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FACING ANTIMICROBIAL RESISTANCE AND STRENGTHENING THE IMMUNE SYSTEM: ONLINE INFORMATIVE AND EDUCATIONAL RESOURCES[1]

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Abstract:
The article presents informative and educational documents downloadable for free from the internet that consist of text, graphs, images, videos and a comic book. They can also be used in the school for teaching units. *According to the World Health Organisation, antimicrobial resistance is among the top 10 global public health threats*. Resistance to antimicrobials, which include antibiotics, antivirals, antifungals and antiparasitics, results in the loss of their efficacy. In fact, germs that have antibiotic-resistance traits in their DNA can survive a treatment and reproduce, which leads to resistant strains. Antibiotics are often *overprescribed, overused and misused.* This contributes to accelerating the emergence of antimicrobial resistance, which results in prolonged illness, the need for more expensive and intensive care, and even disability or death. Hygiene and vaccines may reduce infections and consequent antibiotic use, while a healthy diet, physical activity, forest visits, yoga, qigong and other techniques may strengthen the immune system. Environmental release of antibiotics from urban sewage systems, hospitals, farms and the pharmaceutical industry may contribute to antibiotic resistance. The pharmaceutical industry can be encouraged to drive the change through labels that ensure compliance with standards for responsible production. Some documents report the results obtained in countries where antimicrobial resistance has been tackled in human and animal farming sectors. By 2050, inaction may result in 10 million deaths yearly and a cumulative cost of 100 trillion $US. The "One health" approach is a worldwide accepted concept by which the health of humans, animals and the environment are interconnected and interdependent. Several documents deal with the links between biodiversity loss and increased infection risk for humans. A war may intensify the problem as a consequence of, e.g. lack of hygiene, overcrowding and hindered contact tracing.

[1] FRONTEGGIARE LA RESISTENZA AGLI ANTIMICROBICI E RINFORZARE IL SISTEMA IMMUNITARIO: RISORSE EDUCATIVE ED INFORMATIVE IN RETE

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Keywords: online educational resources, antibiotic overuse, antimicrobial resistance, hygiene, strengthen the immune system, healthy environment

Riassunto:
L'articolo presenta documenti informativi ed educativi scaricabili gratuitamente da internet che consistono in testi, grafici, immagini, video ed un fumetto. Il testo è basato esclusivamente sui suddetti documenti, che possono essere utilizzati per attività didattiche. Secondo l'Organizzazione Mondiale della Sanità, l'antimicrobico-resistenza è tra le prime 10 minacce per la salute pubblica globale. La resistenza agli antimicrobici, tra i quali sono compresi antibiotici, antivirali, antimicotici e antiparassitari, provoca la perdita della loro efficacia. Germi con caratteristiche genetiche che li rendono resistenti agli antibiotici possono sopravvivere a un trattamento e riprodursi; ciò porta alla formazione di ceppi resistenti. Gli antibiotici sono spesso prescritti con molta facilità, usati eccessivamente e male. Ciò contribuisce ad accelerare l'emergere della resistenza antimicrobica, che si traduce in malattie prolungate, necessità di cure più costose e intensive, persino disabilità o morte. Igiene e vaccini possono ridurre le infezioni e il conseguente uso di antibiotici; sana alimentazione, attività fisica, passeggiate nei boschi, yoga, qigong e altre tecniche possono rafforzare il sistema immunitario. Antibiotici provenienti da reti fognarie urbane, ospedali, fattorie e industrie farmaceutiche possono contribuire all'antibiotico-resistenza. L'industria farmaceutica può essere incoraggiata a guidare il cambiamento attraverso marchi che garantiscono una produzione rispettosa dell'ambiente. Alcuni documenti riportano i risultati ottenuti in paesi ove l'antimicrobico-resistenza è stata affrontata con successo, sia nel settore umano che nell'allevamento animale. Entro il 2050, in mancanza di iniziative utili, si prevedono 10 milioni di decessi l'anno e un costo cumulativo di 100 trilioni di dollari USA. L'approccio "One health" è un concetto accettato a livello mondiale in base al quale la salute degli esseri umani, degli animali e dell'ambiente sono interconnessi e interdipendenti. Vari documenti trattano i legami tra la perdita di biodiversità e l'aumento del rischio di infezioni per l'uomo. Le guerre possono intensificare il problema a causa di mancanza di igiene, sovraffollamento ed un tracciamento dei contatti ostacolato.

Parole chiave: risorse educative online, uso eccessivo di antibiotici, resistenza antimicrobica, igiene, rinforzare il sistema immunitario, ambiente salubre.

1. Aims of the teaching unit

The article is aimed at increasing knowledge and awareness of the importance of the correct use of antimicrobials, and of a healthy lifestyle that strengthens the immune system and reduces the risk of infections and the need for drugs. Social stability and the conservation of ecosystems are also of paramount importance.

2. Materials and methods

The paper presents informative and educational resources downloadable for free from the internet; they consist of text, videos, graphs, images and a comic book. This article, unless otherwise stated, is exclusively based on the quoted documents.

The documents can be used by teachers with the method felt as most appropriate.

3. Introduction

According to the World Health Organisation, antimicrobial resistance (AMR) is among the top 10 global public health threats facing humanity (1). As a consequence of AMR, antimicrobials, which include antibiotics, antivirals, antifungals and antiparasitics, over time, lose their efficacy. This may imply, prolonged illness, the need for more expensive and intensive care (2 fig. 1), and sometimes disability or death. Antibiotics are the most commonly prescribed medicines in the world (3). Many medical procedures, e.g. surgery, cancer chemotherapy, dialysis treatment, organ transplantation, treatment of diabetes, asthma and rheumatoid arthritis are dependent on effective antibiotics (1 / 4 > About Antibiotic Resistance / 5 page 24).

Such treatments, especially when combined with a weakened immune system often consequent to the treatment itself, increase the risk of infections. The lack of effective antibiotics makes recovery difficult and is, sometimes life-threatening (5).

Antibiotic-resistant infections may require prolonged recovery and the use of second- or third-line treatments, these latter can be harmful to patients because of side effects. For instance, the prescription of colistin has been discontinued for many years since it *may cause kidney failure*; now this medicine is back in use as a *last option* in countering resistant gram-negative bacterial infections (6).

Sometimes, there are no treatment options available for resistant infections (6).

In 2019, an estimated 4.95 million deaths were associated with bacterial AMR, of which 1.27 million were directly attributable to drug resistance (7).

According to "Tackling Drug-Resistant Infections Globally: Final Report and Recommendations", *by 2050, inaction may result in 10 million deaths yearly and a cumulative cost of 100 trillion $US* (6 graph page 11).

According to a World Health Organisation document, the world must act and invest now to address AMR, or pay far more in the future (8).

According to a World Bank document, a successful containment of AMR can benefit all countries, while inaction may harm all countries and result in a *GDP reduction between 1.1% and 3.8% by 2050* (2 page 56).

4. How AMR spreads

Antibiotics save lives, but *their use pressures bacteria and fungi to adapt; consequently, germs having antibiotic resistance (ABR) traits in their DNA can survive and multiply* (4 > About

Antibiotic Resistance / 9 video). A table and an image provide a few examples of the defense strategies that germs use against antibiotics (4 > About Antibiotic Resistance).

The genes for resistance can be shared with other germs not previously exposed to antibiotics. An image shows how ABR moves directly from germ to germ (4 > About Antibiotic Resistance).

A document deals with resistance mechanisms (10 from page 21).

A document provides explanations and images on AMR (11).

The World Health Organisation provides several educational infographics on AMR (12).

A comic book (13) and an animation (9) deal with antibiotic resistance.

In health care facilities, during or after surgery, using catheters or ventilators, patients can get serious infections, sometimes antibiotic resistant. An image and explanations help to better understand (4 > Where Resistance Spreads).

Resistant infections, in the past associated with healthcare facilities, now are also seen in the wider community (6).

Antibiotic resistance (ABR) can spread in the community, from food to people or between people and animals. ABR can easily spread across the world when people travel and/or receive care in another country (4 > Where Resistance Spreads / 4 > About Antibiotic Resistance).

Page 14 (5) shows how ABR occurs and provides examples of how it spreads. ABR is globally reaching high levels; it occurs naturally in bacteria, but misuse of antibiotics accelerates the process (14 graph). In countries without standard treatment guidelines, antibiotics are likely to be overprescribed by doctors and veterinarians, and over-used by people.

In countries where antibiotics can be bought without a prescription, the situation is even worse; internet sales further amplify the problem (1 > Antibiotic resistance / 6 / 3). When patients bypass clinicians and diagnostics, they may *purchase antibiotics clinically not appropriate*. Furthermore, in many countries, private-sector healthcare providers and pharmacies may *recommend prolonged antibiotic therapy for economic rather than for clinical reasons* (3).

Antibiotics do not work against viral diseases, such as cold, flu and COVID-19 (4 > About Antibiotic Resistance).

Diarrhoeal illness causes 1.1 million deaths per year and is frequently treated with antibiotics despite the fact that as many as 70% of the cases are caused by viruses, against which the antibiotic is ineffective (6).

A graph (6 page 36) shows the proportion of people that use antibiotics unnecessarily for respiratory issues in the US.

In immunocompromised patients, ongoing viral replication and long-lasting drug exposure create the conditions for the selection of resistant strains. Patients that receive the antiretroviral therapy can acquire drug-resistant HIV or, people can be directly infected with HIV that is already drug-resistant. The World Health Organisation

recommends the substitution of a new drug for the former, now ineffective in more than 50% of the infants newly diagnosed with a drug-resistant strain of HIV (1).

According to "The State of the World's Antibiotics 2021", AMR has reached epidemic proportions, while remaining out of sight for most of the general population (3). AMR is quickly emerging for pathogens causing HIV, malaria and typhoid fever, which threatens the progress in their control.

In UK, for instance, carbapenem resistant E. coli more than doubled between 2008 and 2013 (6).

Appendix 1 (3) provides, a lot of information, including both AMR and antimicrobial use by country. Appendix 3 provides information sources for some indicators, for instance, a UNICEF document on the proportion of the population using improved drinking water sources.

Figure 2 (3) shows the Drug Resistance Index across countries. A higher index reveals where AMR poses a more significant problem. In low and middle-income countries, a high Drug Resistance Index may depend on a low level of antibiotic effectiveness consequent to limited access to newer and more effective antibiotics. Figure 3 shows the increase in antibiotic use between 2000 and 2015 in some countries.

4.1 Tackling AMR in humans

Antibiotics save lives, and more people die for lack of access to antimicrobials than for AMR; this is particularly true in the majority of low- and middle-income countries. For this reason, global efforts and coordination should be aimed at mitigating AMR, while providing access to antimicrobials clinically appropriate and affordable for all (6 / 3 / 1 >Children's immature immune systems threatened by increasing 'superbugs').

A document provides tips aimed at preventing the spread of ABR for individuals, policymakers, health professionals, the healthcare industry, and the agriculture sector (1 > Antibiotic resistance).

Contact tracing consists in tracking individuals who are infected and people who have been in contact with them that, in turn, are at risk of infection. Implementing this strategy is resource intensive, but it has proven successful in limiting the transmission of several infections (5).

The spread of infections can be reduced, for instance through personal and food hygiene, and safer sex (4 > Where Resistance Spreads).

A common experience is the use of masks to slow the spread of Covid-19, as often recommended by health authorities.

Vaccination, investments in water, sanitation and hygiene infrastructure are among the most cost-effective means aimed at reducing the burden of infectious diseases and the need of antibiotic treatment (3 / 6).

According to a study that involved India, Indonesia, Brazil and Nigeria, nearly 500 million courses of antibiotics per year are used to treat diarrhoea, while universal access to safe water and sanitation could prevent 60% of this burden (6).

In developed countries, as many as 7-10% of all hospital inpatients, and one out of three among those admitted in intensive care units, can catch a healthcare-associated infection. The situation can be even worse in countries where healthcare facilities suffer serious constraints. The single most effective, and simple, rule in the prevention is hand hygiene of the clinicians, but it is not strictly observed (6).

The implementation of antimicrobial stewardship in health facilities is essential (3). *A rapid diagnostic test* may help doctors in understanding whether a patient has an infection and if this latter is viral or bacterial, thus prescribing the most appropriate medicine, and only if really needed (6).

An educational document (15) deals with a *test aimed at determining which antibiotic is more effective against the microorganism of interest*; an image visually easy to understand compares the effectiveness of different antibiotics. A video shows how the test is carried out in the laboratory (16).

According to the Swedish government, between 2009 and 2017, the number of antibiotic prescriptions filled per year fell by about one million without apparent adverse effects on the population (17).

A document describes the steps aimed at improving antibiotics use in Sweden, and the lessons learnt. When *large and unexplained differences between geographical areas and clinics became easily available to everybody*, a strong interest was generated, which led to interventions that resulted in reduced antibiotic use (18 figure 1).

In Sweden, the government expects that the prescriptions, *regardless of the form of care*, are based on quality-assured and fast diagnostics aimed at preventing unnecessary and incorrect antibiotic use (17).

A report on ABR of the Centers for Disease Control and Prevention provides updates on improvements that result from prevention activities, additional actions needed to protect people, and challenges in healthcare and in the community (10 Executive Summary).

According to a World Health Organisation document, when taking antibiotics, the full treatment must always be completed even if we feel better, failing which the growth of antibiotic-resistant bacteria is promoted (19).

5. Discovery of new antibiotics and successful re-use of an old antibiotic

The rate of discovery of new antibiotics has fallen since the 1980s, for reasons that include a decline in investments in research (6 / 1).

In the past, gonorrhea was successfully treated with penicillin but in 2013, as a consequence of ABR, this antibiotic was effective in only 80% of gonorrhea cases. This means a probability of failure as high as 20%, which is considered too risky and makes other antibiotics preferable. *Conversely, a diagnostic for gonorrhea can inform about the cases where penicillin is effective and can be used.* This may reduce the selective pressure for resistance on the most recently used therapies, thus prolonging their effectiveness (6 page 39).

5.1 Antimicrobials and environment

Crops are sprayed from airplanes with pesticides that include antibiotics and fungicides *important in human medicine* (10 pages 13 and 20).

Antibiotics can reach the environment from urban sewage systems, hospitals, farms and especially from pharmaceutical industries. The consequent contamination of soil, crops and water may contribute to AMR (6).

In a river where active pharmacological ingredients were discharged, a study has found antibiotic concentration much higher than that which is routinely found in the blood of a patient taking the drug (6 page 30).

Globally, very few if any, standards and systematic monitoring of emissions of such substances exist. The authors recommend the introduction of regulatory standards. The pharmaceutical industry can be encouraged to drive the change, for instance, by creating an internationally recognised label that may ensure a production without environmental release of dangerous levels of antibiotics (6 pages 20 and 31).

Unused drugs are to be returned to pharmacies for a *correct waste management aimed at reducing their dissemination in the environment* (17).

5.2 Links between gut microbiota, food, antibiotic use and disease risks

"The Microbiota and Immune System Crosstalk in Health and Disease" deals with the influence that gut microbiota exerts on hormones and immune system function (20). A good balance in the gut microbiota is essential for our health. The profound change in gut microbiota composition consequent, for instance, to a high-fat diet is associated with several disorders such as obesity, diabetes, and metabolic syndrome.

Ultra-processed food may lead to a gut microbiome that promotes inflammatory diseases. Conversely, whole-plant food favours the growth of bacteria that degrade the fibre and produce beneficial metabolites (21 / 22).

According to the Harvard School of Public Health, diet plays an important role in determining what kinds of microbes live in our gut (22).

While targeting bacterial pathogens, antibiotics may also induce disturbances of the microbiota, which can result in the development of chronic autoimmune conditions (23).

According to "Antibiotic use and its consequences for the normal microbiome", the worldwide use of large amounts of antibiotics is also based on the perception, among health professionals and public, that antibiotic use is nearly safe. In contrast, according to a growing body of evidence, *antibiotic exposure in young children* is associated with an increased risk of several diseases that include obesity, diabetes, allergies, celiac disease and asthma (24).

A study has found a link between prenatal exposure to antibiotics and low birth weight (25).

A UK study has found a 60% higher probability of developing rheumatoid arthritis in people exposed than in not exposed to antibiotics. Further studies are necessary in order to better understand whether this is consequent to microbiota

disturbances or to infection (23). Interestingly, however, while *people with antibiotic-treated upper-respiratory tract infection developed rheumatoid arthritis*, this association was not observed in the untreated cases.

According to "Oral antibiotic use and chronic disease: long-term health impact beyond antimicrobial resistance and *Clostridioides difficile*" (25), *oral antibiotic use is associated with increased risk of colon cancer*, while higher exposures are linked to significantly larger effects. Table 1 (25) summarises previous studies on antibiotic-cancer associations, table 2 deals with selected studies on the associations of antibiotic exposure and chronic disease.

Page 25-26 (5) deal with adverse drug events associated with antibiotics. For instance, these latter may imply allergic reactions, or interfere with other drugs that the patient is already taking for another condition. Any patient having a side effect from antibiotics should immediately communicate it to the doctor. Furthermore, scientists are also learning that even other drugs, such as metformin, have important effects on microbial populations (24).

According to the authors, the impact on the microbiota of intravenous antibiotic use is not yet understood (25). It is hypothesised that antibiotic courses may lead to the loss of microorganism species of our microbiome, probably including some that may have important metabolic functions (24 / 4 > About Antibiotic Resistance). Since most of the microbiome is inherited from the mother, such losses are cumulative across generations (24).

The decline in microbiota diversity was observed in the US earlier than in countries where modernisation, including drinking water chlorination and antibiotic use, began later (24 Figure 1).

Water chlorination provides *immense health benefits*; yet, the potential disturbance to the infant microbiome consequent to the microbicidal properties of chlorine has to be investigated. The Australian infant feeding guidelines recommend the use of tap water previously boiled; the removal of residual chlorine prevents significant exposure during a sensitive period in life (26).

The document discusses health risks associated with the trihalomethanes formed from the reaction between chlorine and natural organic material found in water supplies (26).

According to the author, *we may need to recover, in our microbiome, the diversity that has been lost*. This is an important scientific frontier that requires a lot of research.

5.3 Boosting the immune system: a healthy diet may help in fighting infection

According to "How to boost your immune system", much remains to be understood about the necessary conditions for getting the best from our immune system. However, according to this document of the Harvard Medical School, *balance and harmony are essential for its functioning* (27).

Poor diet and malnutrition may affect immunity; a good regular nourishment is essential for a strong immune system. *Micronutrient malnutrition* is surprisingly common

in the elderly, even in affluent countries; older people should discuss it with their doctor (27).

According to "Undernutrition, infection and immune function", *vitamin A, iron, zinc and copper are nutrients of central importance for an efficient immune system* (28). Low birth weight is often associated with deficiencies in important nutrients and with increased disease risks.

To protect the human body from pathogens, the skin surface, as well as the linings of gastro-oesophageal, genitourinary and gastrointestinal tracts should be intact. The cells constituting these parts of the body produce protective substances, and a *good nutritional status is essential in maintaining their activity and functions, that include protection from infections. Even the production of, e.g. immunoglobulins and cytokines requires a sufficient protein intake* (28).

"How much protein do you need every day?" provides some tips on protein intake (29).

According to the document (28), breast-feeding in infants plays an important role thanks to the protective substances that human milk contains.

A document, rich with links and available in multiple languages, deals with healthy diet (30 / 30 > My plate tool). A special attention is dedicated, inter alia, to risks and benefits of alcohol.

A document of the Harvard School of Public Health deals with nutrition and immunity; several links help to expand the knowledge on the subject (22).

While inflammation is an important step in the immune response, the low-grade chronic inflammation associated with obesity can lead to tissue damage and overwhelm the immune system (22).

Among the factors that can depress our immune system are smoke, air pollution and excessive alcohol consumption (22).

Among the nutrients identified as critical for growth and function of immune cells are vitamin C, vitamin D, zinc, selenium, iron, and protein. Our immune response can be altered by the deficiency of single nutrients. Diets limited in variety and low in nutrients, such as a diet based primarily on ultra-processed foods high in refined sugars and red meat, low in fruit and vegetables, may have a negative influence on the immune system (22).

A good quality diet can prevent nutrient deficiencies, while in particular situations, vitamin and mineral supplement may help to fill nutritional gaps (22). In the final part of the document the reader can explore the links found in the image of "Healthy Eating Plate".

A document of the National Institutes of Health entitled "Nutrient Recommendations: Dietary Reference Intakes" can be used for an in-depth study (31).

A FAO document, entitled "Food-based dietary guidelines" provides information for more than 100 countries, often in the *local language, adapted to nutrition situation, culinary cultures and eating habits* (32).

5.4 Managing chronic stress: yoga, qigong and tai chi

Sleep is important; in fact, during this time a cytokine is released that fights infection. Conversely, chronic mental stress is involved in the release of cortisol, which suppresses the inflammation initially needed in the activation of immune cells, and the action of white blood cells (22).

Social support, such as positive relationships with family and friends, helps to sustain people at times of chronic stress (33).

The stress response may suppress the immune system, which can imply an increased susceptibility to cold and other illnesses. Inter alia, chronic stress can contribute to the development of high blood pressure, which is an important risk factor for heart disease (34 / 34 > Learn More).

We cannot avoid chronic stress, but we can develop healthy ways to respond to it. Several relaxation techniques and a video may help us to reach a state of profound rest (34 / 34 > relaxation response / 22 > short mindful breathing exercise - Video).

Deep breathing may help us to disengage the mind from distracting thoughts and sensations, while practicing progressive muscle relaxation. Qigong and yoga may also help us and improve our flexibility and balance (34 > relaxation response). Yoga, tai chi and qigong induce calm (33).

According to a review, tai chi and qigong are recommended as a health intervention aimed at strengthening the immune system (35).

According to "Yoga and immune system functioning: a systematic review of randomized controlled trials" (36), although the scientific evidence is not yet completely consistent, this practice can down-regulate pro-inflammatory markers. Yoga provides further beneficial effects regarding cell-mediated and mucosal immunity and, differently from pharmacological therapies, has no side effects and can be implemented as a complementary intervention.

Table 1 (36) summarises characteristics and findings of the randomised controlled trials included in the review. Further studies are necessary in order to establish whether the practice of yoga, carried on for a longer time, may provide more consistent results.

5.5 Physical activity and immune system

Exercising or walking, shortly after feeling stressed, may contribute to relieve muscle tension (33).

Physical activity and healthy diet are beneficial for the organism and contribute to a healthy immune system (27).

According to "Physical Activity Guidelines for Americans 2nd Edition", for instance, adults should practice 150 to 300 minutes per week of moderate physical activity, preferably spread throughout the week. A more prolonged activity may provide additional benefits (37 page 56).

For school-aged youth, between 6 and 17, at least one hour of moderate-to-vigorous physical activity daily is recommended. The physical activity should include aerobic, muscle strengthening and bone-strengthening exercise (37 page 48).

The document, also deals with particular situations, such as physical activity in relation with chronic health conditions, disabilities, older age and pregnancy (37).

Similar guidelines have been promoted in many countries with a strong expectation of a *wide range of health benefits, that include improved immune function*. According to "Physical inactivity is associated with a higher risk for severe COVID-19 outcomes: a study in 48440 adult patients", inactive people, compared to those that consistently meet the guidelines, had a higher risk of hospitalisation, admission to intensive care unit, and death. The related odds ratios observed are, respectively, 2.26 – 1.73 – 2.49 (38).

While a moderate physical activity may lower the incidence of infection, prolonged bouts of strenuous exercise may lead to depression of the immune function, which generally lasts 3-24 hours. Whereas, after a prolonged strenuous activity, this immune dysfunction may last even longer (39).

5.6 Effect of natural environments on our immune system

Humans have evolved spending more than 99.99% of their time in natural environments, *which implies that our functions are best adapted to natural settings rather than to modern, built-up environment* (40). Nature therapy may boost our weakened immune function through the exposure to natural stimuli and consequent physiological relaxation.

According to "Physiological Effects of Nature Therapy: A Review of the Research in Japan" (40), visiting a forest lowers pulse rate, blood pressure and salivary cortisol level; this latter is a marker of stress hormone. A boosting effect on immune functions has been demonstrated after forest therapy.

An US document summarises the quantifiable health benefits, both mental and physical, associated with forest visiting. Many benefits are provided by airborne substances emitted by the plants, the phytoncides, that we breathe in the forest (41).

Among other beneficial health effects, a Chinese study has found a better feeling of comfort in subjects exposed to forest environments than in those exposed to urban environments (42 graph in fig. 4). As shown in fig. 3, the subjects exposed to a forest environment also exhibited a significantly lower serum cortisol concentration; this latter is a stress marker.

The yards of some Finnish urban daycare centres have been modified covering part of the gravel with forest floor, sod, planters for growing annuals, and peat blocks for climbing and digging (43). During the 28-day experiment, with children spending an average 1.5 hours outdoors, changes in skin and gut microbiota were observed, which were accompanied by changes in the immune system. According to the authors, this kind of intervention may have a prophylactic function in reducing the risk of immune-mediated diseases in urban societies (43).

6. The "One Health" concept and the importance of ecosystem conservation

"One Health" is a worldwide accepted concept by which the health of humans, animals and environment are interconnected and interdependent (44). For instance, as many as 75% of emerging human pathogens are of animal origin.

Two videos deal with the One Health concept (45 / 44 > What is One Health? From concept to action).

A review deals with the enormous possibilities that forests provide in promoting human health and, at the same time, warns of the risks associated with ecosystem degradation. In fact, *biodiversity loss, deforestation and climate change can be linked to the emergence of some infectious diseases* (46).

Some US documents presented hereafter deal with Lyme disease, and may help to understand more in depth the concept. Notoriously, this bacterial disease is transmitted to humans by ticks previously infected when taking a blood meal from infected hosts.
According to "The ecology of infectious disease: Effect of host diversity and community composition on Lyme disease risk", the *ubiquitous white-footed mouse* is the animal, whose parasitisation results in the highest percentage of infected ticks. In a biodiversity-rich habitat, thanks to less infective hosts found in abundance, the percentage of infected ticks is low; this is called "dilution effect" (47).

In biodiversity-rich environments several animals can eliminate mouse and ticks; whereas in fragmented forests, as a consequence of low animal diversity, the white-footed mouse has less enemies and is more abundant (48).

In the US, forest destruction and fragmentation reduced mammalian diversity, while increasing the population density of the white-footed mouse and human exposure to Lyme disease. *A higher percentage of infected ticks and a nymph density 3 times higher have been observed in smaller than in larger forest fragments* (49 fig. 1C).

According to "Increase in Lyme disease mirrors drop in red fox numbers", a greater number of red foxes would have consumed larger amounts of the small mammals that transmit Lyme disease to ticks. The decline of red fox is attributed to growing populations of coyotes, now top predators replacing wolves and mountain lions extinct. In fact, the coyote exhibits a strong attitude to killing foxes, to such an extent that these latter give up building dens when there are coyotes around (50).

7. AMR in animals

Antimicrobial use in animals is nearly three times higher than in humans, and is rapidly increasing as a consequence of the enormous growth in human consumption of animal proteins. Antibiotics are not only used against infections, but also for promoting a faster growth in animal farming (3).

"Stop using antibiotics in healthy animals to prevent the spread of antibiotic resistance" is a World Health Organisation document whose key message is summarised by the title (51).

According to studies, 75-90 percent of antibiotics are excreted from animals unmetabolised, thus entering the sewage systems and water courses (6).

The use as fertiliser of untreated or un-composted animal manure, from animals that have been given antibiotics, can contribute to spreading in soil and water antibiotic residues and resistant germs (4 > Where Resistance Spreads).

A document provides information on the good practices aimed at increasing the animals' ability to withstand disease, and biosecurity measures that can be taken to prevent introduction and spread of infectious agents (18 > Food animals> Prevent Infection> Food animals).

In Sweden, antibiotics have not been used as a growth promoter since 1984 and, over time, there has been a strong decrease in group treatment. Figure 4 (17) shows the decrease in the sales of antibiotics used for animal farming; in this country, notifiable resistant bacteria are not common.

According to "What has been done to minimize the use of antibacterial and anti parasitic drugs in Norwegian agriculture?", in the fish farms of this country between 1987 and 2011, the *annual consumption of antibacterial drugs has decreased from 48 to 1 tonne* (52). Figure 1 shows the increase in vaccine use and the simultaneous decrease in antibiotic use.

In Norway, the *water constitutes a major route of Infectious Salmon Anaemia transmission to fish farmed in the net pens in the sea*. This may occur through sediments or infected escapees, or vectors belonging to the local fauna (52 / 53).

A distance of at least 5 km between aquaculture units where the fish are farmed is recommended to reduce the risk of passive transmission of Infectious Salmon Anaemia.

This distance is considered safe and for this reason, where necessary, such aquaculture units were re-located. Other important measures were taken, for instance, year class separation and fallowing (52 / 53).

Mixing in the same site smolts originating from different hatcheries is associated with an increased risk of diseases (53).

High intensity livestock farming implies a reduced distancing between animals which, combined with a low level of genetic diversity, facilitates the spread of diseases. The frequent use of drugs in intensive livestock farming may lead to select drug resistant parasites (54).

Nowadays, a lot of antibiotics that are used as last resort for humans are also being utilised by animal farmers. Urgent action should be taken by an international panel (6). Meat labels that contain information about antibiotic use may help the consumer in making informed purchase decisions, that may include *selecting antibiotic-free products* (6). *ABR is growing* and all countries need to develop strategies aimed at reducing the consumption of antibiotics, in both terrestrial and aquatic farming. *Among the options, there is also a reduction in the number of animals raised for food* (3).

8. War and AMR

In 2001, for instance, *more than half of the outbreaks of international importance have been observed in conflict-affected countries* (55).

According to "Deadly comrades: war and infectious diseases", in conflict-affected countries, there are the conditions for new diseases to emerge and/or other diseases to resurge (55). Among the conditions that may increase the incidence of infectious diseases, there are: *lack of clean water and sanitation, overcrowding, migration and poor living conditions*. Furthermore, in war-torn areas, the sanitary infrastructure may collapse, which may hinder prevention and control programmes, such as vaccination. Late detection of new pathogens and delayed control measures, improper or incomplete use of antibiotics, and lack of regulatory controls may also contribute to ABR (55).

According to a World Health Organisation document (56) the war hindered the containment of the Ebola virus in Sierra Leone, Guinea and Liberia. Here, years of civil war and unrest left health infrastructures, road systems and telecommunications in poor conditions. In this situation, calls for help, public information campaigns, communication of alerts, transportation of patients to treatment centres and of samples to laboratories, are greatly delayed. In addition, the high mobility of people across borders, driven by poverty, hindered activities aimed at the control of the disease, such as contact tracing (56).

According to "Antimicrobial Resistance & Migrants in Sweden: Poor Living Conditions Enforced by Migration Control Policies as a Risk Factor for Optimal Public Health Management", migrants are exposed to AMR as are all mobile populations. Besides suffering lack of access to medical care, they suffer financial, social and cultural stress, often intensified by the inadequate and crowded conditions encountered in refugee camps (57).

The psychological impact of enhanced migration controls may force the migrants to consider their personal health care as secondary to the many other problems, which may interfere negatively with an optimal public health management (57).

According to the authors, health assessment of migrants should be made upon their arrival, *while reassuring them that this has no influence on their right to stay in the host country*. Interestingly, however, in Europe high rates of AMR transmission from migrants to host population have not been observed (57).

When people are displaced and relocated to temporary settlements or camps, mortality rates can be even 60 times higher than baselines. Clearly, prevention and control measures are necessary (55).

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Conflict of Interest Statement
The author declares no conflicts of interest.

About the Author

The author is a former middle school teacher, and wrote about 65 educational papers starting 35 years ago. Areas of interest: Health Education, Environmental Education and Prevention of Natural Disasters. The author has a University Degree in Biology.

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