modernization of markets does not eliminate the risk of these spaces becoming major conduits for the spread of disease[71].

From the correlated standpoint of the climate emergency and AMR, the notion that this is the system the world needs to feed itself, especially in view of the global growing population, remains highly arguable. Between the 1960s and today, the world population has more than doubled and global food production has more than tripled[72]. Yet, challenges related to access to food have been increasing since 2014, and the proportion of people affected by hunger jumped in 2020 due to the Covid-19 pandemic. It continued to rise to 9.8 percent of the global population in 2021 according to FAO[73]. This is not due to lack of availability of food. In fact, nearly a third of all food produced each year is squandered or lost before it can be consumed[74].

The mainstream justifications for continuing industrialized animal husbandry, albeit in a more sustainable fashion, neither address the vast evidence of meat consumption's impact on human health[75] nor the enormity of meat waste. According to USDA data from 2010, Americans throw out 26 percent of meat, poultry and fish at the retail and consumer level. US meat production rose 10.3 percent from 2011 to 2018, while food waste decreased only by 1 percent[76]. The number of invisible dead animals that never make it to the plate is growing[77]. There is hardly any other food that damages human health, pollutes our environment and the climate as badly as meat. In a recent report, the

70 Wertheim-Heck S., Raneri J.,(2019). Choosing between supermarkets and wet markets. in *SciDev.Net*, 18th December 2019, https://www.scidev.net/asia-pacific/opinions/choosing-between-supermarkets-and-wet-markets/.

71 Zhang L., (2021). China and the UN Food System Summit: Silenced Disputes and Ambivalence of Food Safety, Sovereignty, Justice, and Resilience. In *Development* 64, 303–307 (2021). https://doi.org/10.1057/s41301-021-00323-y.

72 https://www.oecd.org/agriculture/understanding-the-global-food-system/how-we-feed-the-world-today/

73 https://www.fao.org/newsroom/detail/un-report-global-hunger-SOFI-2022-FAO/en

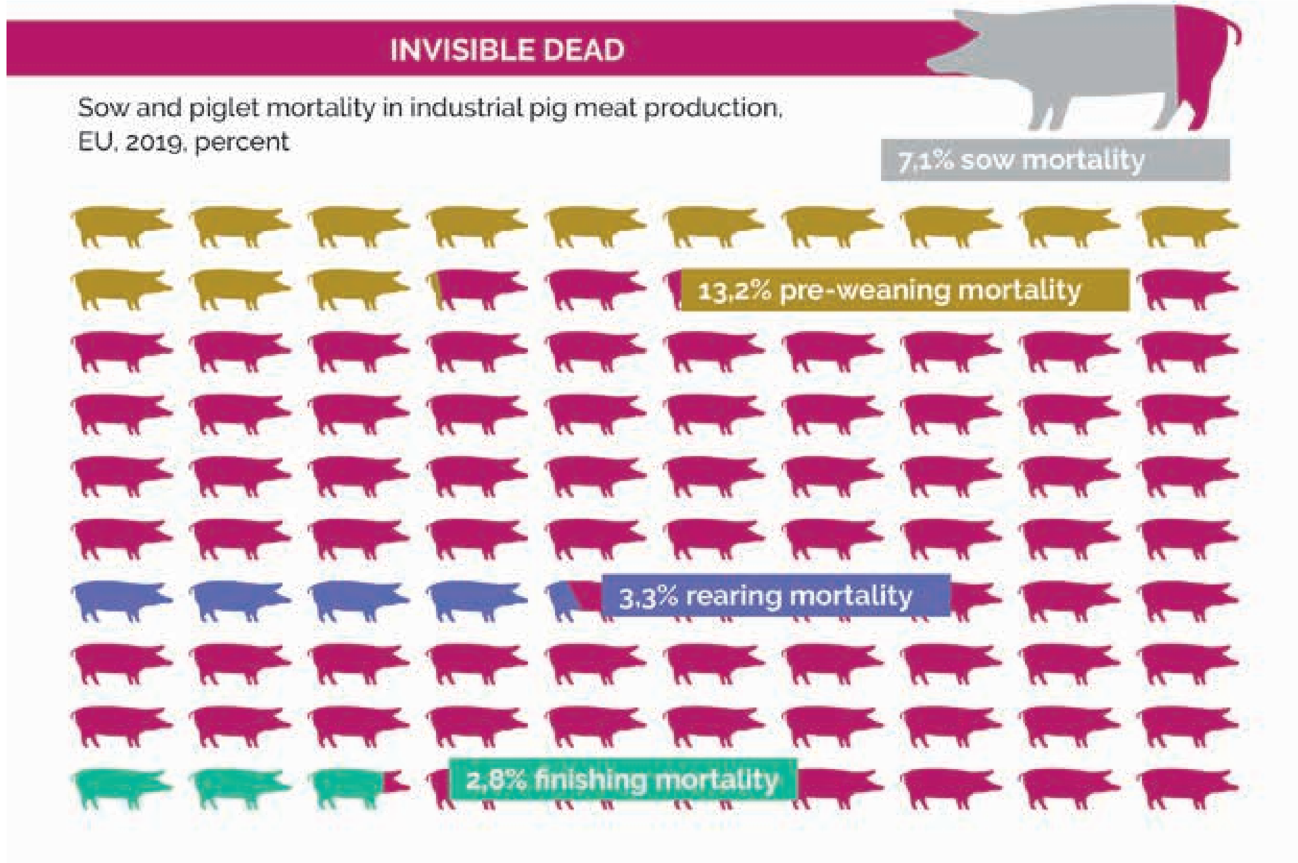
74 https://www.wfp.org/stories/5-facts-about-food-waste-and-hunger

75 Papier K., Knuppel A., Syam N., et al. (2021). Meat consumption and the risk of ischemic heart disease: A systematic review and meta-analysis. *Critical Reviews in Food Science and Nutrition*, 20th July 2021, DOI: 10.1080/10408398.2021.1949575.

76 Torrella K., (2022). Billions of animals are slaughtered every year — just to be wasted. The staggering toll of food waste on animals. *Vox*, 30th January 2022.

77 https://eu.boell.org/en/MeatAtlas

UN Environment Protection Agency (EPA) has highlighted the immense environmental benefits that would come from reducing animal product waste. Industrially produced animal-sourced products typically demand much more land, water and energy[78] and contribute to 56-58 percent of greenhouse gas emissions, while providing 37 percent of our protein and 18 percent of our calories[79]. Yet, no government in the world currently understands how meat consumption and production can be significantly reduced.



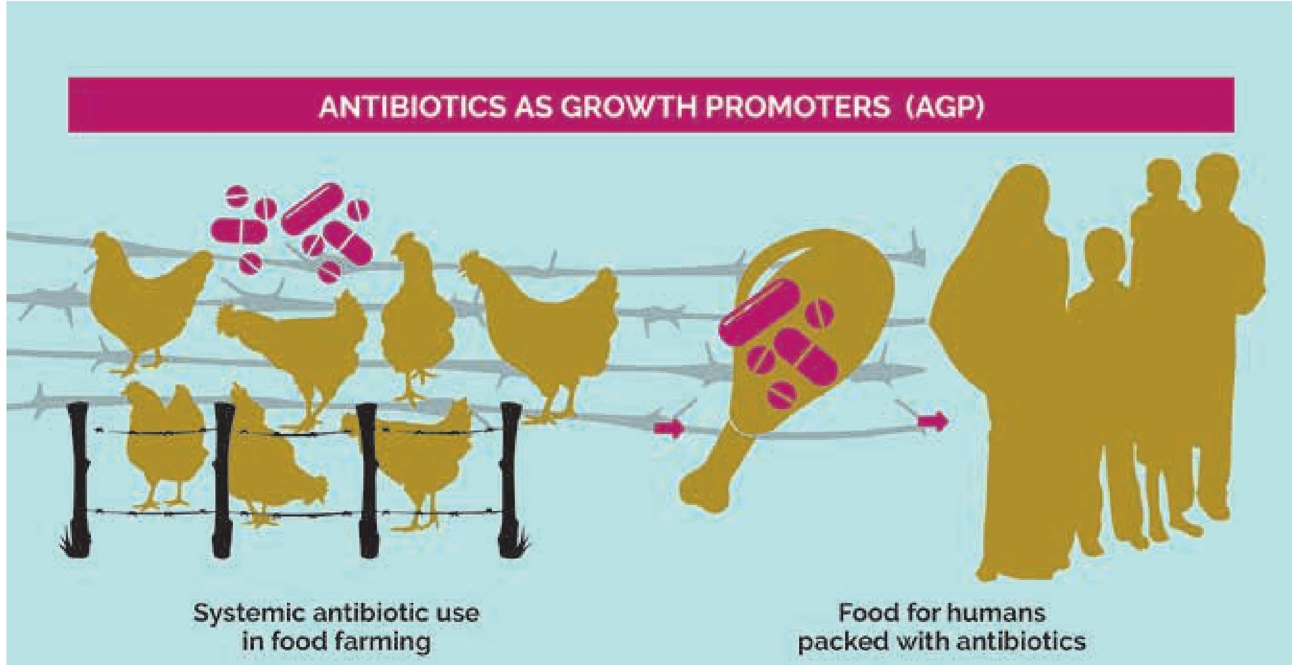
In 2018, global meat production reached 342 million tons, which corresponds to an increase of 47 percent compared to 2000. If the sector continues to grow as it has until now, almost 360 million tons of meat will be produced and consumed worldwide in 2030[80]. This trend produces ecological effects that will have repercussions on land use, animal concentrations and increased antibiotic use. It will also impact supply chains, packaging and transport, with more antibiotics used for prolonging shelf life of processed food, and increased food waste. Infection prevention and control (IPC) measures - required for properly organized health systems - are by all means urgently needed, and policymakers have to prioritize these operations. Regulations on animal welfare in the industrial system are also necessary. But these strategies alone will not suffice to tackle

78 https://ourworldindata.org/land-use-diets

79 Poore J., Nemerek T., (2018). Reducing food's environmental impacts through producers and consumers. *Science*, 1st June 2018, Vol.360, Issue 6392, pp.987-992, https://www.science.org/doi/10.1126/science.aaq0216

80 https://eu.boell.org/en/MeatAtlas

the collateral AMR spread, even if antibiotic use were reduced. The gravity of today's problem calls for a bolder food system vision to overcome the era of AMR pandemic threat.



3.2 Ban on antibiotics as growth promoters

Obviously, one would imagine that banning antibiotics in animal husbandry is the solution to all problems. But is it, really?

The use of antibiotics as growth promoters (AGP) has been completely banned in Europe and in the UK since 2006[81], and was banned in the US in 2017[82], but in Europe as elsewhere the ban is violated by the continued legal practice of "meta-prophylaxis", rarely if ever investigated: when an animal is proven sick, if it is parked with 1,000 or 10,000 other animals, then antibiotics will be administered to all via their food-drink in the name of 'preserving the health of animals'.

The organization Alliance to Save Our Antibiotics discovered recently that serious misuse of antibiotics in farmed animals continues in the US. The antibiotic growth promoter carbadox is fed to more than half of the pigs raised for food[83]. The antibiotic is completely banned in Europe, Australia, Canada and the United Kingdom because it has been shown to cause cancer in some animals.

81 https://ec.europa.eu/commission/presscorner/detail/en/IP_05_1687

82 https://www.accessscience.com/content/u-s-bans-antibiotics-use-for-enhancing-growth-in-livestock/BR0125171

83 https://www.saveourantibiotics.org/news/press-release/evidence-of-serious-misuse-of-antibiotics-in-farmed-animals-in-us-australia-new-zealand-and-canada-exposes-public-health-threat-of-trade-deals/

The Food and Drug Administration (FDA) has been dealing with the carbadox issue for some time now, with multiple initiatives from civil society organizations: vigorous pushback from industry and stalling by the agency have so far put in bind all efforts to ban the use of this antibiotic in the US[84], where the animal versus human antibiotic use remains lopsided. One paradigmatic case has to do with McDonald's[85] policy for using antibiotics in its supply chain. Several advocacy groups have objected that the company has backtracked on a commitment made four years ago to set targets for reducing the use of medically important antibiotics by the end of 2020. McDonald's has apparently quietly altered its policy so that targets are no longer visible[86].

With the aim of separating antibiotics from human and animal use, the WHO Advisory Group on Integrated Surveillance of Antimicrobial Resistance (AGISAR), established in 2008, had sought to protect a list of "Critically Important Antibiotics" (CIA) forbidding husbandry use of at least the most important antibiotics for human health.

China is the first country in the world for AGP use: a groundbreaking study of AMR in the pig industry across mainland China only illustrates the extent of the disaster[87]. India introduced limits for antibiotics' residues in meat only in 2011 and AGP are currently the norm. In Australia, Brazil, Canada, Mexico, New Zealand and other countries from Latin America antibiotics are used for therapeutic purposes and as growth promoters. In the wake of the World Health Assembly (WHA68) adoption of the global action plan on antimicrobial resistance (May 2015), the WHO published its "Guidelines on the Use of Medically Important Antimicrobials in Food-Producing Animals" in November 2017 that recommended stopping the use of antibiotics routinely to promote growth and prevent disease in healthy animals[88]. The initiative provoked an international storm, as often happens when health interests clash with the industrial lobbies' profits and productivity enhancement concerns. The strong attack on the WHO guidelines from the US Department of Agriculture (USDA)[89] revealed how significant and widespread the use

84 Rhodes H.,(2022). FDA needs to follow through on its plan to ban carbadox in animal feed. *Stat News*, 15th April 2022, https://www.statnews.com/2022/04/15/fda-follow-through-long-stalled-plan-ban-carbadox-animal-feed/

85 Silverman E., (2021). McDonald's accused of dragging its feet on goal of reducing antibiotic use in beef supplies. *Pharmalot*, 29th november 2021, https://www.statnews.com/pharmalot/2021/11/29/mcdonalds-antibiotics-superbugs-livestock-beef/

86 Silverman E., (2022). McDonald's is criticized for leaving antibiotic reduction targets off its menu. *Pharmalot*, 26th July 2022, https://www.statnews.com/pharmalot/2022/07/25/mcdonalds-antibiotics-resistance-livestock-beef-chicken-pork/.

87 E.coli were isolated in 1,871 samples from pigs and their breeding environment and AMR was found in E.coli in all the provinces in mainland China. Multi-drug resistance was detected in 91% of isolates and resistance to last resort drugs was found, including colistin, carbapenems and tigecycline. One heterogeneous group of O-serogroups and sequence types among the multidrug resistant isolates were also identified. These isolates harbored multiple resistance genes, virulence factor-encoding genes and putative plasmids. Cfr. Peng Z., Hu Z., Li Z., et al., (2022). Antimicrobial resistance and population genomics of multidrug-resistant *Escherichia coli* in pig farms in mainland China. *Nature Communications,* 2 March 2022, https://www.nature.com/articles/s41467-022-28750-6.

88 https://www.who.int/news/item/07-11-2017-stop-using-antibiotics-in-healthy-animals-to-prevent-the-spread-of-antibiotic-resistance

89 https://www.usda.gov/media/press-releases/2017/11/07/usda-chief-scientist-statement-who-guidelines-antibiotics

of human-health-needed antibiotics for meat is in the US. The economics of antibiotics[90], always concerned that restrictions in use of antibiotics in animal farming may affect market-level outcomes, including output and price, proves to be a major obstacle in the long way to policy change, and not only in China!

AGP in animal productions were banned a few years ago in Chile, Turkey and South Korea. While EU data indicate decreases in antibiotic use[91] (in France, for example, 728 tons of antibiotics were sold to humans against 471 for animals in 2018), showing that strict regulations can lead to significant antibiotic reduction, there is an outstanding gap in not including meat imports.

The 6th edition of the Annual Report on Antimicrobial Agents Intended for Use in Animals[92] released in June 2022 by the World Organization for Animal Health (WOAH, formerly OIE) provides some positive indications. In 2020, the use of antimicrobial agents in animals for growth promotion is no longer a practice in 108 out of 157 countries (69 percent), while the use of growth promoters is still reported by 40 out of the 157 (26 percent) countries participating in the WOAH survey. However, the landscape remains very mixed. Colistin, considered as Highest Priority Critically Important Antimicrobial for use in humans, is still used by the six major producers. While the number has been reduced by half over the four years up to 2020, empirical evidence shows that the use of antibiotics in food animals has sharply increased in several developing nations and it is estimated that antibiotic utilization will grow by 67 percent by year 2030, with almost twice this increase in countries such as China, Brazil, India, South Africa and Russia[93].

Besides, factory farms cannot exist without antibiotics. They depend on drugs to keep sick animals alive in conditions that would otherwise kill them and that are endemic on factory farms. The legal practice of "meta-prophylaxis" is not the only way to bypass the regulations in countries.

One investigation by animal advocacy group Farm Forward has torn the veil of the fraud of the animal welfare certifications that deceive conscientious consumers through sham packaging and labeling, promoting the illusion of animal well-being while concealing the extent of animals' illness and suffering[94]. Another team of journalists investigating the increasing reports of bacteria-related infection in the US documented that Poultry suppliers - including Perdue, Pilgrim's Pride, Koch Foods, Foster Farms and Tyson - sold tens of thousands of products contaminated with potentially deadly Campylobacter bacteria between 2015 and 2020[95]. "Separate government records also show that between January 2015 and August 2019, the same 12 major US poultry companies broke food safety rules on at least 145,000 occasions – or on average more than 80 times a day"[96] .

As we write this report, some British supermarket pork meat has got infected with a resistant variant of enterococci bacteria. Among the contaminated pork products some were sold under the well-known "Red Tractor assured" and RSPCA-assured labels for organic products[97]. Similar cases of contaminated food have made the news multiple times in 2022, and this trend is surely a growing health concern in Europe.

3.3 *Aquaculture and antimicrobial resistance*

According to the FAO, aquaculture "is understood to mean the farming of aquatic organisms including fish, molluscs, crustaceans and aquatic plants. Farming implies some form of intervention in the rearing process to enhance production, such as regular stocking, feeding, protection from predators, etc. Farming also implies individual or corporate ownership of the stock being cultivated"[98].

Aquaculture involves cultivating freshwater, brackish water and saltwater populations under controlled or semi-natural conditions. Mariculture, commonly known as marine farming, refers specifically to aquaculture practiced in seawater habitats and lagoons, opposed to in freshwater aquaculture. Pisciculture is a type of aquaculture that consists of fish farming to obtain fish products as food. Over 400 aquatic species are farmed around the world. Of fish farmed for food, most – about 63 percent (51 million mt) – come from inland ponds or tanks growing freshwater finfish like carp and tilapia.

Mariculture makes up the remaining 37 percent (31 million mt) and includes bivalve mollusks (17.3 million mt, including oysters and mussels), finfish (7.3 million mt, mostly salmon) and crustaceans (5.7 million mt, mainly shrimp)[99].

Domesticating aquatic species involves fewer risks to humans than land animals. Many major human diseases have originated in domesticated animals, while no human

90 https://www.ers.usda.gov/publications/pub-details/?pubid=45488.

91 EU yearly data show a decrease in antibiotic use https://www.ema.europa.eu/en/news/sales-antibiotics-use-food- producing-animals-drop-across-eu

92 https://www.woah.org/app/uploads/2022/06/a-sixth-annual-report-amu-final.pdf

93 Hao Van T.T., Yidana Z., Smooker P.M., et al. (2020). Antibiotic use in food animals worldwide, with a focus on Africa: Pluses and minuses. *Journal of Global Antimicrobial Resistance*, Volume 20, March 2020, pp. 170-177. https://doi.org/10.1016/j.jgar.2019.07.031.

94 Farm Forward (2020). The Dirt on Humanewashing. A Farm Forward Report on Consumer Deception in Animal Welfare Certification, Beta, December 2020, https://www.farmforward.com/#!/blog/farm-forward-report-exposes-the-dirt-on-humanewashing/farm-forward.

95 Savage S., Wasley A. et al., (2022). Superbugs on the Shelves: Diseased Chicken Being Sold Across America. *The Bureau of Investigative Journalism*, 16th March 2022, https://www.thebureauinvestigates.com/stories/2022-03-16/superbugs-on-the-shelves-diseased-chicken-being-sold-across-america#:~:text=Yet%20between%202015%20and%202020,the%20Bureau%20of%20Investigative%20Journalism.

96 Ibidem.

97 Wasley A., Savage S., (2022). Deadly Superbug Found in British Supermarket Pork. *The Bureau of Investigative Journalism*, 5th July 2022, https://www.thebureauinvestigates.com/stories/2022-07-05/deadly-superbug-found-in-british-supermarket-pork

98 https://www.fao.org/fishery/en/statistics/global-aquaculture-production/en

99 https://www.fao.org/3/ca9229en/online/ca9229en.html#chapter-1_1

pathogens of comparable virulence have yet emerged from marine species[100]. In addition, the decline in wild fish stocks has increased the demand for farmed fish[101]. Fish farming accounts for almost half of the seafood humans eat[102] . This diverse and growing industry produced 82 million metric tons of seafood in 2018 (FAO, 2020)[103].

Aquaculture is an especially important economic activity in Northern European countries, South Korea, Japan, and China. The Chinese Bureau of Fisheries reports that between 1980 and 1997, aquaculture harvests grew at an annual rate of 16.7 percent, jumping from 1.9 million tonnes to nearly 23 million tonnes. In the early years of 2000s, China accounted for 70 percent of world production[104]. Aquaculture in the U.S. represents a $1.5 billion industry annually, a figure that places the U.S. relatively low on a global scale as an aquaculture producer—17th in total aquaculture production—but it is one of the top consumers of aquaculture imports. More than 90 percent of seafood in the U.S. comes from outside of the country, and around half of that total number comes from farm-raised seafood[105]. In recent years, salmon aquaculture has become a major export from southern Chile, especially from Puerto Montt, Chile's fastest-growing city.

100 https://www.dpi.nsw.gov.au/fishing/aquatic-biosecurity/pests-diseases/animal-health/fish-diseases-and-human-health

101 Naylor R.L., Goldburg R.J.; Primavera J.H., et al., (2000). Effect of aquaculture on world fish supplies. *Nature*, 29th June 2000, 405 (6790): 1017–1024.https://www.nature.com/articles/35016500

102 Edwards P., Zhang W., et al., (2019). Misunderstandings, myths and mantras in aquaculture: Its contribution to food supplies has been systematically over reported. *Marine Policy*, Volume 106, August 2019, https://doi.org/10.1016/j.marpol.2019.103547.

103 https://www.fao.org/3/ca9229en/online/ca9229en.html#chapter-1_1

104 Xuepeng L., et al., (2011). Aquaculture Industry in China: Current State, Challenges and Outlook. *Reviews in Fisheries Science*, 19(3):187–200, 2011, DOI: 10.1080/10641262.2011.573597.

105 https://www.globaltrademag.com/u-s-states-with-the-largest-aquaculture-industry/

BOX 3.

OCEANA'S STRUGGLE CHALLENGING THE SALMON FARMING INDUSTRY IN CHILE

The salmon farming industry in Chile is one of the nation's most profitable businesses. Its growth is largely due to low labor costs and free use of water resources, yet this success has come at a great cost. The indiscriminate use of antibiotics in the production of farmed salmon puts at risk the health of wildlife that inhabits areas surrounding the cages, as well as the human population consuming the fish. For the first time in 2009 the Chilean government revealed that the national salmon industry had used roughly 385 tons of antibiotics, 600 times more than Norway, the main producer of farmed salmon in the world. The disclosure, in response to a request for access to public information that the international marine conservation organization, Oceana, made to the Minister of Economy, revealed that approximately a third of the antibiotics were quinolones, not allowed in countries which are important destinations for Chilean salmon, such as the USA. Between 1998 and 2015, 95 percent of tetracyclines, phenicols and quinolones imported by Chile were for veterinary purposes, mostly salmon farming.

Oceana's campaign seeks to drastically reduce the number of antibiotics in aquaculture. A tough battle: in 2020, Chile used 2,500 times more antibiotics than Norway to produce a ton of salmon. As a first step, Oceana's strategy is calling for more transparency, and advocating to get disaggregated information on the drugs used. The idea is that disaggregated data may reduce antibiotics' use since they allow 1. national and international consumers to make informed decisions; 2. civil society to oversee the Chilean authorities' work in antibiotics' reduction; 3. academia to develop research and design better farming plans.

The Fisheries Services, the administrative body that oversees salmon farming, is formally mandated to publish the information on the type and quantity of antibiotics the salmon industry is using. However, access to data from individual companies requires a special procedure, to which companies consistently pushed for denying disclosure of any information. Upon Oceana's litigation, companies' denials were ruled out by the Chilean Courts, in favor of transparency requirements. It took four long years to win the case. Oceana is now pushing the Congress to pass a new law so that all information on antibiotic use, disaggregated by companies, automatically becomes available to the public. While this legislative process is coming to an end, with broad political support towards this provision, we can't help wondering how many more years will be required to see the transformations that the One Health approach would demand.

Welfare in aquaculture can be impacted by a number of issues such as stocking densities, behavioral interactions, disease and parasitism. That is why aquaculture is a culprit companion to the meat industry as far as antibiotic use is concerned, hence becoming an important source for the development and selection of antibiotic-resistance genes. Similar to what was described for meat production, the world growth of aquaculture has been accompanied by a growth in antibiotic use, whether this production is done in the open ocean or in fish tanks[106]. Among other countries, South Korea and Japan massively cultivate fish in the coastal areas. In these countries, antibiotic drugs are regularly and directly poured into the ocean to favor fish growth.

Scientific evidence shows that the drugs favor the accumulation of ARM and ARG in the surrounding free-living bacteria[107] but also in the bacteria living in the sediments of the ocean floor. Aquaculture using large fish tanks follows similar practices, and AMR and ARG are discharged through the wastewater, sometimes directly into the wild aquatic environment, thus polluting rivers and all other water systems[108].

The Mediterranean Sea represents a 'hot spot' in terms of climate change and antibiotic resistance in aquaculture, with increasing threats to biodiversity - scientific research has shown that AMR can pervade in the microbiome of fish and shellfish - and

106 Recently, copper alloys have become important netting materials in aquaculture because they are antimicrobial. By inhibiting microbial growth, copper alloy aquaculture cages avoid costly net changes that are necessary with other materials.

107 Germond A., Kim S.J., (2015). Genetic diversity of oxytetracycline-resistant bacteria and tet(M) genes in two major coastal areas of South Korea. *Journal of Global Antimicrobial Resistance*, 3rd September 2015, (3):166-173. https://pubmed.ncbi.nlm.nih.gov/27873706/.

108 Suzuki S.,(2021). Persistence of antibiotic-resistance genes in aquaculture environment. *AMR & The Environment: A Global and One Health Security Issue*. AMR Think-Do-Tank, 2021.

human health[109]. Like in meat production, waste disposals can be functioning, weak or nonexistent depending on the country. Moreover, the frequency and severity of this is rarely monitored, if not at all. Lack of regulation, enforcement of norms, substantive fines and action when norms are violated largely contribute to the transmission of pathogens. While it has been demonstrated that fish farming can do with very little or no antibiotics, middle income countries with budding but fast expanding aquaculture have been left out of campaigns to stop antibiotic use.

3.4 - Fungicides' impact on public health - the dystopia of azoles

Fungi infections have a huge economic impact in agriculture, such as in cereals and vineyards. The need for the discovery of new fungicides is pushed by incentives for food security and economic profits. The fungicide family of azoles is one of the most used products. While it is hard to find quantitative data about the use of azole in each sector, the rice industry (especially in Asia) strongly rely on azole[110]. Dr Justin Beardsley from the University of Sydney, a world expert on fungal AMR who conducted key research in Vietnamese rice and shrimp agriculture, has written: "Antifungals in general, and azoles in particular, contribute significantly to food security [...] In this setting, agricultural azole use will expand, adding further selective pressure on to human pathogens. This effect is likely to be especially acute in areas such as the Mekong Delta where regulation of agrichemicals is weak, profit margins are slight, and the land is farmed intensively"[111], warning against the health risks of anti-fungal AMR.

Asia is also arguably leading the business of aquaculture, notably in South Korea, Japan and China, where azoles like antibiotics are used and poured directly into seawater or fish tanks, hence contributing to the spread of resistance organisms or genes in the water environment[112]. In Europe, the mass production and export of plants and flowers, particularly from Italy, is sustained with the use of azoles-related fungicides, among copper and other herbicides[113].

The profit-driven, azole-sustained practices in industry entail extremely high costs. It has been established that the compound contributes massively to the emergence of

109 Pepi M., Focardi S., (2021). Antibiotic-Resistant Bacteria in Aquaculture and Climate Change: A Challenge for Health in the Mediterranean Area. *International Journal of Environmental Research and Publish Health,* 26th May 2021, 18(11), 10.3390/ijerph18115723.

110 Jørgensen L.N. & Heick T.M. (2021). Azole Use in Agriculture, Horticulture, and Wood Preservation – Is It Indispensable? Front. Cell. Infect. Microbiol., https://www.frontiersin.org/articles/10.3389/fcimb.2021.730297/full

111 Beardsley J, Bashir M., et al., (2021). AMR in Fungal Infections: At the intersection of Sustainable Agriculture and Human Health Threats. In *AMR & the Environment: A Global and One Health Security Issues,* AMR Think-Do-Tank, Geneva, 2021. pp. 49-55.

112 Germond A. and Kim S.J., (2015) Genetic diversity of oxytetracycline-resistant bacteria and tet(M) genes in two major coastal areas of South Korea. *Journal of Global Antibiotic Resistance*, 3: 166-173

113 http://www.arpat.toscana.it/notizie/arpatnews/2020/097-20/arpat-fitofarmaci-nelle-acque-nel-territorio-pistoiese

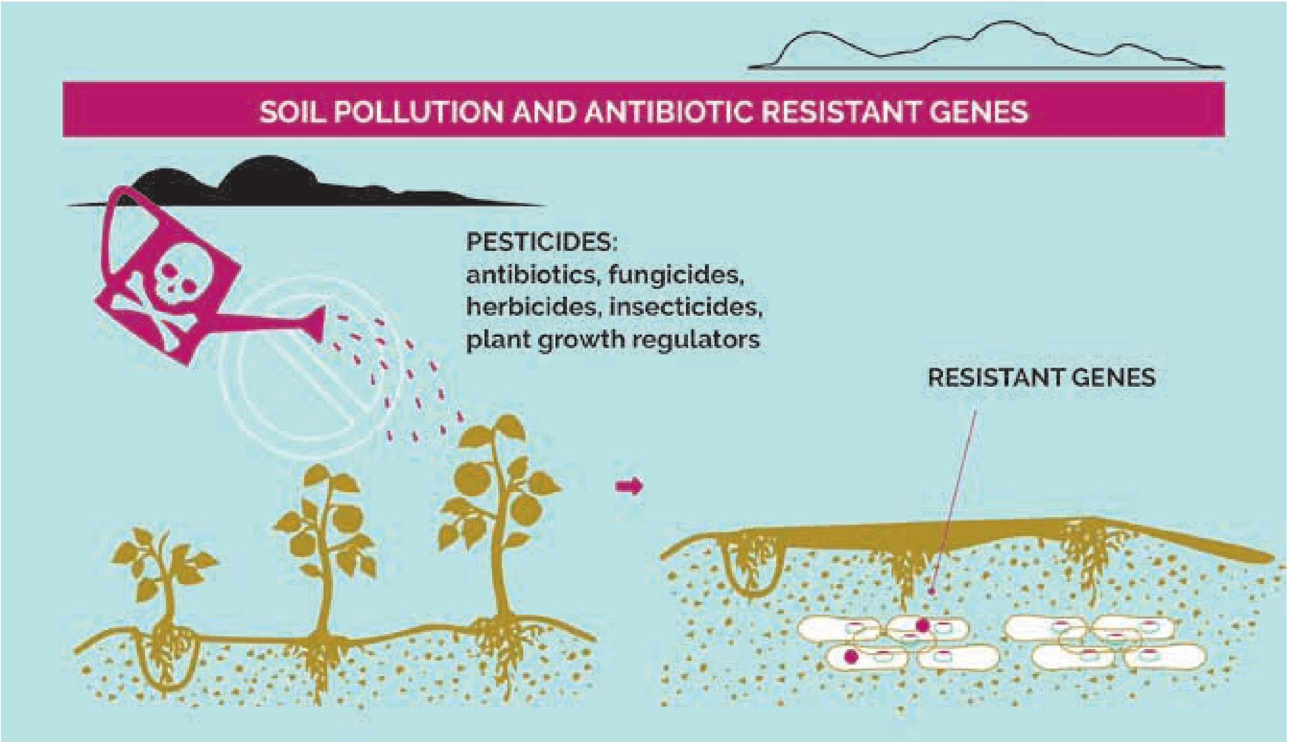
resistant pathogens that can affect millions of people. A recent publication acknowledges that: "recent studies postulate an ex vivo evolution of resistance in the environment as a result of exposure to agricultural chemicals [...] This supports the hypothesis that the widespread use of azole fungicides in agriculture is coupled to widespread isolation of azole-resistant Aspergillus fumigatus from environmental sources"[114]. In fact this is more than a hypothesis. The highest number of cases reported from Europe of the azole-resistant human pathogen A. Fumigatus speak of a reality that is closely associated with key reservoirs of azole-resistance in plant-based agricultural settings, gardens and hospitals[115]. The molecule of azoles is easily dispersed in the environment and several studies already confirm its prevalence in water and wastewater[116].

The health implications of this uncontrolled use of fungicides may be more ominous than expected, and spanning over several generations. A major forgotten problem, among others, is that azole-based medicines make use of the same molecules adopted in both human and veterinary health to treat fungus infection. It looks like little hope is left for people or animals infected by azole-resistant fungus infection. The risk of cross-infection urgently needs addressing with a One Health approach[117].

3.5 Soil pollution and the thriving of antibiotic resistant genes

Pesticides include a variety of products used as bactericides, including antibiotics, as well as fungicides, herbicides, insecticides, and plant growth regulators, among others. As technologies targeting organisms that are deemed threatening, pesticides are used for ruling ecologies through death, exerting selective pressure on the organisms that they target, thereby favoring some forms of life over others. In this sense, pesticides can be considered active agents in shaping agrarian processes. However, their application to plants and plant products reaches further to non-target organisms, meaning that one must consider the consequences of these chemicals' use on all the components of the plant production environment—direct and indirect, intended and unintended.

The use of pesticides is paradoxically associated with a loss in their effectiveness. Resistance to specific active substances in pesticides has prompted the search for new more effective products in the pursuit of agricultural profitability. In the United States alone, the cost of crop losses directly due to pesticide resistance is estimated to be approximately 1.5 billion USD per year[118]. From this point of view, the often indiscriminate use of pesticides in agriculture interacts with people and environments in a way that creates uncertainty, remakes political ecologies from the field and even changes, in many ways, the social status of farmers.



Strict controls in some countries allow for the tracking of pesticide use in various sectors, but on a global scale some of the best estimates can only be derived from proprietary sales data[119]. In 2016, the global plant protection market was estimated to represent about 63 billion USD in annual sales, with an increase predicted at 5 percent annually for the next 5 years with the largest portion of growth attributed to the Asian Pacific region[120]. In the United States, over 4000 different antimicrobial pesticide products containing over 275 different active ingredients are available in the market[121].

The use of antimicrobials in crop cultivation is very poorly monitored, however, if compared to the veterinary and medical arenas: only 3 percent of the 158 countries assessed by the FAO and WHO indicated they had any kind of regular assessment of

114 Rhodes J., Abdolrasouli A., et al., (2022). Population genomics confirms acquisition of drug-resistant *Aspergillus fumigatus* infection by humans from the environment. *Nature Microbiology,* vol 7, 663–674, (2022). https://doi.org/10.1038/s41564-022-01091-2.

115 Burks C., Darby A., et al., (2021). Azole-resistant *Aspergillus fumigatus* in the environment: Identifying key reservoirs and hotspots of antifungal resistance. *Plos Pathogens,* 29th July 2021, https://doi.org/10.1371/journal.ppat.1009711.

116 Assress A.H., Nyoni H., et al., (2020). Occurrence and risk assessment of azole antifungal drugs in water and wastewater. *Ecotoxicology and Environmental Safety,* 15th January 2020, 187:109868, https://www.sciencedirect.com/science/article/abs/pii/S0147651319311996.

117 Werweij et al. (2020) The one health problem of azole resistance in *Aspergillus fumigatus*: current insights and future research agenda. *Fungal Biology Reviews*, Vol 34, 4, 202-214. https://www.sciencedirect.com/science/article/pii/S1749461320300415.

118 Pimentel D., Burgess M., (2014). Environmental and economic costs of the application of pesticides primarily in the United States. *Integrated Pest Management*, Springer, New York, NY, USA, 2014.

119 http://www.researchandmarkets.com/reports/41.

120 Miller S.A., Ferreira J.P., et al., (2022). Antimicrobial Use and Resistance in Plant Agriculture: A One Health Perspective. Agriculture, 2022, 12, 289, https://www.fao.org/3/cb8821en/cb8821en.pdf

121 USEPA (2017). What Are Antimicrobial Pesticides? Available online: https://www.epa.gov/pesticide-registration/what-are-antimicrobial-pesticides

the types and amounts of antibiotic use on crops[122]. Yet the soil is a primary reservoir of microorganisms that produce antimicrobials. Arable soil and edible crops form particularly vulnerable ecosystems for antibiotic resistant genes (ARGs) transmissions via horizontal gene transfers, due to the application of chemical pesticides, livestock manure and sludge[123], and metals, often in conjunction with each other.

Several studies have shown that heavy metal pollution have modified bacterial communities in soils and alter ecosystem functioning: the presence of metals in biocides and fertilizers induce bacterial resistance, including antibiotic resistance[124]. Widespread use of copper, zinc and arsenic contaminates the environment from their past use in industrial sites. Industrial heritage and its pollution impacts on the prevalence of environmental AMR have largely been neglected[125]. The same dynamic applies to agriculture, irrigation from deep wells and wood preservation. Copper for instance is intentionally applied for treating plant diseases even in organic production systems; it's widely used on grapes[126] and many other crops to control various fungal and bacterial infections. Copper and zinc oxide are frequently added to animal feeds to control disease and improve growth, especially in young animals. Other elements, such as cadmium, chromium, molybdenum, nickel, tin, and vanadium are used as micronutrients in livestock and poultry diets. Unabsorbed metals are excreted in the feces and these metals accumulate in the soil, amended with manure from the animals fed with these products. In addition, chemical fertilizers intentionally added to the soil may be contaminated with small amounts of lead and cadmium. Only recently have the associations between heavy metal use and antimicrobial resistance been reviewed[127], but research is finally gaining ground in this field.

Arsenic-containing pesticides and herbicides have also been extensively used for horticulture. Agent Blue (Dimethylarsenic acid) was sprayed over crops and forests by US military forces in Vietnam during the Vietnam war as a defoliant at rates 10-times higher

122 FAO and WHO (2019). Monitoring global progress on addressing antimicrobial resistance. FAO, WHO, 2019a. p. 66. https://apps.who.int/iris/bitstream/handle/10665/273128/9789241514422-eng.pdf?ua=1.

123 Zalewska M., Blazejewska A., et al., (2021). Antibiotics and Antibiotic Resistance Genes in Animal Manure – Consequences of Its Application in Agriculture. *Frontiers in Microbiology*, 29th March 2021, https://www.frontiersin.org/articles/10.3389/fmicb.2021.610656/full.

124 Singer A., (2017). How chemicals and heavy metals contribute to antimicrobial resistance. *The Pharmaceutical Journal*, 15th February 2017, https://pharmaceutical-journal.com/article/opinion/how-chemicals-and-heavy-metals-contribute-to-antimicrobial-resistance. Also: Yazdankhah S., Skjerve E., et al., (2018). Antimicrobial resistance due to the content of potentially toxic metals in soil and fertilizing products. Microbial Ecology in Health and Disease, 2018; 29(1): 1548248, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7273308/.

125 Rodgers K., McLellan I., et al., (2019). Can the legacy of industrial pollution influence antimicrobial resistance in estuarine sediments?. *Environmental Chemistry Letters,* 17**,** 595–607 (2019). *https://doi.org/10.1007/s10311-018-0791-y*.

126 In Italy, on average, viticulturists apply 14 kg of copper fungicides per hectare per year on vineyards, https://www.aramis.admin.ch/Grunddaten/?ProjectID=18963.

127 Wang Y., Chan K.K.J., et al., (2017). Plant Uptake and Metabolism of Nitrofuran Antibiotics in Spring Onion Grown in Nitrofuran-Contaminated Soil. *Journal of Agricultural and Food Chemistry*. 11th May 2017, 65, 4255–4261. https://pubs.acs.org/doi/pdf/10.1021/acs.jafc.7b01050.

than what is used domestically[128]. Other arsenic-containing insecticides and herbicides, approved for horticultural purposes and later discontinued in many countries, may still be in use in some low and middle income countrie[129]. As with copper and zinc, animal manure may also be a source of arsenic. Aside from the toxic effects of these elements on plants, animals, and people, concern is growing that these metals have the potential to co-select for resistance in bacteria, as has been documented[130].

3.6 – The truth, please, about glyphosate

Not many are aware that glyphosate, as well as being a herbicide, is also an antibiotic drug. Glyphosate, the active ingredient in Monsanto's Roundup, is perhaps one of the most successful products in the history of the pesticides industry, as it presents relatively low toxicity to humans (compared to other herbicides) combined with an impressive efficiency in wiping out most weeds. It is indeed the most heavily used agri-chemical ever in human history. Glyphosate has been used in disproportionate quantities worldwide, with a massive increase of its use over 40 years, as it lowered overall agricultural production costs, notably for cereals. It also allowed for mass introduction of hybrid seeds and genetically engineered crops now grown on more than 175 million acres in the United States and more than 440 million acres around the globe[131]. The decrease in machine costs and especially labor costs has led to the success of glyphosate in industrial grain production to an enormous extent, from high income industrial settings to local farms, municipal gardens, private lawns globally. The product is costing human health immensely along with the impact of the global discharge in the soil and water environment which is tremendous[132].

The role of glyphosate in the emergence of the antimicrobial pandemic has come to the fore as scientists have intently started to witness the emergence of multidrug resistant (MDR) bacteria from the intertropical zones, where antibiotic use in humans remains quite low. The glyphosate molecule blocks the shikimate pathway found in plants and in microorganisms, but which is absent in mammals or humans. Therefore, it ought to be perfectly safe for humans and mammals, or so the marketing story went for forty years. It has taken the wild animals living in the outskirts of Nairobi carrying MDR

128 Bencko V., Foong F.Y.L., (2017). The history of arsenical pesticides and health risks related to the use of Agent Blue. *Annals of Agricultural and Environmental Medicine*, 2017;24(2):312–316, http://www.aaem.pl/The-history-of-arsenical-pesticides-and-health-risks-related-to-the-use-of-Agent-Blue,74715,0,2.html.

129 Punshon T., Jackson B.P. et al., (2017). Understanding arsenic dynamics in agronomic systems to predict and prevent uptake by crop plants. *Sci. Total Environ*. 2017, 581–582, 209–220.

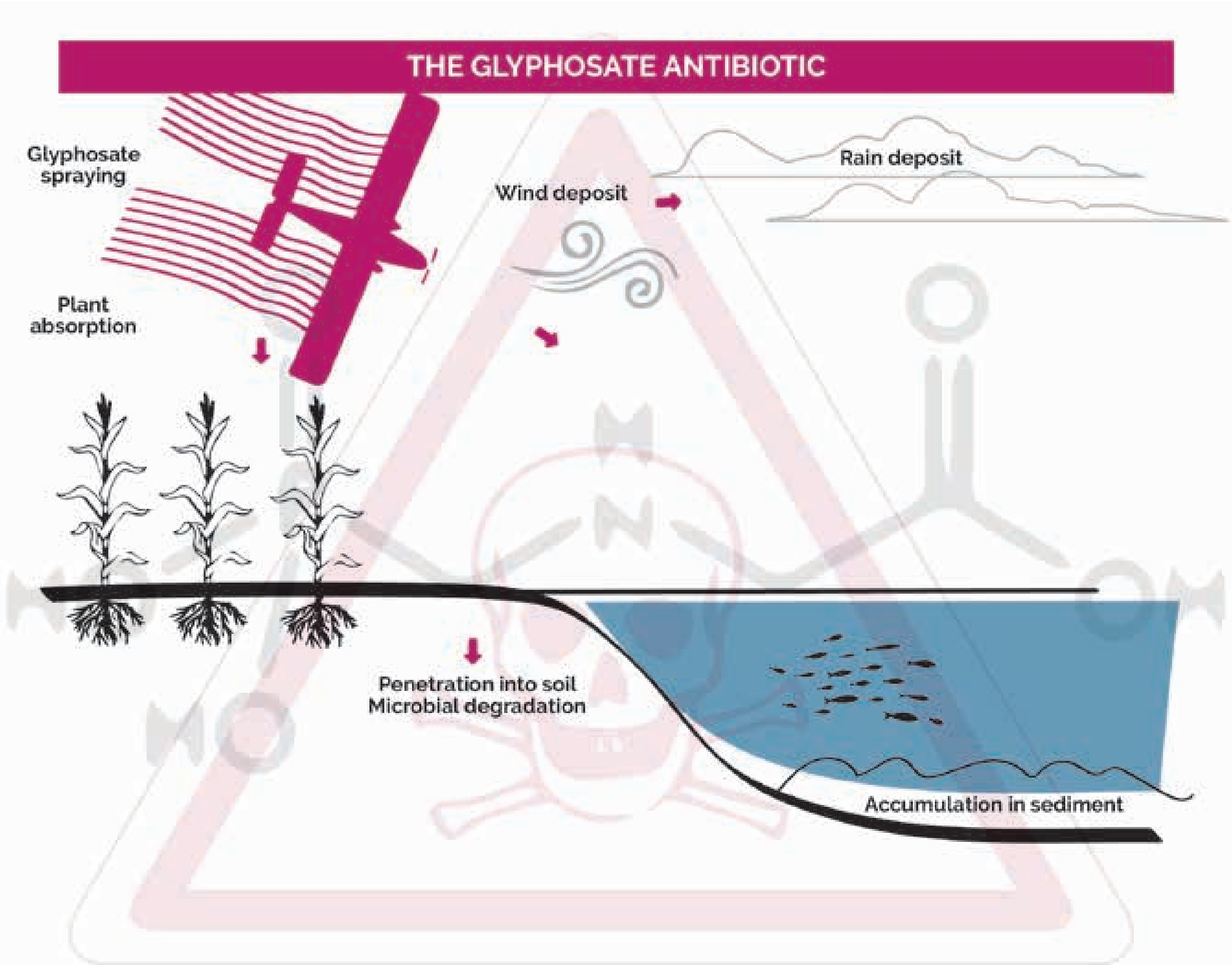
130 Baker-Austin C., Wright, M.S., et al., (2006). Co-selection of antibiotic and metal resistance. *Trends Microbiol.* 2006, 14, 176–182.

131 Food Democracy Now and Detox Project (2016). Glyphosate: Unsafe on Any Plate: Alarming Levels of Monsanto's Glyphosate Found in Popular American Foods. 2016. Food Democracy Now, https://usrtk.org/wp-content/uploads/2016/11/FDN_Glyphosate_FoodTesting_Report_p2016-3.pdf

132 https://lebasic.com/en/pesticides-a-model-thats-costing-us-dearly/.

Escherichia Coli to ring the alarm bell, alongside the remote tribes living in Tanzania with MDR bacteria in the absence of any significant exposure to antibiotics[133].

Products similar to glyphosate, targeting the same metabolic pathway, have been developed. The literature targeting the shikimate pathway to develop antibiotics, antifungic, parasiticides and herbicides is indeed abundant. What has been purposefully forgotten is the impact of glyphosate and these products on the human and animal gut microbiota containing millions of microorganisms. Recent research on the effects of pesticides, herbicides, including glyphosate, on animal health and patterns of behavior has been performed[134]. As an example, baby carp fish subjected to low doses of glyphosate showed deleterious effects on brain, liver, immunity, gut permeability and even swimming capacity!



133 Raoult D., Hadjadhj L., Baron S.A., et al.(2021). Role of glyphosate in the emergence of antomicrobial resistance on bacteria?. *Journal of Antimicrobial Chemotherapy,* 24th April 2021, Volume 76, Issue 7, July 2021, pp. 1655–1657, https://doi.org/10.1093/jac/dkab102.

134 Jadeja Niti B., Worrich A., (2022). From gut to mud: dissemination of antimicrobial resistance between animal and agricultural niches. *Environmental Microbiology,* Feb. 16 2022, https://sfamjournals.onlinelibrary.wiley.com/doi/full/10.1111/1462-2920.15927. - Toxic effects of glyphosate on the intestine, liver, brain of carp and on epithelioma papulosum cyprinid cells: Evidence from in vivo and in vitro research Xianglin Cao et al. https://doi.org/10.1016/j.chemosphere.2022.134691

Back in 2003 the Monsanto Company registered glyphosate as a key antibiotic against a very wide array of bacterial pathogenic families, including those on the WHO list of ESKAPE[135] pathogens that have been associated with deadly outbreaks. Indeed, the patent description entails a large listing of all pathogenic species it might be active against. Quoting from the patent itself, we highlight a few key ESKAPE bacteria (as well as fungi) in the extremely large list of bacterial families listed in the patent as targets:

> "Susceptible organisms include, but are not limited to all species of the family Pseudomonadaceae, including Pseudomonas aeruginosa, all species of the family Enterococcaceae, including Enterococcus faecalis and Enterococcus faecium. Susceptible organisms include Helicobacter pylori, Candida albicans and Pneumocystis carinii. Susceptible organisms include all species of the family Campylobacteriaeae, including but not limited to Campylobacter jejuni."[136]

Despite this, for some time there has been a near absence of publications linking glyphosate uses and AMR. Research has recently tried to fill that gap. In 2015, a scientific study associated E. coli and other AMR bacteria with herbicides including glyphosate[137]. Another research group came to the same conclusion in 2017[138]. As written earlier, in 2021 a team of experts spotted the discrepancy in the intertropical zone between level of antibiotic use in humans and high levels of AMR from different ecosystems, which led to glyphosate. One can imagine the quantities of glyphosate that has been dumped in monocultures like rice fields or corn crops, probably the most widespread GMOs in the world, cultivated massively in the intertropical zone, particularly in Asia. Glyphosate and antibiotic resistance have arisen in fungi and bacteria in parallel. Shifts in microbial community composition in soil, plants and animal guts have been seen.

135 ESKAPE is an acronym comprising the scientific names of six highly virulent and antibiotic resistant bacterial pathogens: https://en.wikipedia.org/wiki/ESKAPE.

136 Monsanto Patent of 2003, then 2010. https://patents.justia.com/patent/7771736. It is interesting to note that *Campylobacter jejuni* is said to be found in 95% of chicken carcasses in the EU.

137 Sublethal Exposure to Commercial Formulations of the Herbicides Dicamba, 2,4-Dichlorophenoxyacetic Acid, and Glyphosate Cause Changes in Antibiotic Susceptibility in *Escherichia coli* and *Salmonella enterica* serovar Typhimurium. https://doi.org/10.1128/mBio.00009-15

138 Van Bruggen A.H.C., He M.M, et al., (2017). Environmental and health effects of the herbicide glyphosate. *Sci Total Environ,* 2018 Mar;616-617:255-268. https://pubmed.ncbi.nlm.nih.gov/29117584/

BOX 4.

MEXICO'S MOVE TO BAN GLYPHOSATE BY 2024[139]

Since the inception of its mandate, the current government of Mexico has begun working on a food systems' transformation with an intersectoral approach, as the only one that may deliver results, and the creation of an ad hoc inter-institutional and interdisciplinary group (Grupo Intersectorial de Salud, Alimentación, Medio Ambiente y Competitividad - GISAMAC), including international and civil society organizations.

Among the different actions pointing to the goal of healthy food from production to plate, one priority has been the prohibition of transgenic maize cultivations and the gradual ban on glyphosate use by 31 January 2024. The decision came through a Presidential decree in December 2020.

The purchase, distribution, promotion and importation of glyphosate has progressively reduced to allow a transition towards alternatives of sustainable food systems that are culturally appropriate, while granting comparable production levels and health security for humans, animals and the environment. In Mexico, 50 percent of imported glyphosate is applied to maize and citrus fruits.

The National Committee on Science and Technology is mandated with setting yearly recommendations towards a progressive phasing out of the herbicide's use. This will end with a definite ban in 2024. The 2022 amount is already 50 percent lower than 2021, based on follow up scientific investigations and constant consultations with authorities and producers, confirming that viable alternatives to manage weeds in different crops and secure productions exist, eliminating the need for glyphosate use.

The Decree has also prohibited glyphosate distribution by the federal programs, as has happened in the past, in the context of a multipronged strategy aiming at agro- ecological solutions.

The Mexican move need not remain an isolated story. Replicating this strategy will help strengthen capacity to fight back against industry's moneyed interests, which buy political influence to act against regulations at multiple scales.

139 https://g2h2.org/wp-content/uploads/2022/04/Wednesday-Cecilia-Elizondo.pdf

The level of tolerance for glyphosate levels in water and food was raised in the USA under the Barack Obama administration, precisely when the 21st Century Cures Act to help accelerate medical product development, was signed into law[140]. We should finally note the fact that glyphosate is registered in the US Patent Application 20040077608[141] as an antiparasitic - we have earlier explained that the term AMR also applies to parasitic diseases. Could the unrestrained and unregulated use of glyphosate in the developing world partly account for the convergence of biological and resistance threats that makes malaria resurgent, posing a unique challenge to the global health community?[142]

140 https://www.fda.gov/regulatory-information/selected-amendments-fdc-act/21st-century-cures-act

141 https://www.freepatentsonline.com/y2004/0077608.html.

142 WHO (2021). World Malaria Report 2021. World Health Organization, Geneva, 6th December 2021, https://www.who.int/teams/global-malaria-programme/reports/world-malaria-report-2021

4. THE GLOBAL DISCHARGE OF CHEMICALS

It is important to remember that when a human being or an animal is given antibiotics, about 80 to 90 percent of the dose taken is not metabolized. Instead the antibiotics go directly through the bowels thus heading directly into wastewater. In particular, animal farming and meat processing generate large amounts of waste. These considerations are a stark reminder of the concerns raised in the previous sections, where we highlighted the conditions through which food is produced and processed. It is clear that all the steps of the food chain processing pose issues relating to the emergence or spread of AMR.

In 2013, a survey published in France reported that pesticides were detected in 93 percent of the 2600 sample sites, which included urban and natural environments. For example, Glyphosate and glyphosate-associated metabolites were prevalent in the environment. In 2019, a meta-analysis conducted on 72,000 data points from multiple surveillance programs revealed that water surfaces in France were contaminated 43 percent by glyphosate and 63 percent by aminométhylphosphonic acid (AMPA), one of its metabolites[143]. Another recent survey in May 2022 provides a clear picture of the pollution occurring in metropolitan France, with a high prevalence of pharmaceutical compounds and other products such as metals being detected in the environment[144]. AMR spread remains a dynamic threat. In a detailed list of effects on animals, the survey reports neurotoxic and immunotoxic effects, hormonal changes, behavioral change, gonadic modification, embryo death, increased parasitic charge. Together, these symptoms are massively contributing to the decline of natural fish and crustacean populations, among others.

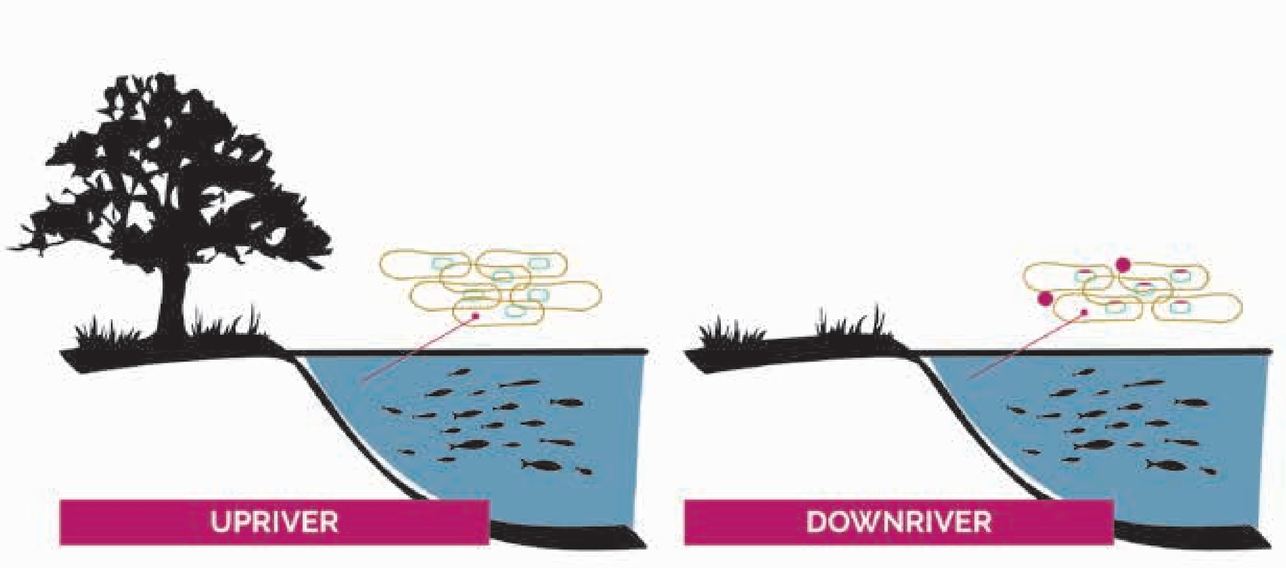
4 1 – Discharge in water in urban settings a global phenomenon: key consequences on healthcare facilities

The discharges of wastewater containing animal bacteria into water flows and soil are environmental concerns that are rarely addressed. In low-income countries, the management of meat waste is simply lacking; for example, blood is spilled into wastewater and not treated separately. But the discharge of chemicals in wastewater goes far beyond the animal or agricultural sector. Domestic, urban and industrial wastes need also to be included. Unsurprisingly, chemicals and synthetic compounds dispersed

143 Carles L, et al., (2019). Meta-analysis of glyphosate contamination in surface waters and dissipation by biofilms. *Environmental International*, 214:284-293, https://www.sciencedirect.com/science/article/pii/S0160412018323286?via%3Dihub.

144 The study gathered 46 experts from 18 institutions under the lead of INRAE and Ifremer institutes. Researchers performed a large meta-analysis of data available for France from 2000 to 2020. More than 4000 references documents have been screened.

in the environment are accumulated especially in the downriver sediments (samples where substances are found are indicated with red spots).



The waste generated by the medical and pharmaceutical sector, in particular, requires specific sterilization steps and appropriate waste management policies. Globally, an estimated 80 percent of all industrial and municipal wastewater is released into the environment without any prior treatment, with detrimental effects on human health and ecosystems[145]. This ratio is much higher in the least developed countries, where sanitation and wastewater treatment facilities are grossly lacking. In Sri Lanka for example, only 4.1 percent of its infrastructures is connected to a wastewater system[146].

Collecting and treating dangerous products is an obvious step, but identifying the hot-spots of pollution is crucial. Healthcare structures in particular are hot-spots for the rise, development and spread of all types of AMR: bacterial, viral, parasitic and fungus resistance[147]. In many ways, there is a parallel between health centers and CAFOs - both constitute concentrations of bodies, conducive for the spread of AMR infections . Animals in CAFOs, humans in hospitals and health centers, experience similar conditions, the latter often being elderly or immuno-depressed humans such as as in cancer under chemotherapeuticsor with open flesh (after surgery or accidents). As for most hospital facilities in Africa, the stark reality is that there is still a lack of Infection Prevention and Control (IPC).

One ECDC study in 2015 reported that 63.5 percent of Hospital-Acquired-Infections

145 UN Water- UNESCO, (2021). Valuing Water, The UN Water 2021 Report. UN Water and UNESCO, 2021, https://unhabitat.org/sites/default/files/2021/07/375751eng.pdf.

146 P.H. Sarath Gamini, (2020). Project direct at the Sri Lankan National Water supply and Drainage board http://www.waterboard.lk/, article http://www.waterboard.lk/web/images/contents/media/articles/challenges_in_the_water_sector_and_waste_water_sector.pdf

147 https://www.technologynetworks.com/immunology/videos/hospitals-are-hotspots-for-antibiotic-resistant-germs-358867.

cases – which affected 1 in 5 patients - were antibiotic-resistant bacteria (426 277 out of 671 689 cases), resulting in 72.4 percent (23 976 of 33 110) of attributable deaths[148]. No information currently exists regarding the spread of resistance from bacteria in the hospital to the soils in the environment. As we have seen, the mechanism for bacteria developing resistance is acquired through gene mutation or horizontal gene transfer. This enables organisms to acquire resistance to a single antibiotic and be receptive to many mobile genetic elements. In clinical settings, hospital wastewater for antibiotic resistance are key sites of interest as organisms may acquire resistance to multiple antibiotics becoming multidrugresistant, resulting in difficulty treating patients in clinical environments[149].

Major institutions recommend having appropriate measures and governance to limit sanitary risks around healthcare infrastructures or research centers. A public health approach is essential, including policies for improving the collection and treatment of dangerous products with a monitoring system in place. In Japan for example, research centers and healthcare facilities are required to collect their dangerous waste in numerous separate containers. They are sterilized whenever possible, then handed to a private company for advanced treatments. All of which requires proper governance and the properly trained staff.

Nosocomial infections are an increasing problem, and not only for high income countries. A technical medical rethinking of the hospital buildings, with appropriate heat ventilation systems and adequate organization of the patients' flux and spacing is indispensable. But this is only one step. AMR deeply challenges the way in which disease management systems are organized today. Given the high risks of infections with resistant bacteria or fungi in hospitals and healthcare centers, the very function of health facilities should be reconsidered to embrace a broad definition of disease prevention and health promotion, with emphasis placed on those environmental factors that can safeguard human health. Health personnel must be adequately trained to gain full ownership of the required prevention categories that the health and climate emergencies have revealed, in the wake of the Covid-19 pandemic. Even in the case of infectious diseases this entails the need for more territorial medicine infrastructures, out of hospitals, as an effective strategy in the interest of public health when dealing with health emergencies. Covid-19 has provided evidence of the advantages of this approach, including in poorly-resourced settings.

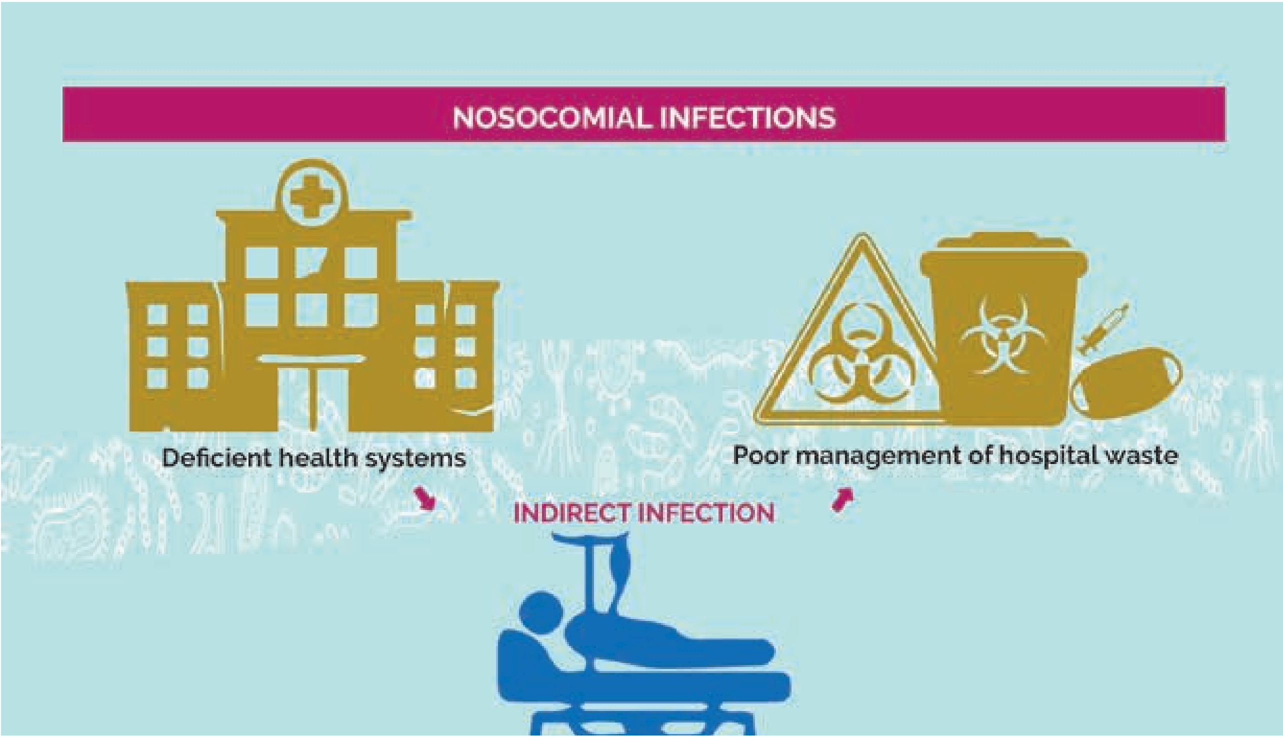
Bold policies are also needed, at the environmental level. A handful of countries have attempted to take action. In early 2020, the Indian Ministry of Environment, Forest and Climate Change published a draft of Environment (Protection) Rules for manufacturing bulk drugs. The draft listed out antibiotic residue effluent limits for 121 types of antibiotics in its

148 Cassini A., Diaz Hogberg L., et al., (2018). Attributable deaths and disability-adjusted life-years caused by infections with antibiotic-resistant bacteria in the EU and the European Economic Area in 2015: a population-level modelling analysis. *Lancet Infect Dis.*, published 5th November 2018, https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(18)30605-4/fulltext.

149 Kunhikannan S., Thomas C.J., et al., (2021). Environmental hotspots for antibiotic resistance genes. *Microbiologyopen*, 2021 Jun; 10(3): e1197.https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8123917/

Paragraph D –– probably the first such major attempt, in the world, to introduce stringent limits on dumping from pharmaceutical producers[150]. In 2017 the central government had launched the National Action plan on antimicrobial resistance, acknowledging that India is among the nations with the highest burden of bacterial infections.

An estimated 410,000 children aged five years or less die annually of pneumonia and overall crude mortality is 417 per 100,000 persons as of 2017, the plan stated[151]. In addition, a major study published in 2017 found excessively high levels of antibiotic and antifungal drug residue in water sources, particularly around a major drug production hub in the city of Hyderabad[152], as well as high levels of bacteria and fungi resistant to those drugs. Scientists believe the drug residues originated from pharmaceutical factories.



The Indian draft rules were set to limit entry of hazardous antibiotics by not allowing for dilution in the receiving water body, setting clear norms on waste and water management for the pharmaceutical industry: "We emphasized that India should not wait for other countries to set such standards as we are one of the biggest antibiotic producers and it is our own problem to fix," said Amit Khurana, one of the experts from the Center for

150 Vishnoi A., (2021). Green ministry drops antibiotic effluent limits from new rules. *The Economic Times*, 13 August 2021 https://economictimes.indiatimes.com/industry/healthcare/biotech/pharmaceuticals/green-ministry-drops-antibiotic-effluent-limits-from-new-rules/articleshow/85283831.cms?utm_source=contentofinterest&utm_medium=text&utm_campaign=cppst.

151 *ibidem.*

152 Lubbert C., Baars C., et al.,(2017). Environmental pollution with antimicrobial agents from bulk drug manufacturing industries in Hyderabad, South India, is associated with dissemination of extended-spectrum beta-lactamase and carbapenemase-producing pathogens. *Infection*, 45, 2017, 479-491, https://link.springer.com/article/10.1007/s15010-017-1007-2.

Science and the Environment (CSE), the oldest NGO on environmental matters in India[153]. This call for action however ended up being perceived as a disadvantage by the Indian pharmaceutical sector, which forced the government to retract on what had been a very serious and intelligent policy program. The Ministry finally dropped the specification of antibiotic residue limits from the Rules in 2021, under significant pressure from the pharmaceutical industry associations: their argument was that India would lose its competitive edge in the market, and in their stiff competition with China[154]. Up until now, there are no regulatory systems in the world specifically aimed at curtailing antibiotics in wastewater in order to limit antibiotic resistance.

The Wellcome Trust has published a seminal study on the logistics and requirements to treat wastes generated by the pharmaceutical industry[155], primarily reviewing concerns over how environmental regulations will affect the antibiotic manufacturing sector. The study maps out global antibiotic supply chains and their vulnerabilities, with a focus on manufacturing of Active Pharmaceutical Ingredients (APIs) as these pose a very high risk of antibiotic discharge to the environment and represent a possible supply bottleneck. The world heavily relies on Asia for APIs: India and China are home to nearly 70 percent of API manufacturing sites, with China producing two to three times greater volumes per site than India. As the largest global API exporter (40 percent)[156], China houses 71 percent of the manufacturing sites for reaction intermediates of key antibiotics such as amoxicillin and ampicillin[157]. The report, written with the Boston Consulting Group (BCG), ends up striking a devious balance and backing the very mild voluntary regulations of AMR Industry Alliance, to fill the structural lack of legislations in this arena worldwide. Any regulatory framework requires upgrading treatment technology and monitoring of wastewater which – so the report argues – might drive up prices, push suppliers out of the market, disrupt supply chains and affect global access to antibiotics especially in low-and-middle income countries.

The market-focused recommendations that the Wellcome Trust study formulates run contrary to the rigorous Indian plan used as benchmark. Tight regulating and monitoring

153 Davies M., (2020). India to ban antibiotics pollution from pharma factories. *The Bureau of Investigative Journalism*, 7th February 2020, https://www.thebureauinvestigates.com/stories/2020-02-07/india-to-ban-antibiotics-pollution-from-pharma-factories https://www.reactgroup.org/news-and-views/news-and-opinions/year-2020/antibiotic-pollution-india-scores-a-global-first-with-effluent-limits/

154 Vishnoi A,(2021). Green ministry drops antibiotic effluent limits from new rules. *The Economic Times*, 13 August 2021, https://economictimes.indiatimes.com//industry/healthcare/biotech/pharmaceuticals/green-ministry-drops-antibiotic-effluent-limits-from-new-rules/articleshow/85283831.cms?

155 https://wellcome.org/ "Understanding the antibiotic manufacturing ecosystem. A view of global supply chains, pressure points, and implications for AMR response. PNEF debate.

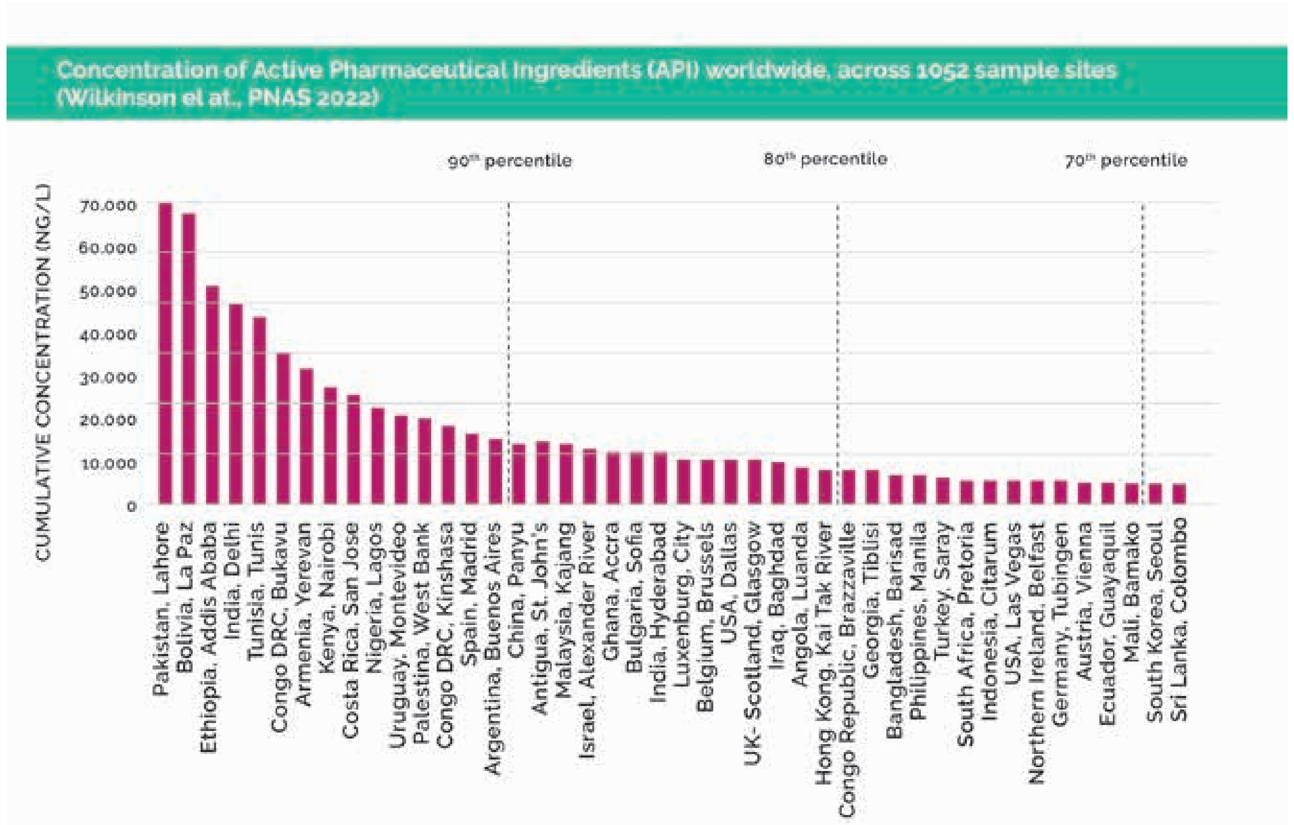
156 Hampson J., (2021). The Chinese API Market. *Insights,* Mantell Associates, 2021, https://www.mantellassociates.com/blog/2021/06/the-chinese-api-market?source=google.com.

157 According to KPMG, the Chinese API market has now diversified to over 2,000 API molecules and more than 7,000 API manufacturers (the number of manufacturers has increased by five times in the last five years) with an annual production capacity exceeding 2 million tonnes while the Indian industry has around 1,500 plants that manufacture APIs. Cfr. https://www.cnbctv18.com/healthcare/why-china-has-an-edge-over-india-in-api-manufacturing-6331911.htm

exist in many other areas of pollution and discharges from industrial manufacturing processes, in several countries. Why should pharmaceutical producers remain an exception? The question is why don't we already regulate antibiotic levels?

4. 2 – *The first worldwide survey of sites polluted by active pharmaceutical ingredients*

Evidence of the adverse effects that the presence of pharmaceuticals in rivers causes to environmental and human health has mounted significantly, yet until recently there was overall sparse and splintered knowledge about the phenomenon.



Studies available have been mostly conducted in North America and Western Europe[158]. A first world survey to quantify the prevalence of active pharmaceutical ingredients (APIs), and more generally synthetic chemicals, in waters and rivers has been undertaken in a collaborative work of over 80 universities, and published in early 2022.

158 In France, quite a unique system of pharmacovigilance was set in place at the beginning of 2017 as a multi-institution partnership led by the Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail (ANSES) for the national surveillance effort. Its action plan aims to assess and reduce the risks linked to biologically active products, including a wide range of molecules such as APIs. The network and its partners have expertise in monitoring substances in the different water types: surface waters, groundwater, rivers, wastewater plants and oceans, with a comprehensive approach.

In this first global reconnaissance of pharmaceutical pollution in rivers, authors have monitored 1,052 sampling sites along 258 rivers in 104 countries of all continents, thus representing the pharmaceutical fingerprint of 471.4 million people[159].

The research reveals the notable concentration of API in major sampled sites, mostly cities. Importantly, authors show that the presence of these contaminants in surface water poses a considerable threat to environmental and/or human health in more than a quarter of the studied locations globally.

159 Wilkinson J.L., Boxall A.B.A., et al., (2022). Pharmaceutical pollution of the world's rivers. *Proceedings of the National Academy of Sciences (PNAS)*, Vol. 119, No. 8, 22 February 2022, https://www.pnas.org/doi/10.1073/pnas.2113947119.

BOX 5.

The release of active pharmaceutical ingredients (API) in soils and rivers. Interview with Prof. John Poté, PhD, Head of Environmental Microbiology Group, Environment and Water, University of Geneva and professor at Kinshasa University[160].

You have just participated in this breakthrough study searching for Active Pharmaceutical Ingredients (API) in water streams. What was the original concept of this study?

J. Poté: Our concept was to undertake a study on rivers worldwide in the context of One Health and climate change. As we have written (127 authors representing 86 institutions around the globe), the pollution of the world's rivers by medicinal products is a problem that poses risks both for aquatic ecology and for the selection of AMR. This resistance will never be contained at the level of one country or one region. Data are available for only a small number of APIs. This is one of the reasons why the National Swiss Fund funded us. Without funding, development, and implementation of rigorous wastewater and waste treatment systems, talks of achieving the Sustainable Development Goals will be meaningless.

You explain in one recent article that a lot of data on API concentrations are available for the US, Europe, and China, but no data for most countries (121 out of 196).

J. Poté: We do not have data on AMR in sub-Saharan Africa, except for a few in Senegal and in the Democratic Republic of Congo, which I have undertaken, and where we have been able to popularize the results. There is a gigantic gap. In fact, it is expensive to undertake such studies. In almost all low and middle income countries, people take antibiotics without prescription and there is open defecation, with no waste treatments overall. That is obviously true of the animals, also. Q: We should not forget farming and husbandry?

J. Poté: Absolutely, I think it is necessary to bring the clinicians and the veterinarians together here. The big problem in countries, among many others, is the lack of investment in waste treatment and environmental quality! When we talk about One Health, we most of the time forget the environment. We need to do a lot of advocacy. Some regions are paying a heavy price. For example: in La Paz (Bolivia), we found the most polluted sampling site in Rio Seke, with an API concentration of 297 µg/L. This sample came from a site where there were both untreated sewage dumps and garbage dumps along the river banks.

Same troubling conditions we found in Costa Rica. In Africa, massive pollution is due to non-recycling of sewage and waste. Vegetable cultivations need enhanced examinations. The most contaminated samples came from Ethiopia, DRC, Kenya, Nigeria, Tunisia. But we must also mention countries like Pakistan, India, Bangladesh and China in Asia. Finally, Armenia and Palestine are of grave concern.

Several antibiotics and antifungals, included also in the WHO Essential Medicines List, are found at very high concentrations: ciprofloxacin, metronidazole, trimethoprim, itraconazole, Sulfamethoxazole.

J. Poté: Indeed! Ciprofloxacin, for example, is found above safety limits at 64 sites. And the exceeding of these limits reaches records for metronidazole at one site in Bangladesh (Barisal), with concentrations 300 times higher than the safe target. In middle and low-income countries, we find a lot of variation in antimicrobials, correlated with the lack of sanitation, the lack of medicines regulation, the lack of regulation in industrial processes. This is a huge challenge, the magnitude of which has not yet been grasped.

160 Prof. John Poté was interviewed by Garance Upham in Geneva on 14th April 2022.

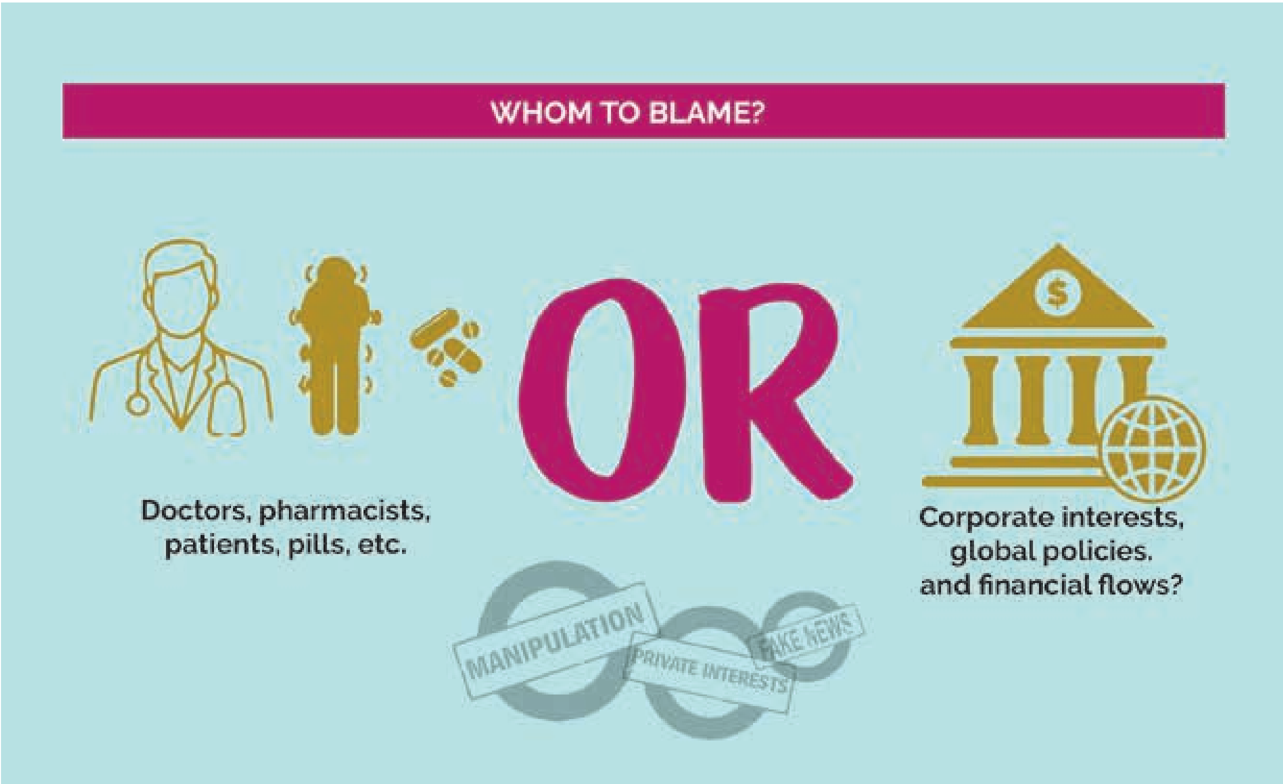
5. THE INGENIOUS AMR NARRATIVE AND ITS DEVILISH DETAILS

AMR is first of all a political issue. Until now, most efforts have been targeted towards technical and local approaches; only recently politicians in some countries have become engaged. However, as antimicrobial resistance has globally gained traction since 2015, the institutional discourse at international and national level has gradually developed its narrative along a somewhat misleading twofold message:

Stewardship is urgently needed for the lone medical doctor so he/she does not over-prescribes antibiotics and does not overuse them with patients. The same applies to the lone patient so he/she does not buy drugs over the counter, goes to the end of the prescription, does not use leftovers.

The world urgently needs new more potent antibiotics and appropriate treatments, as well as vaccines and diagnostics.

This narrative contains a number of problematic implications.



5.1 The blame game

Policies and health institutions dealing with antimicrobial resistance, at all levels, have devoted most of their attention and communication on misuse of antibiotics in human medicine as one of the key drivers of AMR. Infact, only in recent years has the animal farming dimension of the problem started to emerge, as well its environmental implications. The attention has been heavily indulged in medical doctors' practices. We know well that the individual responsibility narrative serves highly ambiguous corporate purposes in the current deregulated economy. The food industry's propaganda which attributes the responsibility of obesity to the individual consumers' lack of physical activity masterfully exemplifies the strategy, just like the carbon footprint approach - with its navel-gazing carbon neutrality tools - hatched by the fossil fuel industry[161]. The blame game designed to place responsibility for the AMR problem on medical doctors, pharmacists and consumers, carefully deconstructed by Clare Chandler's anthropological lens[162], makes no exception.

Poor awareness or scarce access to health care services, and a laissez-faire attitude among medical doctors who prescribe broad spectrum drugs, and antibiotics for viral diseases and upper respiratory tract infections, are undoubtedly common conditions worldwide. They result from different contextual factors, and are often combined with absence of policy regulations and lack of societal awareness on these drugs. In LMICs, however, viral infections often come accompanied by bacterial ones, so the landscape is indeed more complex than routinely represented. Of course, because antimicrobial resistance is increasing, it is important to encourage the medical community and societies to improve their antibiotic knowledge and habits. Health centers stewardship - defined as "the careful and responsible management of something entrusted to one's care"[163] - and infection prevention and control (IPC) in human health are essential avenues.

The problem arises when the efforts aimed at reducing AMR mainly herald the arresting but deceptive idea that individual doctors and patients' wrong behavior is the major trigger. The syndemic nature of antimicrobial resistance should be glaringly clear at this point, and it calls not only for a radically different narrative, but also for colossal policy re-interpretations and changes. Human medicine is not the determinant causing harm to individuals and societies by driving the selection of resistance.

161 Schendler A., (2021). Worrying About Your Carbon Footprint Is Exactly What Big Oil Wants You to Do. In *The New York Times,* 31st August 2021, https://www.nytimes.com/2021/08/31/opinion/climate-change-carbon-neutral.html.

162 Chandler C.I.R., Hutchinson E., et al.,(2016). Addressing Antimicrobial Resistance Through Social Theory: An Anthropologically Oriented Report. London School of Hygiene & Tropical Medicine, 2016. :https://www.researchgate.net/publication/313482751_Addressing_Antimicrobial_Resistance_Through_Social_Theory_An_Anthropologically_Oriented_Report

163 WHO (2017). Global framework for development and stewardship to combat antimicrobial resistance: draft roadmap. Geneva, World Health Organization, 2017.

5.2 A product-based approach

Like Covid-19, AMR must be recognized as a public health and socio-economic disaster just waiting to happen, and that remains today not fully understood in all its complex implications. While antibiotic resistance threatens to undermine modern health care, cancer treatments, care of premature babies, surgery and much else, the neoliberal conceptualization of health as individual, apolitical and technical allows little room to question its determinants and interrogate powers. The product-based framing of the problem inherently reduces multiplicity of perspectives and insights, and validates concentrating resources within individuals and institutions that are most aligned with this prevailing strategy.

The refusal by national and international institutions to adequately define the AMR origin for what it is, the perfect storm of a seemingly intoxicating economic model, represents in itself an enormous challenge to the notion that something relevant will be done about this crisis. AMR is broadly looked at through a disease-specific lens, a product-based approach, and ultimately through the iteration of the research and development (R&D) and access discourse that has dominated the global health agenda for infectious diseases over the past two decades. In fact, AMR does not completely fit into the global statistics that have a single disease focus[164]. Bacteria are everywhere and the systemic nature of the problem, as well as the policy implications it entails, call for a different, wider and deeper lens.

But for the past decade, the clamor in international AMR policy debates has been loud on the alleged need for new products: new antibiotics, new antivirals, new antifungal and anti-parasites as the main solution to antimicrobial resistance. The problematic economic models that fuel the fire are not mentioned. The story repeats itself: the determination of the processes that contribute most to risks and ill health remains sidelined, depoliticizing the causes of AMR and exclusively prioritizing biomedical solutions. This approach is attracting most funding and recognition.

Hardly any novel antibiotics have been developed in the last decades[165], and pharmaceutical companies have progressively withdrawn from the development of these antibiotics. Small companies do exist, but their patents have been bought by the large companies and, worse, they are driven to failure due to difficulties in accessing public funding, contrary to what happens to large companies.

In June 2018 Novartis exited the market, bringing the total number of companies involved in antimicrobial drug development to six[166]. So on the one hand, a new market-

164 https://www.reactgroup.org/news-and-views/news-and-opinions/year-2022/the-silence-is-killing-us-time-to-listen-to-the-facts/.

165 Freire-Moran L., et al., (2011). Critical shortage of new antibiotics in development against multidrug-resistant bacteria - Time to react now. *Drug Resistance Updates,* 14(2). 118-124.

166 https://hansard.parliament.uk/lords/2019-05-02/debates/C52B84FA-B81F-4D16-8479-D63E1D818652/AntimicrobialResistance.

failure narrative for antibiotics has been fashioned to justify the pharma industry's reluctance to get involved. Pharmaceutical companies - it is said - find it less profitable to invest in antibiotic research and development (R&D) compared to other disease areas, because any new class of antibiotics is likely to be prescribed only very sparingly rather than as a first-line treatment during its patent life, reducing the revenue potential and market value[167]. On the other hand, the debate has shifted to the ingenuity required to get pharma companies on board. Governments are devising old and new incentives' schemes to attract them[168], including longer monopoly prices, the Netflix Subscription Pricing, or new models delinking the payments made to companies from the volumes of antibiotics sold, basing the payment instead on national pharma agencies-led assessment of the value of the medicines[169]. This comes down to the value-based pricing approach that pharma companies have particularly cherished in the last decade, turning the very notion of "essential medicines" upside down. The problem is that prioritizing industry-driven demands for greater returns is bound to set the price barrier for novel antibiotics very high, making new drugs resemble financial derivatives[170].

The product-based approach based on fostering research and development (R&D) of new antimicrobial therapies[171] serves as a response to economic models developed by the OECD[172], among others, claiming that policies targeted to tackle AMR are highly cost-effective. Boosting incentive schemes for more medical innovation is of course an enticing strategy for drug developers who are the primary feeders of antibiotics resistance via their active role in the industrial livestock breeding pipeline. As we have seen already, 70 percent of global antimicrobials are fed to intensively farmed livestock[173] - and the controversial co-optation of veterinarians in the system[174].

167 European Observatory on Health Systems and Policies (2019). Averting the AMR crisis: What are the avenues for policy action for countries in Europe?. WHO 2019, WHO Regional Office for Europe, https://apps.who.int/iris/bitstream/handle/10665/331973/Policy-brief-32-1997-8073-eng.pdf?sequence=1&isAllowed=y.

168 Savic M., Ardal C.,(2018). A Grant Framework as a Push Incentive to Stimulate Research and Development of New Antibiotics. *The Journal of Law, Medicine and Ethics,* 17th July 2018, https://doi.org/10.1177/1073110518782911. More recently, Morel C.M., Lindhal O., (2020), Industry incentives and antibiotic resistance: an introduction to the antibiotic susceptibility bonus. The Journal of Antibiotics, 73, 421-428, (2020), https://www.nature.com/articles/s41429-020-0300-y. Finally, Ardal C., Ploy M-C., et al., (2021). D 9.2 A strategy for implementing multi-country incentives in Europe to stimulate antimicrobial innovation and access. EU-JAMRAI, 31 March 2021, https://eu-jamrai.eu/wp-content/uploads/2021/03/EUjamrai_D9.2_Strategy-for-a-multi-country-incentive-in-Europe_INSERM-FHI.pdf

169 https://www.chathamhouse.org/2015/10/towards-new-global-business-model-antibiotics-delinking-revenues-sales and also https://www.nice.org.uk/news/blog/world-antimicrobial-awareness-week-2020.

170 Dentico N., (2019). La più cara del reame. *Salute Internazionale*, 14th October 2019, https://www.saluteinternazionale.info/2019/10/la-piu-cara-del-reame/.

171 https://ec.europa.eu/assets/sante/health/amr/docs/amr_20220126_co02_en.pdf.

172 https://www.oecd.org/els/health-systems/Antimicrobial-Resistance-in-G7-Countries-and-Beyond.pdf

173 Prince C., (2021). Driven by Profits from Antibiotics, Animal Health Industry Is Feeding Risks of 'Superbugs' & Next Pandemic. *Health Policy Watch*, 28th July 2021, https://healthpolicy-watch.news/failure-to-manage-antimicrobial-resistance/.

174 Hernandez E., Llonch P., et al. (2022). Applied Animal Ethics in Industrial Food Animal Production: Exploring the Role of the Veterinarian. *Animals* 12(6):678, March 2022, https://www.researchgate.net/publication/359087206_Applied_Animal_Ethics_in_Industrial_Food_Animal_Production_Exploring_the_Role_of_the_Veterinarian.

Along with new drugs, the development of new vaccines is now called for to help counter the problem. In its first collation of vaccine candidates in preclinical and clinical development as of 2021, the WHO issued an urgent call to step up investment and research into vaccine candidates that can tackle the problem of drug-resistant bacteria. In this new WHO report[175], 61 vaccine candidates in various stages of clinical development, and 94 candidates in preclinical development, are listed. Obviously, pharmaceutical solutions such as vaccines and new drugs can be life-saving and contribute to improving population health. However, faced with the systemic dimension of the AMR phenomenon, the approach that the WHO takes with its latest report appears a stark reminder that, even in pandemic times, the global health agenda remains firmly performing its ideological function of legitimizing, and possibly strengthening the existing ill-health inequities that are rooted in unhealthy power relations and governance structures. Often these remain hidden from view and from critical investigation[176].

175 WHO (2022). Bacterial vaccines in clinical and preclinical development 2021. World Health Organization, Geneva, July 2022, https://www.who.int/publications/i/item/9789240052451

176 Kim H., (2021). The Implicit ideological function of the global health field and its role in maintaining relations of power. *BMJ Global Health 2021,* https://gh.bmj.com/content/bmjgh/6/4/e005620.full.pdf.

6. THE BABEL TOWER OF AMR GLOBAL GOVERNANCE

On March 17, 2022 the United Nations Tripartite Partnership for One Health, bringing together the FAO, WHO and OIE formally became the Quadripartite as it welcomed a new partner, the United Nations Environment Program (UNEP)[177]. The long overdue inclusion aims to accelerate coordinated strategy on human, animal and ecosystem health and finally better integrate the environmental dimension of the AMR phenomenon, including the gaps in recognizing long ignored causes and impacts. The merger between global environmental and health governance is not only intuitive — it is necessary. Yet, a colossal challenge to the prospect that any truly significant measures will be pursued to confront the AMR silent pandemic lies in the very governance structure created to tackle the problem: an institutional path of progressive chaos, fragmentation and ex-post coordination that is hard to comprehend and justify.

6.1 Global surveillance of AMR - the WHO GLASS

Several international initiatives have taken shape since the WHO launched the Global Antimicrobial Resistance and Use Surveillance System (WHO GLASS)[178] in October 2015, the "first global collaborative effort to standardize AMR surveillance". GLASS requires countries joining the system - 109 so far - to report whatever limited data they have collected. However, since data collection remains very problematic in most Low and Middle Income Countries (LMICs), as well as in High Income Countries (HIC)[179], recent World Health Assemblies have launched several new regional/national hubs aimed at increasing the data management issue, at the expense of capacities for medical sciences. With the pretense of funding WHO core data management activities, new data hubs were developed in Berlin, (complementing the already existing Global AMR R&D Hub), a surveillance Data Hub in London, so that the number of reporting sites has increased, especially in Europe.

Latest UN estimates show that only about a fifth of the National AMR Programs (NAPs) are fully funded and somewhat operational[180], which demonstrates how weak GLASS and other such systems are in the face of the exploding AMR crisis. Lack of reporting facilities and similar structural constraints refrain countries from participating in the WHO reporting mechanism. These limitations need to be considered and addressed. Yet, can we really

177 https://www.unep.org/news-and-stories/statements/joint-tripartite-and-unep-statement-definition-one-health.

178 WHO GLASS. "Global Antimicrobial Resistance and Use Surveillance https://www.who.int/initiatives/glass.

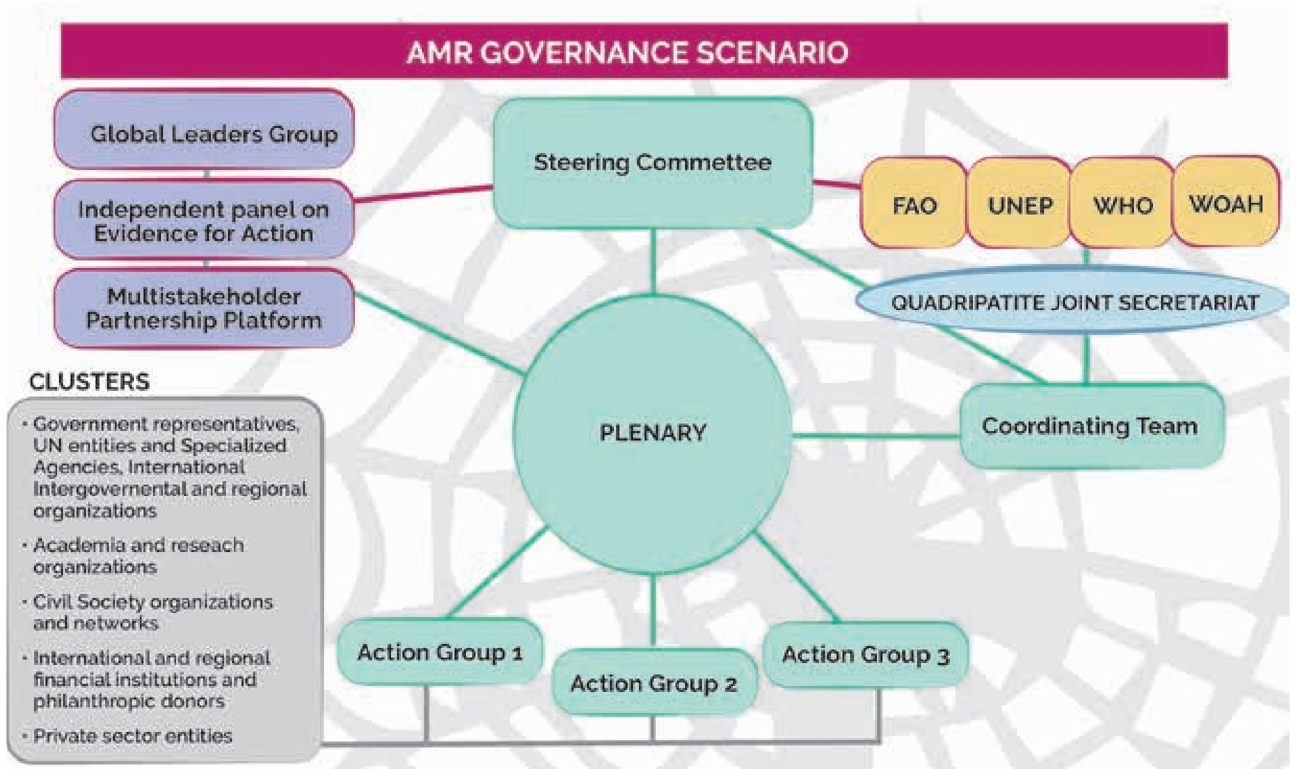
179 At a Parliament briefing in London in 2019, the UK Special Envoy for AMR, Prof. Dame Sally Davies, was heard campaigning to force the UK hospital system to record cases of AMR: https://hansard.parliament.uk/lords/2019-05-02/debates/C52B84FA-B81F-4D16-8479-D63E1D818652/AntimicrobialResistance.

180 https://www.fao.org/3/cb3690en/cb3690en.pdf#page=16.

presume to even have a glimpse of the AMR situation in countries from few medical records? Where is the One Health strategy, grounded on interdisciplinary collaboration, bound to stem from? Who is to inform about wastewater surveillance, when countries in over half of the world lack a wastewater treatment system and centralized institutions to care for AMR, beyond a vertical or medicalized approach?

6.2 A nightmare governance scenario for a silent tsunami

To be effective, action to combat antimicrobial resistance has to be global. In addition, as we have seen, AMR is inherently an intersectoral challenge with a complexity of its own, the burden of which is disproportionately faced by both low and middle income countries. With the endorsement of the Global Action Plan (GAP) on AMR in 2015[181], the 194 WHO member states committed to integrating the five objectives and corresponding actions of the GAP into national action plans (NAPs) on AMR. But while "there is not time to wait", as the report of the UN Interagency Coordination Group on antimicrobial resistance (IACG) spells out in its very title[182], shaping the AMR global governance has taken much time and energy since. The process is ongoing.



In developing its recommendations, the IACG was inspired by the urgency to focus on promoting and supporting a One Health approach to antimicrobial resistance; strengthening existing systems and mainstreaming efforts to combat antimicrobial

181 https://www.who.int/publications/i/item/9789241509763.

182 https://www.who.int/publications/i/item/no-time-to-wait-securing-the-future-from-drug-resistant-infection

resistance so as to leverage gains across the Sustainable Development Goals (SDGs); supporting mobilization of all stakeholders, including governments, international organizations, academia, civil society and the private sector, at global, regional, national and local levels, with a strong emphasis on enabling country-level action and with due consideration to country-specific context, capacity and infrastructure. All recommendations, the report insists, should be practical and feasible to implement. The enunciation of this roadmap would sound reasonable if the coordination on antimicrobial resistance had been shaped ex-ante at the United Nations and if power relations among the cluster groups currently involved in shaping the governance framework had been balanced and regulated. But this by no means is the case.

In the face of serious governance drawbacks, the UN has orchestrated a sequence of public consultations[183] that may appear to render the AMR governance outline more democratic and acceptable, including to critics. But its byzantine arrangement is clearly poised to thwart collective efforts to address AMR at the global level. One major obstacle is the limited knowledge on how to design effective multidisciplinary global governance mechanisms[184], especially at a time of multistakeholderism. The willful reproduction of the multistakeholder model, today so fashionable at the UN, while pursuing the explicit goal of combating AMR, is doomed to implicitly impair any serious intention at fixing AMR through politics of systemic change.

As if the Tripartite (now Quadripartite) UN-agency composition were not enough - AMR decisions have to be confirmed in a sequence by the four respective assemblies each time - the global AMR governance is further convoluted due to the following complementary structures:

The One Health Global Leaders Group on Antimicrobial Resistance (The Global Leaders Group, GLG)[185] launched in November 2020 and led by Sheik Hasina, Prime Minister of Bangladesh and Mia Amor Mottley, Prime Minister of Barbados. The GLG consists of world leaders and experts from across sectors working together to accelerate political action on antimicrobial resistance (AMR). It collaborates globally with governments, agencies, civil society and the private sector through a One Health approach to advise on and advocate for prioritized political actions for the mitigation of drug resistant infections through responsible and sustainable access to and use of antimicrobials.

The Multi Stakeholder Partnership Platform, currently in the making, which is expected to attract over 200 members "representing different stakeholder voices and a balance across regions, driving multidisciplinary actions at global, regional, and national levels through Action Groups working on key issues of multi-sectoral interest and developing

183 https://amr.solutions/2021/08/25/survey-from-who-fao-oie-unep-on-a-multi-stakeholder-amr-platform-18-sep-due-date/

184 One preliminary recognition of this problem emerged with the WHO first indicative note to illustrate the complementarity of governance structures for antimicrobial resistance published in July 2020: https://cdn.who.int/media/docs/default-source/antimicrobial-resistance/information-note-governance-structures-amr.pdf?sfvrsn=710f00f3_2.

185 https://www.un.org/pga/75/wp-content/uploads/sites/100/2021/04/GLG-2-pager-for-HLD-280421_final-1.pdf

action plans". The idea is that the variety of stakeholders, including the private sector, academia and civil society organizations, will build momentum and generate for high-level advocacy drive to tackle AMR globally[186].

The Independent Panel on Evidence for Action (IPEA), made up of a core group of experts with proven knowledge, strategic skills and experience in areas relevant to antimicrobial resistance. Panel members should represent a wide range of geographic regions, relevant disciplines and sectors. Panel members should have experience in developing and communicating across the science-policy and policy-practice interface. Public consultation was held for this as well[187].

The (so far) unspecified Action Groups complete this scene, raising further concerns. Several apprehensions have been voiced during the public processes, including by the civil society organizations gathered in the Antibiotic Resistance Coalition (ARC), among others[188].

It is not evident or clear what leadership role the UN agencies will accomplish in this Babel Tower landscape, where the intergovernmental decision-making prerogative - the entitlement which allows for direct exchanges of country challenges and perspectives - is somewhat diluted and dispersed. At the same time, the AMR plethoric governance configuration creates bubbles of interest, including within the UN system, based on the individual agencies' respective and potentially overlapping mandates (between FAO and WOAH). The breadth of stakeholders included and entities created is not only problematic in terms of fragmentation (hence of coordination), but the uneven playing field displayed in the current arena also risks being conducive to asymmetric representation and uneven influence capacity.

Each of the new bodies listed above pose important, unresolved questions over governance. The GLG composition, as described in the IACG recommendations, leaves the door open for considerable conflicts of interest. In fact, the current composition already includes representatives holding fiduciary and financial conflict of interests - for instance, the Vice President of the General Council of Merck & Co., INC. - combined with questionable AMR expertise - as is the case for the President of MARS Inc Innovation. Considering the role of corporate interests in the development of the AMR crisis, the fact that these should be peacefully incorporated in the AMR platform in the absence of ground rules, opens serious legitimacy concerns, especially when considering the failure to arrive at a joint consensus among the Tripartite agencies over the use of antimicrobials in food animal production. The Independent Panel on Evidence for Action Against Antimicrobial Resistance might provide a way of overcoming the governance paralysis across the agency processes. However, with this Independent Panel being supported by the Tripartite Secretariat, the risk is that the Independent Panel may not be independent.

186 https://www.fao.org/antimicrobial-resistance/news-and-events/news/news-details/en/c/1417587/.

187 https://www.who.int/publications/m/item/public-discussion-draft-terms-of-reference-independent-panel-on-evidence-amr

188 https://static1.squarespace.com/static/5c3784843c3a534eadd60de4/t/614633aae8a3b539f401868e/1631990699004/Antibiotic+Resistance+Coalition+submission+to+AMRPlatform+Questionnaire_17Sept2021.pdf.

6.3 AMR National Action Plans (NAPs): more shadows than lights

Globally, two thirds of member states, including LMICs, have adopted National Action Plans (NAPs). These have been developed in a very short period of time if compared to NAPs in other policy areas[189]. More than 95 percent of member states report back to the UN agencies on national progress with regards to AMR policies. The good news is that the profile of AMR is increasing and these steps mark a positive achievement in terms of AMR awareness.

However, the challenge is not so much to write a NAP, as it is to implement it. Since many NAPs were put together in haste to meet the World Health Assembly-imposed deadlines, many of them failed to incorporate a One Health approach right from the start, and are exclusively focused on the healthcare agenda concerning human antibiotic prescriptions and use. The animal and environmental dimension of the problem in most cases is lacking altogether. Also, many of them fall short on monitoring or accountability.

But as we have demonstrated so far, AMR is a major development issue with multiple drivers: low awareness or distorted narratives about AMR, sub-optimal regulatory processes, the unchecked leveraging capacity of the corporate sector at all levels, pathogenetic industrial models and poor access to healthcare, inadequate wastewater treatment management schemes, and often use of LIMCs territories for discharging of HICs' industrial wastes. Consequently, NAPs must take a systems approach to addressing these various determinants. The major barriers to NAP implementation in LMICs (and also in several HICs) revolve around four key areas:

- Knowledge on AMR: A lack of reality-based understanding and knowledge of AMR, often due to a reductionist narrative of the problem, as well as a lack of public pressure and difficulty to convince decision makers;
- Governance and Coordination: Fragmented governance systems in countries with poor inter-sectoral coordination and scarce resource mobilization combine, with inadequate infrastructure, to make NAP implementation difficult.
- Finances: Due to a lack of political will and competing healthcare priorities, many NAPs face financial barriers, resulting in inadequately budgeted resources for implementation.
- Lack of Data: Decision making on AMR programs requires evidence, but many LMICs do not have effective data collection systems to provide such information.

189 Munkholm L., Rubin O., (2020). The global governance of antimicrobial resistance: a cross-country study of alignment between the global action plan and national action plans. *Globalization and Health*, 16, 109 (2020), https://globalizationandhealth.biomedcentral.com/articles/10.1186/s12992-020-00639-3.

7. TURNING THE TIDE: CONCLUSIONS AND THE (LONG) WAY FORWARD

Nearly 25 percent of global deaths are attributed to economic decisions affecting the environment[190]. AMR makes a paradigmatic case of the human role in ecological degradation and the cycle of negative impacts that such degradation impose on human and animal health. In this sense, AMR is also an exemplary demonstration of how environmental equity and health equity are closely interlinked[191]. The Human Rights Council acknowledged this nexus in October 2021, when adopting a breakthrough resolution on the human right to a safe, clean, healthy, and sustainable environment, stating that: "sustainable development [...] and the protection of the environment, including ecosystems, contribute to and promote human well-being and [...] the enjoyment of the highest attainable standard of physical and mental health"[192].

International and national efforts to combat AMR grew consistently in the last two decades and culminated in the adoption of the WHO Global Action Plan on Antimicrobial Resistance in 2015. Despite these efforts - geared towards novel drug development, bans on the indiscriminate use of antimicrobial drugs for humans, restrictions for veterinary uses, and raising public awareness - scientific studies show that in many countries we measure increased concentrations of synthetic chemical compounds in the environment (most of which are of industrial origin), and increased prevalence of resistant organisms. This bears witness to the failure of the previous action plans in preventing the emergence of AMR, due to lack of holistic approaches linking human activities with the environment and cutting the emissions of molecules susceptible to cause the emergence of AMR-genes and deadly pathogens.

AMR arises, develops and travels in the environment, via a range of industrial determinants that produce the phenomenon well beyond its natural dynamics. The AMR containment strategy, with policies aimed at reducing and regulating the use of antibiotics, has long been fostered by the UN agencies. But containment alone proves inadequate today in the face of a syndemic challenge on the verge of exploding, accelerated as it is by the climate emergency. Specious regulation initiatives take years, and they happen to be routinely obstructed by vested interests. What to do with AMR, now that this silent yet mounting health emergency makes Covid-19 an altogether manageable crisis?

Climate change and the pervasiveness of the AMR problem call for a more reality-

190 IISD (2022). Health in the Global Environmental Agenda: A Policy Guide. International Institute for Sustainable Development in collaboration with the Global Health Academy, University of Edinburgh, January 2022, https://www.iisd.org/system/files/2022-01/health-environment-nexus.pdf.

191 IISD (2022). Health in the Global Environmental Agenda: A Policy Guide. International Institute for Sustainable Development in collaboration with the Global Health Academy, University of Edinburgh, January 2022, https://www.iisd.org/system/files/2022-01/health-environment-nexus.pdf.

192 https://www.ohchr.org/en/statements-and-speeches/2022/04/right-healthy-environment

based and science-driven approach. We have dangerously warmed and polluted our world already. The decisions policymakers make today will determine the course of the future; the convergence of multiple crises that we witness, particularly after the Covid-19 pandemic, demands the imperative of people and planet first: a drastic change of course. SARS-CoV-2 has seeded a deeper understanding of the globalization's pathogenesis that only large scale holistic perspectives, and new sets of organizing principles and ideas, can address[193]. We face so many overlapping and intersecting crises that we cannot afford to fix them one at a time. Of course, when we are dealing with scenarios so profoundly embedded in global political economies, changing routes is no easy game. The vision for integrated solutions, and the political determination to work for humanity's survival on this planet, are necessary. This is no time for piecemeal policy-making.

To cut the emissions of molecules susceptible to causing the emergence of AMR-genes and deadly pathogens, a new set of bold policies is the only way forward. Positive anthropogenic action is the only alternative, and a possible one. The vision we propose here is that the international community, regional institutions and national policy-makers attack the root causes of syndemic AMR and its corollaries of diseases urgently adopting policies that can stop the constant exploitation of nature and its rampant undesirable effects on ecosystems. One Health is the only route that can put an end to this endless war against the planet and help reach out to the systemic determinants of AMR, through the fundamental health and environment nexus. Different countries will have different needs and priorities, but antimicrobial resistance, as we have tried to demonstrate, is a global threat and as such it must be acknowledged, in its complexity.

We recommend some initial inroads: concrete steps that decision-makers can make to start moving national policies in the right direction.

Key entry points regarding intensive animal farming:

1. Legislation to forbid packing animal concentration with abhorrent parameters in farming sites and aquaculture, to stop of antibiotic use in animal farming, with strict monitoring and heavy penalties for failure to adhere to the norm. This includes stopping drug incentives to veterinarians (following the example of Denmark);
2. Strict regulations against open air animal farms residues: these represent a significant danger in storm-flooding;
3. Enforcement of Infection Prevention and Control (IPC) measures in husbandry farms and of high hygiene standards in slaughterhouses, along with traceability systems. These standards and traceability systems should take into account and be adjusted to different scales, contexts and modes of production;
4. Strict routine regulations and controls in food production factories, effectively assessing the risks of the whole food chain risks that are potentially linked to AMR and addressing them, particularly for the large food chain processing gaps (establishing regular controls of machinery) and the chemicals and antibiotics used in food preparation, often referred to as "black boxes", for secrecy on industrial practices;
5. Enforcement of labor laws to protect and train farmworkers, slaughterhouse employees and meat & fish packers to avoid additional health crises. Support small scale and decentralized livestock producers for the enforcement of such regulations and provision of training ;
6. National/regional legislations to curb public and private incentives to the animal farming industry & redirect financial flows towards agroecology-based systems, particularly those prioritizing the principle of crop and livestock integration, to maintain natural habitats and preserve biodiversity while avoiding anthropogenic AMR.

193 Cousins T., Pentecost M. et. al. (2021). The changing climates of global health. BMJ Global Health, March 2021, http://dx.doi.org/10.1136/bmjgh-2021-005442.

Key entry points addressing industrialized agriculture and crop production (including biofuels and farmed animals' feeding):

A progressive ban of all pesticides and herbicides use. Increasing awareness of chemical governance is a must. Policies need to be enforced with immediate effect and not remain paper proposals, including policies to ban glyphosate, a massively used registered patented antibiotic and anti-parasitic. The route initiated in Mexico, combining phasing out from glyphosate with transitioning to a new agroecological paradigm, with support by the national scientific community, farmers and other concerned actors in this process, offers an important example to learn from.

- Establishment of a science–policy body on chemicals and wastes for advancing knowledge, supporting decisions and constantly delivering new research and evidence to decision-makers.
- An immediate ban on the use of fungicides from the azole family, in rice and aquaculture for exports, as well as in industrial global export production of plants and flowers.

Key entry points tackling industrial pollution and increasing extreme climate events:

- Normative frameworks for water quality protection and wastewater treatments in 56 percent of the world without them. The AMR and climate change crises make it urgent for countries to take all possible measures to contrast water pollution and contamination of water bodies (lakes, rivers, oceans, aquifers, reservoirs and ground waters). Globally, 80 percent of wastewater is released to the environment untreated[194]. Wastewater treatment processes - sewage treatment, industrial wastewater treatment, agricultural wastewater treatment and leachate treatment plants -need to be introduced with a sense of urgency. This is key for AMR prevention and control. Failure to do so implies massive AMR risks, including those associated with flooding or heavy rains events, more frequent worldwide. Wastewater management is an essential first step in the One Health approach for dealing with AMR threats at a time of climate emergency. Policies for a rigorous control on industrial wastes of all kinds need to be introduced at national/regional and international levels, with strict and effective liabilities for companies violating them (the polluter pays principle);
- Strong investments in urban wastewater treatments in all countries. Faced with the increase in the world's population combined with increasing urbanization, access to drinking water and sanitation is still a vital issue for many cities, especially in developing countries. The main objective of wastewater treatment plants is to reduce the flow of pollution discharged into the natural environment. They can also become real plants to produce green energy, raw materials or to reuse treated water. These new actions are part of the sustainable development, circular economy, renewable energy production and global warming initiatives developed by cities and local authorities.
- Public funding schemes for water pollution/contamination control programs. Funding sources for small and rural water quality protection schemes - state revolving funds, grants for wastewater to communities - need to be made available. These may provide effective strategies for communities' engagement in clean water recovery projects, including community surveillance training on antimicrobial resistance;
- Increasing attention to pollution from medical waste and its incineration under the Stockholm Convention and the Plastic Waste Partnership. Monitoring Active Pharmaceutical Ingredients (API) and regulating their release in waterways are essential normative steps. There are currently no global standards to stop API release from pharmaceutical production industrial plants into soils, rivers.

194 https://www.worldbank.org/en/news/press-release/2020/03/19/wastewater-a-resource-that-can-pay-dividends-for-people-the-environment-and-economies-says-world-bank

- Formalizing intergovernmental commitments to address pharmaceutical pollutants. APIs released in waterways need to be monitored very closely and there are today no global standards and national norms to regulate and stop indiscriminate pouring of APIs from pharmaceutical production industrial plants into soils, or water bodies. But plans and laws for avoiding uncontrolled spread of APIs are a minimal first step, given the mounting flooding risks and heavy rain events due to climate change;
- Ban uses of antibiotics in all water bodies. Aquatic environment is key to sustainable development for global society, these ecosystems are of great importance from a biodiversity and economic point of view. But water ecosystems have been deeply affected by a very complex pollution matrix, including a large list of antibiotics, as recorded in high infrastructure countries from the beginning of the XXI century (USA, Germany, Spain, Sweden, and Canada). As well as treatment and management strategies to remove antibiotics, novel strategies must be devised and adopted to stop their release in water bodies worldwide.

Key entry points to avoid and prevent AMR in healthcare centers:

Systematize stewardship of antibiotics, fungicides, antivirals in healthcare. Stewardship programs can successfully be implemented when essential core elements and methods are introduced in healthcare facilities. These elements may vary according to countries' capacities[195] but once they are instituted by the Ministry of Health in nosocomial and other healthcare centres, the culture of infection prevention and control is enhanced and translated into appropriate practices;

- Establish and/or reinforce national-level training on Infection Prevention and Control (IPC) in health centers for all countries with dedicated personnel, adequately trained and paid, and strengthen monitoring the implementation of appropriate cleaning;
- Develop well-designed health centers, with appropriate urban-water, wastewater, and ventilation systems. Airborne infection controls such as local exhaust, high efficiency air filtration, etc. must be routinely implemented.
- Strengthen health systems towards health promotion and disease prevention,

195 WHO (2019). Antoimicrobial Stewardship Programmes in Health Care Facilities in Low- and Middle-Income Countries: A WHO Practical Toolkit. World Health Organization (WHO), Geneva, 2019, https://apps.who.int/iris/bitstream/handle/10665/329404/9789241515481-eng.pdf

including the management of diseases through a network of health-centers adequately equipped and scattered in all territories, to secure proximity to people's needs and promote One Health as the new public health culture for all.

- Formulate and implement NAPs according to a One Health approach. The development of a NAP can be a concrete activity for joint inter-ministerial work (health, agriculture, economic development, trade, finance, environment, social affairs, etc.). Once the vision is set, prioritize its operationalization including through financial investment.

Key perspectives for global research on AMR

- Establish public regional agencies for essential health research aimed to address complex crises like AMR, among others. These agencies need to be public. Publicly funded and publicly steered, as is the case for the European Center for Nuclear Research (CERN) or for space research in the US (NASA). If Covid-19 has once again revealed the key role of public funded research to bring forward needed innovation, the very nature of the AMR emergency requires the convinced mobilization of the public sector for health, just as it does for military research and the like;
- Support co-creation of knowledge and research on plants' compounds and systems found in medicinal plants and preserve biodiversity, as a reservoir of potentially to-be-discovered drugs against infections. Solutions to fight AMR are also present in nature, and as environmental scientists report, we have only uncovered roughly 10 percent of the plant having amazing properties to act in the bacterial world. Most of the rest needs to be researched and identified[196] - high time the world invested in this with a public health purpose.
- The COVID-19 pandemic has underlined the need to partner with the community in pandemic preparedness and response in order to enable trust-building among concerned actors, which is key in pandemic management. AMR makes no exception. Citizen science[197], is a crucial approach to promoting community engagement. By harnessing the potential of digitally enabled citizen science, one could translate data into accessible, comprehensible and actionable outputs at the population level. The application of citizen science in health has grown over the years, but most of these approaches remain at the level of participatory data collection.

Key entry points concerning implementation research (IR) on AMR

Because we know that the environment is where most antimicrobial resistant bacteria take their origin, the world has a responsibility and an obligation to target most efforts and resources on mitigation, control and monitoring of AMR in the environment (soil, waters, air, living beings, etc.). Admittedly, there are many gaps and deficiencies in know-how for applying new, improved or existing methods and practices. Implementation Research (IR) can and must become the center-piece for providing more evidence-base for effective action in AMR. That is why it has to be strengthened in national and regional-level research teams, through support of implementing agencies and policymakers. There are indeed tools, interventions, strategies, policies, intersectoral engagement approaches that have already been shown to work. These should be scaled-up, monitored, and resourced. Lessons learned must be shared.

196 Quave C., (2016). Could Ancient Remedies Hold the Answer to the Looming Antibiotics. *The New York Times Magazine,* 12th September 2016 https://www.nytimes.com/2016/09/18/magazine/could-ancient-remedies-hold-the-answer-to-the-looming-antibiotics-crisis.html. Also, in this regard, Dozier R., (2019). Civil War-Era Plant Medicines Could Help Fight Drug-Resistant Bacteria, Study Finds. *Motherboard. Tech by Vice,* 23 May 2019, https://www.vice.com/en/article/kzmgqx/civil-war-era-plant-medicines-could-help-fight-drug-resistant-bacteria-study-finds.

197 Tan Y-R., Agrawal A., et al, (2022). A call for citizen science in pandemic preparedness and response: beyond data collection. *BMJ Global Health,* 10th June 2022, 2022;7:e009389.
https://gh.bmj.com/content/bmjgh/7/6/e009389.full.pdf

TRANSFORMATIVE POLICIES

Action on AMR Governance

Inroads apart, today's global governance setup for AMR deserves governments' serious consideration if effective national policies are to be encouraged and supported. Since the design is still in its making, bold government interventions are needed in the relevant international fora to:

- raise the conflict of interest dilemmas in the current scenario and advocate for their avoidance /solutions;
- call for the creation of one single body at the UN mandated with tackling AMR in all its intersectoral implications and manifestations - the inefficiencies of the current Quadripartite design, where individual agencies continue their silo work on the same problem, must be brought to the fore by UN Agencies' Member States. The fact that decisions need to be greenlighted by the four separate assemblies irremediably slows down and neutralizes meaningful AMR action at global level.
- challenge the multistakeholder governance paradigm in tackling AMR through concerted action at regional and global level; considering the pervasive corporate responsibility in spreading AMR, the required solutions cannot be mediated with those that have most contributed to the emergence of the crisis. Our current economic paradigm is a threat to ecological stability, and this has to change radically to avoid a catastrophe.

Action for One Health

Moreover, the One Health vision that the international community continues to advocate for, in view of preventing and responding to the next pandemics, calls for a set of ambitious yet doable plans, which include:

A moratorium on intensive factory farming. Ending this destructive food system is urgent, to safeguard animals, our climate, health and the environment. There should be no future for CAFOs and intensive livestock breeding, be it inland or in waters. Every year, factory farming condemns billions of animals to lives of cruelty and suffering for fast profits. Trapped in cages, mutilated and squashed together, pumped full of antibiotics to stay alive. The expansion of factory farming is a major driver of antimicrobial resistance with serious damage to the environment and human health. It must be stopped. Without large-scale imports of crops/ fish food, it would not be possible to produce billions of farmed animals each year at the cheapest possible cost. Combating AMR demands putting factory farming out to pasture - which would have to imply agroecological approaches to animal farming.

A conversion from industrial food systems to scaling up of agroecology. The AMR crisis gives evidence to the fact that time has come to abandon globalization's resource intensive and profit intensive economic food systems that have created havoc in the world, disrupting the planet's ecosystems and causing detrimental impacts on human and animal health. The root of the AMR problem is a growing dependence on a dysfunctional industrial agriculture model that relies on pesticides and economies of scale to accelerate the quantities of food produced, but at the expense of nutritional quality. Large-scale monocultures, genetically engineered crops, and intensive use of chemicals are major contributors to the ARM and climate crises - the outcome of fractured socioeconomic systems. Agroecology is the approach to agriculture that views crops and lands as ecosystems and is concerned with the ecological impact of agricultural practices. Agroecology based on biodiversity produces more food when measured in terms of nutrition per acre, and not in terms of yield per acre, taking into account relationships between different components of the agroecosystem including the human community. This is the way to go if the world is serious about fighting antimicrobial resistance!

Cut off funding to the factory farming industry. The supply and demand chain of cheap meat food produced in factory farming amounts to US$ 2 trillion[198]. Private financial institutions like banks, pension funds and insurance companies have trillions of dollars tied up in companies that are linked to factory farming, like animal producers, feed companies, supermarkets and restaurants. Over the past decade, the World Bank's International Finance Corporation (IFC) has pumped US$ 1.8 billion into major industrial livestock corporations around the world[199]. Development banks must stop funding factory farming. Instead, they should support and help expand truly sustainable farming projects with a focus on plant-based proteins and high animal welfare, that take into account the needs of animals, local communities and the environment. The UN Quadripartite must play a key role to this end.

Reconverting financial flows from the global agrifood system to agroecology. Based on the World Bank's assumptions that the world will need a 70 percent increase in global food production by 2050[200], the World Bank IFC continues its priority investments

198 https://www.worldanimalprotection.org/our-work/food-systems/sustainable-finance.

199 The largest share went to dairy companies ($686 million), followed by producers of pork ($563 million) and poultry products ($353 million). The remainder was lent to or invested in companies specializing in cattle production, fisheries, and livestock feed. See Mukpo A., (2020). World Bank's IFC pumped $ 1.8b into factory farming operations since 2010. *Mongabay.com*, Mongabay Series, Global Commodities, 7th July 2020, https://news.mongabay.com/2020/07/world-banks-ifc-pumped-1-8b-into-factory-farming-operations-since-2010/#:~:text=The%20IFC's%20largest%20investment%20into,for%20nine%20companies%20in%20China.

200 https://openknowledge.worldbank.org/handle/10986/21501.

in agribusiness for its "tremendous potential to enhance food security while creating opportunities and raising income for the world's poor". Boosting production and farmers' earnings is the driving force behind the IFC's US$15.8 billion investment in this sector in 2020[201]. But the global food system is a major contributor to anthropogenic global warming, responsible of 21-37 percent of annual emissions[202]. Investing in R&D for new antibiotics without at the same time divesting from agribusiness is a stark contradiction. Development banks and regional / national institutions must reorient their investment policies towards agroecology and One Health with no hesitation. The UN agencies concerned with AMR must steer this effort in the international development circles building on the wealth of scientific evidence.

Climate change and AMR act as an accelerant to many of our social ills (inequality, diseases, violence) but they can also be an accelerant for the opposite. By presenting our species with an existential threat, they might just be the catalyst the world needs.

We all need to mobilize to avert what Cameroonian philosopher Achille Mbembe calls the longstanding practice of necropolitics[203].

We collectively need to reaffirm the universal right to breathe[204].

201 https://www.ifc.org/wps/wcm/connect/industry_ext_content/ifc_external_corporate_site/agribusiness/priorities/enhancing+food+security/agri_priorities_food+security.

202 Mbow C., Rosenzweig C., et al., (2019). Food Security. In *Climate Change Land: An IPCC Special Report on Climate Change, Desertification, Land Degredation, Sustainable Land Management, Food Security, Greenhouse Gas Fluxes in Terrestrial Ecosystems*,Retrieved from https://policycommons.net/artifacts/458644/food-security/1431487/.

203 Mbembe, A., (2019). Necropolitics. Octobre 2019. Duke University Press.

204 Mbembe A.,(2021). The Universal Right to Breathe. In *Critical Enquiry*, January 2021, DOI: 10.1086/711437.

ABOUT US

The **Society for International Development (SID)** is an international network of individuals and organizations founded in 1957 to promote socio-economic justice and foster democratic participation in the development process. It celebrates its 65th anniversary in 2022. Through programmes and activities at national, regional and global levels, SID strengthens collective knowledge and action on people-centered development strategies and promotes policy change towards inclusiveness, equity and sustainability. SID has approx. 3,000 members and works with local chapters, institutional members and partner organizations in more than 50 countries. SID's activities are facilitated by an International Secretariat with offices in Rome (headquarters) and Nairobi. The Development Journal (published by Palgrave Macmillan) has been SID's flagship publication for 65 years and enjoys broad readership within the development community.

The **AMR Think-Do-Tank**, Geneva International, is an expert group on antimicrobial resistance (AMR). Its objectives are to ensure a better response to AMR through consulting, symposia, meetings, implementation research such as in Africa, publications and online courses on AMR, with a clear focus on the One Health approach. Its scientific board includes 50+ world-experts on AMR from more than 20 countries, with active participation in Asia and Africa.

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