What if we could fight antibiotic resistance with probiotics?

Recent research suggests that the future combat against antimicrobial resistance (AMR) may involve probiotic-based approaches. Their use in our microbial ecosystems, including humans, animals and the healthcare environment, may provide a novel approach which deserves exploration.

Antimicrobials are agents that kill or prevent the growth of micro-organisms, such as antibiotics which target bacteria. The rampant and sometimes inappropriate use of antibiotics in humans, animals and the environment has led to the growing global health threat of antimicrobial resistance (AMR). This refers to the natural adaptation of bacteria to survive antibiotic attack. When resistance has been acquired, it can spread quickly among species. Once such resistance mechanisms exist, it is very difficult to get rid of them.

Multi-drug resistant (MDR) micro-organisms have appeared, making therapeutic treatments difficult, and some of them may become untreatable. More than 33 000 deaths from drug-resistant bacterial infections alone are reported every year in Europe. This figure could rise tenfold by 2050. Targeting AMR is a critical focus for sustainable healthcare in the EU and worldwide. Antibiotic use and AMR are not only related to human health but also to veterinary medicine, agricultural livestock management, and food production. As the antibiotic-resistant strains continue to grow, the use of probiotics as a potential substitute for antibiotics is becoming more popular for human, veterinary and environmental application.

Potential impacts and developments

The microbiota is a collective term referring to the reservoirs of micro-organisms living in the human body, in animals and within the environment. Although the terms are used interchangeably, there is a slight difference between microbiome and microbiota. In fact, ‘microbiota’ refers to the actual organisms (‘bugs’), and ‘microbiome’ to the organisms and their genes. Probiotics are beneficial bacteria found in certain foods or supplements. They are ‘live micro-organisms that confer a health benefit to the host when administered in adequate amounts’, according to United Nations Food and Agriculture Organization/World Health Organization guidelines. Commonly used probiotics include *Lactobacillus*, *Bacillus*, *Escherichia* or *Streptococcus*, however combinations of more than one are common, to achieve maximal effects. Probiotic use is increasingly practised for human, veterinary and environmental applications. Consumption via the gastrointestinal route is the most common application in both human and veterinary uses.

The use of probiotics instead of antibiotics for treating infectious and non-infectious diseases to address the problem of AMR has been explored. Briefly, the idea is that instead of using antibiotics to kill pathogenic microbes, the establishment of commensal and sometimes mutualistic microbes may hinder the growth of disease-causing microbes found in the same host microbial environment. By limiting the use of antibiotics, probiotic use may help to decrease the rate of development of antibiotic-resistant strains resulting from widespread antibiotic use. In addition, there is evidence that maintaining what is considered ‘normal’ microbiota for certain host microbial environments may prevent diseased conditions – that are not necessarily of infectious etiology – and may improve general health outcomes.

Evidence from human studies has shown the potential of probiotics to tackle a number of pathological conditions. Probiotic supplementation may reduce episodes of common infectious diseases, including respiratory tract infections and diarrhoea, particularly for a specific condition, such as *Clostridium difficile*-associated diarrhoea. In addition, probiotic supplementation may reduce the duration of symptoms in otherwise healthy children and adults with common acute respiratory conditions. By decreasing the incidence and severity of common acute infections, probiotic supplementation could be associated with decreased antibiotic use.
Specific sets of subjects – critically ill and oncology patients – may have higher risks of microbiome perturbation leading to infectious disease. Although still unclear, probiotics exert a heterogeneous positive influence in preventing adverse outcomes in these patients. In addition, it is considered that a proportion of antibiotic prescriptions may be a response to emotional rather than medical factors. The recommendation to take a probiotic may offer a tool for doctors, fulfilling the need to reduce patient anxiety. Other human health conditions – not of infectious origin – are now being connected to the human gut microbiota. A common pathophysiological element of these diseases is the deviation from the ‘normal’ human gut microbial ecology. Obesity, diabetes mellitus, irritable bowel syndrome, Crohn’s disease, necrotizing enterocolitis, and several other pathological conditions, are currently being associated with dysbiosis in the human gut microbiota.

In recent decades, antibiotics have been exploited as livestock feed additives due to their effectiveness in increasing weight gain and preventing disease through modifications of the gastrointestinal flora. Since 2006, due to their harmful effect on AMR, the EU banned the use of antibiotics in animal feed, and the European Food Safety Authority (EFSA) has instituted guidelines on the use of food additives in animal products that may potentially spread AMR genes. However, other developed nations, such as the United States of America, have not imposed strict regulatory policies on antibiotic use for livestock. Probiotics, on the other hand, are among the approved additives allowed in animal feed to promote gut flora equilibrium/symbiosis and health. Some beneficial effects of probiotic use in animal feed have been noted. For example, probiotic use in livestock farming of chickens and turkeys shows an increased resistance to Salmonella infections. In addition, probiotic administration reduced overall costs of production of chickens and turkeys. Aquaculture provides another case, where the need to improve safe aquatic production for human consumption has stimulated probiotics development and applications. Probiotics are also applied during all phases of swine production, to mitigate disease, increase product quality and reduce environmental pollutants.

In the healthcare environment, AMR can also contribute to serious healthcare-associated infections (HAI). Persistent contamination of surfaces contributes to infection transmission, which cannot be completely controlled by conventional cleaning. In fact, micro-organisms have the ability to survive for long periods of time on surfaces, from where they are easily transmitted. A review of recent evidence has shown support for a probiotic cleaning hygiene system (PCHS). There is evidence that instead of trying to eradicate all pathogens, for example on hospital surfaces, it may be more effective to replace them with beneficial bacteria, in order to prevent infections. Replacing conventional cleaning with a PCHS is associated with a significant decrease in HAI incidence and a stable decrease in surface pathogens.

Anticipatory policy-making

There is still a lack of clear evidence on how exactly probiotics produce their benefits. It has been suggested that they can act by different mechanisms, comprising secretion of antibacterial chemicals, stimulation and modulation of the immune responses, competition between nutrition and specific adhesion sites, and inhibition of toxic protein expression in gastro-intestinal pathogens. Probiotic use is not exempted from complications: a major issue being acquired antibiotic resistance genes. A risk of pathogenic microbes acquiring antibiotic-resistance genes from probiotic microbes exists, and vice versa, and researchers advise renewed efforts to examine this risk in view of the growing global concern regarding antimicrobial resistance. For example, if undercooked meat is consumed by a livestock animal fed with probiotics containing antimicrobial-resistant genes, this could also be a potential source of AMR in human microbiota. A combined effort at a global level is necessary to implement probiotic screening and regulation for those used in both livestock and human applications. Increased and long-term exposure of probiotics also needs further research. As such, it is imperative to screen microbes effectively for antibiotic resistance genes before using them as probiotics. So far, no worldwide health authority (e.g. WHO, FAO) has taken full responsibility for screening for antibiotic resistance genes in probiotic micro-organisms.

It should be emphasised that the overall success of probiotics in replacing or reducing the need for antimicrobials may be modest, conditional, strain-dependent, and transient. However, any alternative which may reduce the rise of AMR is worth investigating. In addition, there is no one-size-fits-all probiotic that works well for everyone, as the gut microbiome differs between individuals. However, with the development of metabolic engineering and synthetic biology, engineering of probiotics opens up possibilities to design microbes to target specific tissues and cells rather than the whole body and to create novel probiotics with desired characteristics and functionalities. Increasing evidence endorses the role of ecological interactions among humans, animals, and the microbial environment in influencing antibiotic-resistance genes. As such, in addressing the problem of antibiotic resistance, an ecological approach is needed, where both the agricultural use of antibiotics and the clinical prescription of antibiotics in humans and at an environmental level is properly regulated.