The ArmA and RmtB are the main 16S RMTases conferring resistance to AGAs in bacteria, and genes encoding these enzymes are alarmingly spreading from human to animals around the world (Wachino and Arakawa 2012). If co-located with a carbapenemase gene on the same mobile genetic element, ArmA can even cause pandrug resistance (Milan et al. 2016). Also of concern is the identification of resistance RMTases in foodborne bacteria, as food may become a relevant route of resistance transmission (Granier et al. 2011). In addition, the ArmA and RmtC methyltransferases were reported to cause resistance in *Enterobacteriaceae* strains, even to newly developed plazomicin AGA (Zhanel et al. 2012).

1.4.3 Strategies to Modulate the Human Microbiome

Understanding the complex interactions occurring in the gut and how we can manipulate these to benefit human health is one of the key challenges of our time. Personalized medicine solutions with the combined use of probiotics and prebiotics can be key to circumvent antibiotic resistance, including AGAs, and the last resort for many human diseases.

Probiotics have been defined as "live microorganisms that, when administered in adequate amounts, confer a health benefit on the host" (Hill et al. 2014). The use of probiotics or probiotic bacteria to restore the microbiota composition and avoid disease after antibiotic treatment is a well-established approach (Liévin-Le Moal and Servin 2014). For example, *Lactobacillus* spp. have a protective effect against AAD (*L. reuteri*) (Cimperman et al. 2011), while *Bifidobacterium* strains reduce the risk of infections in infancy (Taipale et al. 2016). *Escherichia coli* Nissle 1917 (Mutaflor) is also a known probiotic to fight antibiotic-resistant pathogens (Wassenaar 2016). The development of genetically engineered probiotic lactic acid bacteria to target and compete with specific pathogens or to produce antimicrobial peptides is a promising approach that can drastically reduce the spread of resistance mechanisms (Hwang et al. 2014). However, caution must be taken as probiotic cultures have the potential to carry antibiotic resistance genes themselves, including aminoglycoside resistance genes (Zheng et al. 2017).

Another way to restore and enhance the human gut microbiome is by controlling or modifying the carbohydrate uptake – via controlled diet or supplementation with prebiotics. Prebiotics are substrates that are "selectively utilized by host microorganisms, conferring a health benefit" (Gibson et al. 2017). These compounds are usually nondigestible carbohydrates or fibers, fermented by colonic bacteria to produce beneficial SCFAs (Hamer et al. 2008). High fiber diets and inulin supplementation stimulate the growth of *Bifidobacterium* and reduce the risk of obesity, although the exact molecular mechanism is not clear (Weitkunat et al. 2017; Schroeder et al. 2018). Furthermore, prebiotics can be utilized to alter the side effects of antibiotics. In a recent study, Johnson and