Antibiotics and Antibiotic Resistance All Around Us

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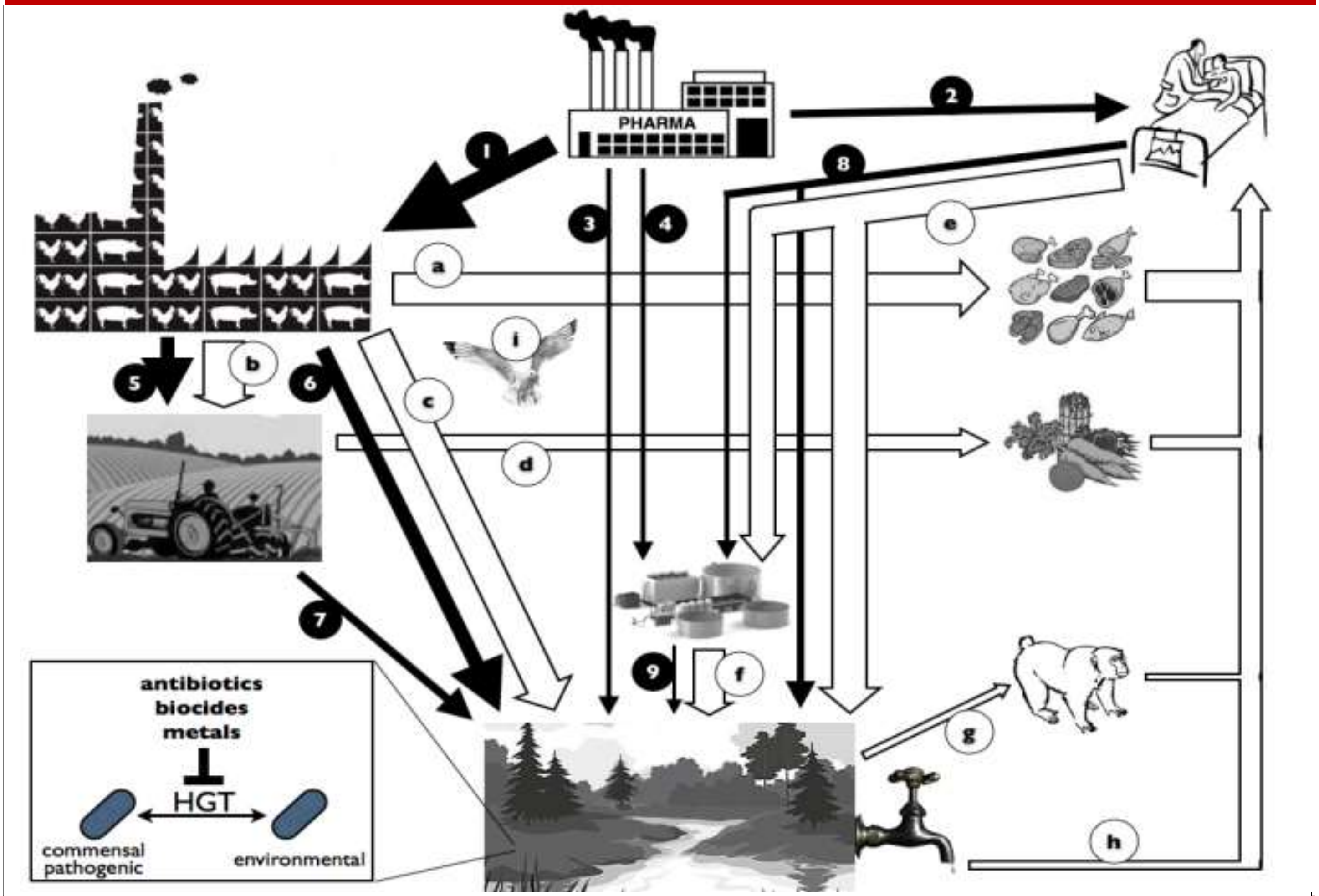
Today, we are experiencing a boom in news on the antibiotic resistance crisis. APUA was founded 35 years ago in response to emerging and rising resistance. In 1994, the notable magazines *Time* and *Newsweek* devoted their covers to the growing resistance threat. But it was not until the current century that a rather curious surge in interest occurred—fueled by the WHO, the USA and EU CDCs, and the White House, among others (a UN General Assembly high-level meeting on antibiotics was scheduled this September[1]). In particular, two multi-resistant organisms triggered this response: first, the so-called "methicillin resistant *Staphylococcus aureus*" (MRSA), especially in the USA; and secondly, the "carbapenem-resistant entero-bacteria" (CRE). More recently, the discovery of a new colistin resistance determinant, although not yet linked to clinical failure of this "last resort" antibiotic, set a scary perspective. While useful in acting as triggers of global responses, these infamous organisms obscure the much graver background of gradually increasing resistance that is emerging in everyday pathogens, and has led to an estimated 700,000 annual deaths worldwide.[2] Furthermore, the causes and consequences of resistance escape the clinical setting. Clinical abuse of antibiotics is not the only – perhaps not even the most important – cause of resistance; and increased morbidity and mortality of infections are not the only consequences.

"In the end, most of the approximately 100,000 tons of antibiotics produced annually worldwide end up polluting the environment.[4]"

Clinical abuse of antibiotics is rampant. Antibiotics used when not needed, coupled with poor choices of drug or dosing, amount to around 50% of medical prescriptions. Ubiquitous self-prescriptions, ranging from 3% in some European countries, to 100% in a couple of African countries[3] (a 35% crude average), may be wrong much more often; but even considering *all* self-prescriptions to be wrong, such abuse would amount to about the same as wrong medical prescriptions. Reduction in the clinical abuse of antibiotics is urgently and globally needed, both by improving medical prescriptions and suppressing self-prescription, Nonetheless, the overall impact will be almost negligible in terms of antibiotic amounts. Approximately 70% (on weight basis) of all antibiotics produced in the U.S. are used in agriculture. Even if all self-prescription and wrong medical usage is reduced to zero, there would only be a 20% reduction in total antibiotic use (25% at best, if considering a 63/37 ratio of agricultural/clinical antibiotic use worldwide).[4] To significantly curb the growing resistance trend, a much more substantial reduction in antibiotic usage is needed.

Except for the therapeutic use of antibiotics on sick animals, all other agricultural usage is morally indefensible. Jeopardizing the health and lives of people to save money in the growing of food animals is simply unacceptable. Resistant organisms are selected in those food animals that ultimately become our foodstuffs and reach our kitchens, causing resistant infections, and/or mobilizing resistance genes to other pathogenic bacteria. But that is just the "tip of the iceberg". Tons of manure from antibiotic-fed animals (containing active antibiotics and resistant bacteria) are spread as fertilizer, polluting soils and vegetables; and thousands of pounds of

Figure 1. Antibiotics and Resistance All Around Us: A Graphic



(Antibiotics - filled arrows; resistant bacteria - open arrows.) Pharmaceutical companies worldwide produce ~100,000 tons of antibiotics per year. Most (63-70%) are used in agriculture and aquaculture **(1)**, while only 30-37% are used in humans **(2)**—both hospitalized or as outpatients. A small amount of active by-products is released to wastewater, either directly into the environment **(3)** or to treatment plants **(4)**. Unmetabolized antibiotics are excreted by antibiotic-fed animals, and end up in manure used as fertilizer **(5)** or as liquid or solid waste dumped into the environment **(6)**. Antibiotics from manure leach into deeper soils and water bodies **(7)**. Unmetabolized antibiotics are also excreted by human patients. In cities, where the majority now live, these drugs end up in the sewage, **(8)** which is dumped directly into water bodies (in developing countries) or into wastewater treatment plants. While few antibiotics survive the treatment processes, some do and are released into water bodies, or persist within sludges that are also dumped **(9)** or used as fertilizer. The bacterial aspects are also complex. Resistant bacteria are selected within antibiotic-fed animals and contaminate their meat **(a)**, while also being released in their feces and spread as fertilizer **(b)** or dumped along with other waste into the environment **(c)**. Vegetables grown on manured soils **(d)** also carry resistant bacteria. People themselves,both, treated and untreated, release enormous amounts of resistant bacteria within feces, that end up in the sewage of cities **(e)**, which is mostly dumped directly, or fed into wastewater treatment plants. While wastewater treatment reduces the overall bacterial load, surviving organisms are the result of intense gene exchange within sludges under many selective pressures, making them particularly resistant **(f)**. Resistant bacteria in soils and waters colonize wildlife **(g)**, and some can even find their way into tap water **(h)**. Birds **(i)** may play a particular role in dispersing resistant bacteria since they feed in many of these different settings and are airborne. The result of releasing bacteria that have been under the effects of high concentrations of antibiotics is not only the direct risk of acquiring a resistant infection. Commensal and pathogenic bacteria (box, bottom left)—loaded loaded with resistance, virulence and mobility genes—come into close contact with environmental bacteria that are often innocuous, but carry ancient resistance genes. Horizontal gene transfer (HGT) can easily ensue, under the selective pressure of antibiotics, other biocides and heavy metals, that are released into the environment due to human activities.

antibiotics are directly applied to water bodies used for aquaculture. This is of course in addition to the un-metabolized antibiotics released by treated patients; the disposal of unused antibiotic pills and solutions from homes and hospitals; and the release of antibiotic by-products by pharmaceutical factories—all going into wastewater and landfills. In the end, most of the approximately 100,000 tons of antibiotics produced annually worldwide end up polluting the environment.[4] At dumping sites, antibiotics reach concentrations above clinical MICs (*e.g.*, in hospital sewage, or in rivers downstream of pharmaceutical factories). They subsequently dilute to sub-MIC levels, which are generally disregarded. However, such "sub-inhibitory" concentrations can still exert effects upon soil and water microbiotas, either alone or along with other human-released biocides. For example, herbicides that lower the bacterial susceptibility to some antibiotics[5] could potentially turn sub-MIC quantities into effective selective pressures. All this environmental disturbance can select for ancient resistance genes in environmental bacteria and promote their mobilization into pathogens. This is presumably what happened with the CTX-M extended-spectrum beta-lactamases and the *qnr* plasmid-bearing quinolone resistance genes. Environmental contaminants can also alter the composition of soil microbiota in unpredictable ways and could affect many geo-biological processes that depend upon soil bacteria.[4]

Along with antibiotics, resistant bacteria are released at staggering amounts into all environments, urban and rural. Resistant bacteria may often also bear dangerous mobile genetic elements (*i.e.*, plasmids, ICEs [integrative and conjugative elements], transposons, integrons, gene cassettes, etc.), which allow the transfer of resistance genes horizontally to other microbes,--enabling the mobilization of ancient resistance determinants. Resistant bacteria that are selected within treated patients and within antibiotic-fed animals are released in their feces into water bodies, either directly (as in most rural and developing-country settings), or after the particularly pernicious process of concentration, gene-rearrangement and selection that occurs at wastewater treatment plants.[4] Open-air fecalism and sewage-disposal contributes to the significant levels of resistant bacteria from urban dust in developing countries. Likewise, airborne animals, especially birds, can mobilize resistant bacteria, including transport from countries that use antibiotics agriculturally into those that have banned such practices.[6] It can be argued that the overall impact of such a release is irrelevant, since resistant bacteria are already much more abundant in clinical settings, and antibiotics would not play a role in a hypothetical outbreak caused by resistant organisms in wild animals. But the ecological impact of the release of resistance and mobility traits into soil and aquatic microbiotas that are also tainted with antibiotics, other biocides and heavy metals, is nearly impossible to assess. In addition, resistant bacteria are frequently reported in wildlife. The health impact upon affected wild animals, and the risk of concocting a modified strain capable of infecting humans and of resisting multiple antibiotics should not be overlooked.[4]

One of the many measures proposed to confront the resistance problem is to create or increase public awareness.[1,7] But this must go far beyond the notions of restraining the urge to get an antibiotic prescription from a physician, and avoiding self-prescription. It is vital that people realize the many aspects of this serious health threat so that they can organize and exert pressure to stop the global abuse of antibiotics.[8] Governments worldwide have been largely negligent, and international organizations (*e.g.*, UN, WHO, FAO) that depend on government cooperation have their hands tied. Only the organized response of societies worldwide can act against the trans-national threat posed by antibiotic resistant pathogens.

References

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References continued on p. 13