

# **Influence of gut resistome on humans with autism spectrum disorder**

## **Abstract**

Present study highlights the Influence of gut resistome on humans with autism spectrum disorder. Environmental stresses such early birth and drug exposure in utero can have an impact on kids with Autism spectrum disorder(ASD).Microorganisms found in wastewaters, hospitals, and animal production waste waters have been found to harbour hundreds of distinct ARGs that encode resistance to a broad spectrum of antibiotics.Environmental variables are currently being considered as potential etiological agents of this condition, as genetics alone is unable to explain its primary origin. Numerous bacteria found in GM have an impact on human health. Furthermore, a microbe that is impacted by birth mode, lifestyle, and genetics is present in the intestine. In order to produce different compounds that affect the host, train the host's immunity, modify drug action and metabolism, regulate gut endocrine function, and eliminate toxins, for example, GM is essential to achieving the intended target for treatment application.

Keywords: gut endocrine function, Autism spectrum disorder, Environmental stresses, Microorganisms

## **Introduction:**

Autism spectrum disorder (ASD) is a major neurodevelopmental issue that affects roughly 1% of the general population is. ASD symptoms include repetitive behaviours and trouble with social communication (Widiger & Costa Jr, 2013). Environmental stresses such early birth and drug exposure in utero can have an impact on kids with ASD (Agrawal et al., 2018; Christensen et al., 2013). Furthermore, the pathophysiology of ASD is associated with maternal infection during pregnancy, which raises the likelihood that the child would experience ASD (Atladóttir et al., 2010). According to the Centres for Disease Control (CDC), one in 54 children in the US has ASD, indicating that the prevalence of ASD is rising globally (CDC, 2018).In certain situations, the diagnosis of ASD can be made as early as 18 months of age. But a definitive diagnosis might take longer to come to, or in certain situations, it might not be discovered until the patient is a teenager or an adult (Yang et al., 2022).The etiology of ASD remains uncertain despite numerous explanations being postulated by environmental and genetic variables (Yang et al., 2022).

According to a wealth of research, alterations in the makeup and function of the gut microbiota (GM) are thought to be crucial components in ASD (Hughes et al., 2018; Özcan & Hsiao, 2022). According to Kovtun et al. (2020), GM plays a part in the direction of communication between the brain and the gut. Additionally, through its interactions with the immune system, the gut microbiome may possibly have an impact on brain function (MacFabe, 2015). Furthermore, long-term disruption of GM, which is linked to the emergence of gastrointestinal (GI) symptoms, may result from early life antibiotic exposure (Fjalstad et al., 2018; Gibson et al., 2016; Krajmalnik-Brown et al., 2015). Nonetheless, according to Schulfer et

al. (2018), antibiotics are necessary for the treatment of a number of illnesses, including TB and gonorrhoea, and alterations in the GM composition may be linked to ASD.

Thousands of different bacterial species make up the gut microbiome, which is also home to a reservoir of antibiotic resistance genes (ARGs) known as the resistome (Kovtun et al., 2020). In a variety of settings, including the gut, soils, human, animal, and ocean, resistome—a collection of antibiotic resistance genes (ARGs) in a microbial community or on a single microorganism—has been studied (Cuadrat et al., 2020). According to Martinez (2014) and Munita and Arias (2016), susceptible bacteria can develop antibiotic resistance by the accumulation of mutations or the acquisition of resistance genes through transformation, transduction, and conjugation. These genes provide the cell with resistance to antibiotics. A mutation can be acquired or innate. Furthermore, the use of antibiotics and bacteria that pose a risk to humans and animals can accelerate the development of antibiotic resistance genes (ARG). Microorganisms found in wastewaters, hospitals, and animal production waste waters have been found to harbour hundreds of distinct ARGs that encode resistance to a broad spectrum of antibiotics (Zhang et al., 2009). To make it easier to characterize and identify ARGs, the Antibiotic Resistance Genes Database (ARDB) is a database that contains the majority of the publicly available data on antibiotic resistance. An extensive amount of information is annotated for each type of resistance and gene, including sequencing, resistance profile, protein databases, ontology, mechanism of action, COG (Clusters of Orthologous Genes), and CDD (Conserved Domain Database) annotations (Liu & Pop, 2009). Examples of ARGs that have been found in the environment include those that are resistant to vancomycin, sulfamethoxazole, trimethoprim, ciprofloxacin, quinolone, or tetracycline (e.g., *sul I*, *sul II*, *tet(A)*, *tet(B)*, *tet(C)*, *tet(G)*, *tet(M)*, *tet(W)*, and *tet(O)*). According to studies, ear infections may raise the chance of ASD, and postnatal antibiotic exposure—particularly the usage of paracetamol and antibiotics—has been linked to ASD (Bittker & Bell, 2018). Compared to their contemporaries, children with autism are known to receive an excessive amount of antibiotic treatment (Kovtun et al., 2020). Furthermore, Sharma and colleagues (2016) provided evidence of a connection between ASD and resistome.

### **Autism spectrum disorder (ASD)**

According to Pulikkan, Mazumder, and Grace (2019), autism spectrum disorder (ASD) is regarded as a severe neuropsychiatric and neurodevelopmental illness with an unclear etiology and pathogenesis. Individual differences may exist in the restrictive, repetitive, communicative, and social issues associated with ASD (Lord et al., 2018). ASD is associated with a wide range of comorbidities, such as abnormalities in sensory processing, impaired neural processing, altered brain development, motor deficits, gastrointestinal (GI) disturbances, deficits in verbal and language communication skills, and impairments in intellect and abstract reasoning (Forsyth et al., 2018). Up to 90% of children with ASD have aberrant sensory perception, which is a characteristic of the illness (Floris et al., 2021; Tavassoli et al., 2014). Furthermore, there is a higher prevalence of GI symptoms in people with ASD, including food intolerance, inflammatory diseases, constipation, flatulence, reflux, gastrointestinal problems, and indicators of irritable bowel syndrome (IBS) (Hemmati et al., 2013). The Centres for Disease Control and Prevention (CDC) stated that roughly one in 44 American children had ASD in 2021, indicating an increase in the frequency of ASD cases. 2.81 incidences of ASD were reported for per 1,000 children in Saudi Arabia, with Makkah and Jeddah having the highest prevalence (Sabbagh et al., 2021). Furthermore, compared to other wealthy nations, the prevalence of ASD is said to be slightly greater (Khan et al., 2020). Moreover, Hayat et al. (2019) estimate that the prevalence of

ASD in the Arab Gulf countries ranges from 1.4 to 29/10,000. Males are more likely than females to have ASD globally. Boys have a 4.5-times greater infection rate than girls (Pourmohamadreza-Tajrishi&Azadfallah, 2019).

ASD manifests in the first three years of life(Hemmati et al., 2021; Kral et al., 2013).Autism can be diagnosed as early as 18 to 24 months of age; at this time, distinguishable symptoms from other developmental delays can be made. As early as 18 to 24 months of age, autism can be diagnosed, and it is possible to differentiate between the disorder's distinctive symptoms and other developmental abnormalities (Zeidan et al., 2022).The diagnosis of ASD can be challenging because its symptoms are similar to those of other psychiatric conditions. Moreover, ASD has a neurodevelopmental basis, and social and non-social symptoms, such as unusually narrow interests, communication and relationship difficulties, and highly repetitive and restrictive behavioural patterns, are used to diagnose the disorder (First, 2010; Jassim et al., 2021).

There is strong evidence that the genetic component of heritability for ASD ranges from 60% to 83%, even when the exact cause of the disorder is unknown (Jassim et al., 2021). Furthermore, a growing body of research indicates that ASD may be brought on by a number of diseases (Rossignol et al., 2014). Environmental variables are currently being considered as potential etiological agents of this condition, as genetics alone is unable to explain its primary origin (Almandil et al., 2019). A growing number of studies employ indirect methods to deduce the etiology of ASD from epidemiological data (Hewitt et al., 2016). Genetics, epigenetics, and environmental variables are only a few of the numerous risk factors for ASD. Though their exact role in ASD is yet unknown, the microbiota is the most important component. It may be able to comprehend the aetiology of ASD through the relationship between ASD and gut resistome (De Angelis et al., 2015; Mead & Ashwood, 2015).All of the genes that confer antibiotic resistance in populations of both pathogenic and non-pathogenic bacteria is known as the resistome. Several investigations have elucidated the connection between gut microbiota and ASD. Constipation is a gastrointestinal syndrome that affects 20% of children with ASD, making up a larger percentage of affected persons than healthy children. By contrast, the ASD person's diarrhoea rate was 19% greater than that of the healthy person. There is substantial evidence linking GM to ASD through effects on the immune system and metabolism (De Angelis et al., 2015; Mead & Ashwood, 2015).

### **Microbiome**

The human gastrointestinal tract (GI) harbours around a thousand distinct species of microbiome. The term "human gut microbiome" (GM) refers to the genes and microorganisms found under environmental settings (Marchesi & Ravel, 2015). Numerous bacteria found in GM have an impact on human health. Furthermore, a microbe that is impacted by birth mode, lifestyle, and genetics is present in the intestine. In order to produce different compounds that affect the host, train the host's immunity, modify drug action and metabolism, regulate gut endocrine function, and eliminate toxins, for example, GM is essential to achieving the intended target for treatment application (Schmidt et al., 2018). According to Sarkar et al. (2010), microbiome alteration results in a key therapeutic target for sustaining the course of treatment and overall wellness of disease.Several investigations have indicated that the immune system, mucosal tissues, and various organs are all impacted by the gut microbiota (Belkaid & Hand, 2014). Variations in the makeup and function of an individual's gut microbiome have been related to inflammatory, metabolic, neurological, cardiovascular, and respiratory disorders

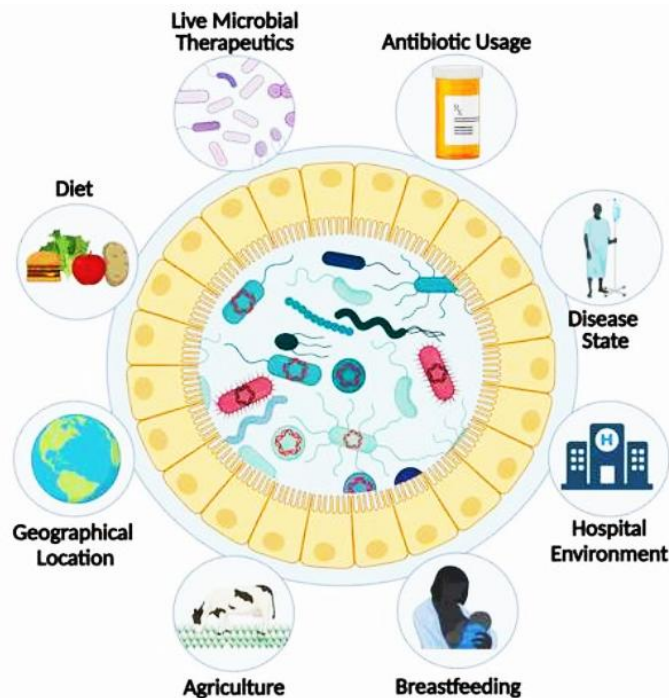
(Zhang et al., 2018). Infection and smoking are the two most significant environmental factors that affect oral/intestinal dysbiosis, arthritic result, and onset (Guerreiro et al., 2018). Since germ-free mice do not develop experimental arthritis, the microbiome may be involved in the disease's aetiology (Scher et al., 2013). One of the hallmarks of chronic autoimmune inflammatory disease (RA) is joint degeneration. Without treatment, the gut microbiota in RA patients differed significantly from that of healthy controls (Scher et al., 2013). According to Wells et al. (2020), there appears to be a reduction in the genetic diversity of rheumatoid arthritis patients when compared to healthy controls. Furthermore, *Prevotella* species, including *Prevotellacopri*, were more prevalent in the compositional level of bacteria in RA patients (Donohoe et al., 2012; Wells et al., 2020). Additionally, *Prevotellacopri* was shown to be more abundant in the colon in recent preclinical phase research on RA patients in European nations, suggesting that dysbiosis occurs before arthritis develops (Alpizar-Rodriguez et al., 2019). The etiology of irritable bowel syndrome (IBS) is linked to dysbiosis in the gut, and there is a decrease in *facalibacterium* and an increase in *collinsella* in RA (Ghoshal et al., 2012; Chen et al., 2016). Numerous researchers have demonstrated that dysbiosis of the gut microbiota may be crucial in neurological and psychiatric illnesses (Rogers et al., 2016).

The gut microbiota of individuals with ASD is different; research found that the number of Prevotellaceae and Porphyromonadaceae was higher in healthy mice compared to autistic mice, as well as an increased number of Erysipelotrichaceae, Alcaligenaceae, and Ruminococcaceae (Hsiao et al., 2013). According to research on animals, the gut microbiota can influence social behaviour, communication, stress, and depression (Bruce-Keller et al., 2018). Furthermore, faecal microbiota transplantation can be used to transfer behavioural features between mice strains (Collins et al., 2013). Furthermore, new research indicates that behavioural characteristic alterations may be influenced by microbiota (Kurokawa et al., 2018). In addition, GM has been linked in numerous studies to the advancement of pancreatic cancer (Half et al., 2019; Pulikkan et al., 2019; Ren, 2017). The study conducted by Ren (2017) revealed that the stool microbiome of patients with pancreatic cancer was more diverse and composed of known lipopolysaccharide (LPS)-producing taxa and pathogens, such as *Enterobacter*, *Veillonella*, *Hallella*, *Selenomonas*, *Prevotella*, and *Klebsiella* species, than the microbiome of healthy controls.

## **Resistome**

A collection of environmental antibiotic resistance genes, or ARGs, is known as an antibiotic resistome (D'Costa et al., 2006). According to Moore et al. (2013), the resistome is formed after birth or the first few months of life. According to Yi et al. (2022), the microbiota serves as a reservoir for resistomes or ARGs. According to Stecher and Hardt (2011), colonization resistance is a method used by the gut microbiota to resist different infections. Numerous factors can have an impact on ARGs, such as the use of live microbial therapies, antibiotics, the severity of the illness, the hospital setting, nursing, agriculture, location, and nutrition (Figure 1) (Crits-Christoph et al., 2022). Utilizing metagenomics based on next-generation sequencing technologies, the human microbiomes and their resistome found in the skin, respiratory tract, and gut have been evaluated. Understanding the dynamics of the human resistome and how it relates to the health sectors is crucial for controlling ARG that flow from the other sectors to the human sector, especially ARG transfer to bacteria that cause disease (Wright, 2019). The human microbiome's commensal bacteria serve as the primary reservoir and route of transmission for clinical ARGs (Surette & Wright, 2017). By interpreting the gut

resistome and contrasting its similarities with pathogens, a number of research have uncovered its function (Forsberg et al., 2012; Raymond et al., 2019; Sommer et al., 2009). A suggested indirect effect has drawn more attention to resistome: commensal species may share their



resistome with pathobionts or pathogens, potentially passing it on to clinically and virulently relevant strains (Murray et al., 2022). Commensal bacteria may be the source of the resistome that supported the discovery of the *vanB* genes in the vancomycin-resistant gut that was separated from *Eggerthella* and *Clostridium innocuum* (Stinear et al., 2001).

### Antibiotic Resistance Genes (ARGs)

A collection of antibiotic resistance genes (ARGs) in a microbial community or on a single bacterium is referred to as a resistome. Resistome has been studied in a variety of settings, including the human gut, soils, animals, and oceans (Figure 2) (Cuadrat et al., 2020). Furthermore, metagenomic whole-genome shotgun sequencing (mWGS) will make additional ARGs available as newly sequenced bacterial genomes become available (Xavier et al., 2016). ARGs are categorised as intrinsic (originating from the producers) or acquired (from other bacteria) resistant (Figure 3) (Hu et al., 2017).

Figure 1. The description of the factors that effect on the resistome. Taken after Crits-Christoph et al. (2022).

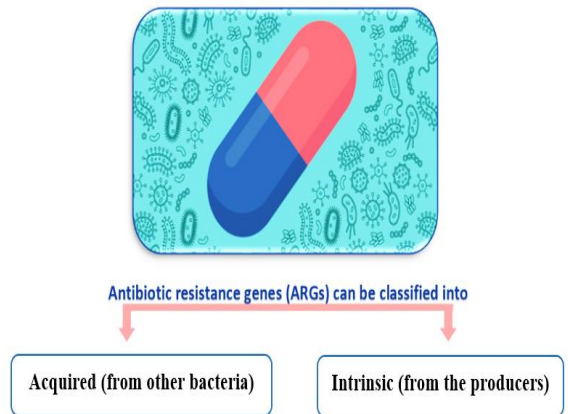
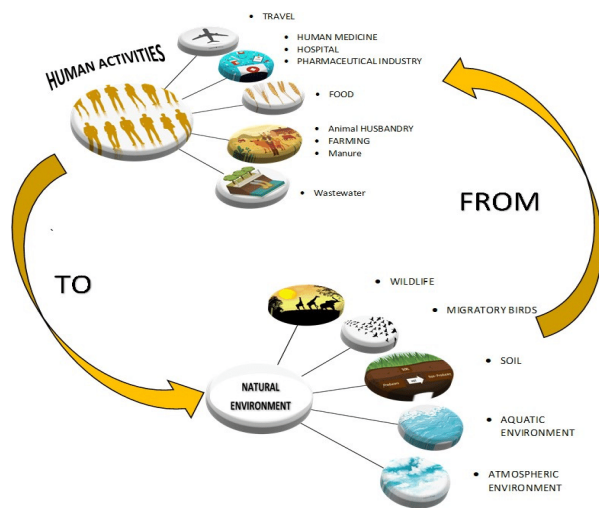


Figure 3. The classification of ARGs. Taken after Hu et al. (2017).

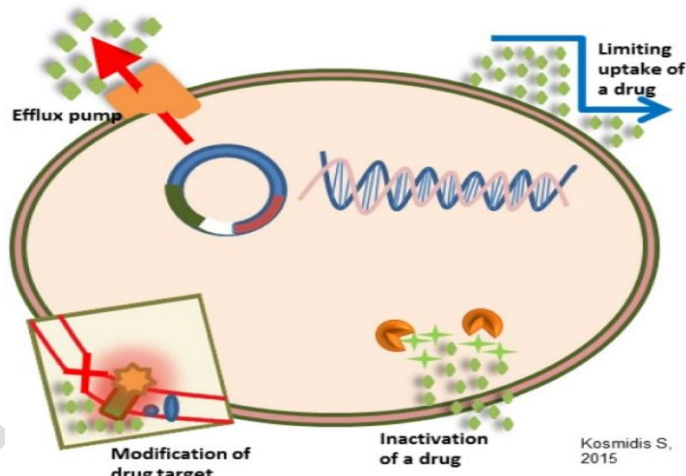


Figure 2. Description of the reservoir of ARGs. Taken after Cuadrat et al. (2020).

ARGs, which shield the cell from antibiotics, can develop from susceptible bacteria by accumulating mutations or obtaining resistance genes through transformation, transduction, and conjugation (Martinez, 2014). Moreover, global cell adaptations, ribosomal protection protein, antibiotic target replacement, inactivation, and antibiotic modifications (Figure 4) are the primary mechanisms of antibiotic resistance. These mechanisms include changing the antibiotic target by lowering the affinity of the binding site for the drug, antibiotic efflux, drug target modification, and drug inactivation were the methods of acquired resistance; drug efflux, limiting uptake, and drug inactivation might be the mechanisms of intrinsic resistance (Reygaert, 2018). As previously indicated, these mechanisms may be innate to the microorganisms or acquired from other microbes (Reygaert, 2018).

The five primary categories of antimicrobial processes are: depolarize the cell membrane, block bacterial pathways, block the creation of proteins and nucleic acids, and inhibit cell walls. Table 1 displays examples of how antimicrobial group-based mechanisms work. Moreover,

resistance levels within the bacterial groupings may vary dramatically. Minimum inhibitory concentration (MIC) is used to quantify susceptibility and resistance. The range of MICs for any given antibiotic among different bacterial species is known as drug susceptibility. The species is thought to have intrinsic resistance to the medication even if it is in the resistant portion of the MIC range. The genes that bacteria acquire and the species they belong to determine their levels of resistance (Reygaert, 2018).

Figure 4. Types of antimicrobial resistance mechanisms in bacteria. Taken after Munita & Arias (2016).

Table1. The actions of ARGs based on the antimicrobial groups. Taken after Reygaert (2018).

Action of ARGs	Antimicrobial drug groups
Inhibit cell wall synthesis	B-Lactams, Cephalosporins, Penicillins
Inhibit protein synthesis	Aminoglycosides, Tetracyclines, Macrolides
Inhibit nucleic acid synthesis	Fluoroquinolones

Natural resistance can be produced by intrinsic genes that are always expressed in the species or by naturally occurring genes in bacteria that are expressed only to the resistant levels following antibiotic exposure. The feature that all bacteria have in common is called intrinsic resistance, and it has nothing to do with horizontal gene transfer or prior exposure to antibiotics (Table 2). For instance, the structure and function of the lipopolysaccharide (LPS) layer in gram-negative bacteria act as a barrier to a wide range of molecules, giving the bacteria an inherent resistance to various antimicrobial drugs. For example, because *Mycobacteria* has a lipid outer membrane, hydrophobic drugs—like rifampicin and fluoroquinolones—have easy access to the cell, while hydrophilic drugs are more restricted in their absorption (Cox & Wright, 2013; Fajardo et al., 2008; Kumar & Schweizer, 2005). Moreover, *Mycoplasma* is inherently resistant to the majority of antibiotics that attack the cell wall, such as  $\beta$ -lactams and glycopeptides (Bébéar & Pereyre, 2005). Gram-positive bacteria have an outer barrier that keeps drugs from entering the cell. For instance, enterococci's cell wall contains polar compounds that hinder cell wall penetration and confer an inherent resistance to aminoglycosides (Cox & Wright, 2013). Gram-positive *Staphylococcus aureus* bacteria are resistant to vancomycin. Vancomycin-resistant *S. aureus* (VISA) strains are those that have produced a thickened cell wall, which hinders the drug's ability to enter the cell and confers resistance (Beceiro et al., 2013; Cox & Wright, 2013).

Table2. Some bacterial species have intrinsic resistance to antimicrobials drugs. Taken after several reports (Cox & Wright, 2013; Fajardo et al., 2008; Kumar & Schweizer, 2005).

Organism	Intrinsic resistance
<i>Bacteroides (anaerobes)</i>	Aminoglycosides, many $\beta$ -lactams, quinolones
<i>Enterococci</i>	Aminoglycosides, cephalosporins, lincosamides
<i>Escherichia coli</i>	Macrolides
<i>Klebsiella spp.</i>	Ampicillin
<i>Acinetobacter spp.</i>	Ampicillin, glycopeptides

The acquisition of ARGs can be made temporarily or permanently. Plasmid-mediated transmission of resistance genes is the most frequent method of acquiring foreign genetic

material; however, bacteriophage transfer is rather uncommon. However, some bacterial species—like *Acinetobacter* spp.—are able to obtain genetic material directly from the environment (Kumar & Schweizer, 2005). Additionally, certain genes, such as those that encode antibiotic-modifying enzymes, drug targets, regulators that regulate drug transporters, and drug transporters, may experience mutations that result in antimicrobial resistance (Martinez, 2014). Moreover, the organism determines a great deal of the mutations that contribute to antibiotic resistance. For example, when *S. aureus* develops a resistance to methicillin, the bacterial growth rate is dramatically reduced (Martinez, 2014). High resistance levels in subsequent bacterial generations may be selected for by using very low or low doses of antibacterial drugs (sub-inhibitory) (Blázquez et al., 2012).

### **Penicillin-binding proteins (PBPs)**

The bacterial cells alter the structure and/or quantity of Penicillin-binding proteins (PBPs), which allows the agents to withstand the effects of numerous antimicrobial drugs. Gram-positive bacteria have this process as one of their resistance mechanisms to  $\beta$ -lactam antibiotics. PBPs are transpeptidases that are involved in the cell wall's peptidoglycan production. Therefore, altering the PBP value, either up or down, has an impact on the drug's capacity to bind. PBPs alter the amount of antimicrobial that binds to that target and results in structural changes. For instance, PBP2a in *S. aureus* causes resistance by acquiring the *mecA* gene, which can either reduce or prevent the capacity of a medication to bind (Martinez, 2014; Reygaert, 2009). Furthermore, by depolarizing a cell membrane, the glycopeptide vancomycin prevents the formation of cell walls and lipopeptides. Because of the thick LPS coating, gram-negative bacteria are intrinsically resistant to these medications (Randall et al., 2013; Wood et al., 2013). Vancomycin-resistant Enterococci (VRE) and methicillin-resistant *S. aureus* (MRSA) are two types of enterococci where resistance to the antibiotic is a major problem. On the other hand, resistance is caused by the acquisition of *van* genes, which alters the structure of peptidoglycan precursors and lowers vancomycin's binding capacity (Beceiro et al., 2013; Cox & Wright, 2013). Furthermore, a mutation in *mprF* is an important mechanism that inhibits the binding of calcium by changing the charge of the cell membrane to a positive state. As a result, daptomycin cannot bind because of the inhibition of calcium (Stefani et al., 2015; Yang et al., 2009). Targeting the ribosomal subunits, antimicrobial resistance can arise through ribosomal methylation or ribosomal mutation (aminoglycosides, oxazolidinones) (Stefani et al., 2015). Additionally, in bacterial and some eucaryotic organisms, such as *Pneumocystis carinii* (VOLPE et al., 1993), *Toxoplasma gondii* (Pfefferkorn et al., 1992), and *Plasmodium falciparum* (Zhang et al., 1991), the enzyme dihydropteroate synthase (DHPS; EC 2.5.1.15) catalyzes the biosynthesis of dihydropteroic acid. Synthetic antibacterial agents include sulfonamides (SULs) and trimethoprim (TMP). While TMP is used to treat acute urinary tract infections, the early SUL chemicals were long used to prevent urinary tract infections. Human cells do not possess this enzyme activity. SUL medications function as DHPS competitive inhibitors, preventing the bacterial cell from producing folate, which results in (GM et al., 1962). Over the past few years, there has been a noticeable increase in TMP resistance along with significant SUL resistance. Pathogenic bacteria have exhibited a remarkable evolutionary adaptability to the presence of TMP and SUL, as evidenced by their methods of resistance and spread. Despite this, Huovinen et al. (1995) reported alterations in the chromosomal architecture and regulatory processes of the *dhps* and *dhfr* genes, which code for the target enzymes DHPS and DHFR, respectively.

### **$\beta$ -lactamases**

A four-sided  $\beta$ -lactam ring makes up the unique core structure shared by all  $\beta$ -lactam medications. Three main mechanisms were identified for resistance to  $\beta$ -lactam medications: the drug being hydrolyzed by  $\beta$ -lactamase enzymes, the drug altering its ability to bind to PBP to prevent interaction, and the existence of efflux pumps that can extrude  $\beta$ -lactam medications (Bush & Bradford, 2016). Various types of efflux pumps, known as multi-drug (MDR) efflux pumps, are capable of transporting larger quantities of chemicals. Their purpose is to remove harmful molecules from the bacterial cell. Furthermore, many of these pumps' resistance level is affected by the carbon source that is accessible (Blair et al., 2014; Villagra et al., 2012). Cephalosporinases and penicillinases, two types of  $\beta$ -lactamases, block  $\beta$ -lactam medications by hydrolyzing a specific location within the  $\beta$ -lactam ring, causing the ring to open. Furthermore, according to Bush and Jacoby (2010), open-ring medications are unable to attach to their intended PBP.

$\beta$ -lactamase enzymes are categorized based on features related to their structure and/or molecular functions. They fall under four major types structurally. Gram-positive bacteria primarily contain  $\beta$ -lactamases from group A (Bush, 2013; Schultsz & Geerlings, 2012). These enzymes can be inherited from the bacterial chromosome or acquired through a plasmid. Gram-negative bacteria belonging to the Enterobacteriaceae family possess  $\beta$ -lactamase genes on their chromosomes. This enzyme is also present in certain other Gram-negative bacteria, such as *Acinetobacter* spp., *Pseudomonas* spp., and *Aeromonas* spp. Enterobacteriaceae is a common family that contains  $\beta$ -lactamase genes transmitted by plasmids (Chancey et al., 2012). The ampicillin resistance gene, *ampC*, chromosomally encodes the first  $\beta$ -lactamase ever described, which was derived from *E. coli*. The majority of the time, this gene is expressed at a low level; nevertheless, mutations lead to an overexpression of the gene. Penicillins and the first generation of some cephalosporins are affected by  $\beta$ -lactamases encoded by the *AmpC* gene (Bevan et al., 2017; Bush, 2013; Pfeifer et al., 2010; Schultsz & Geerlings, 2012). Table 3 displays a summary of the elements of antimicrobial resistance.

Table 3. Examples of antimicrobial resistance elements. Taken after few reports (Bevan et al., 2017; Bush, 2013; Pfeifer et al., 2010; Schultsz & Geerlings, 2012)

Drug	Drug uptake limitation	Drug target modification	Drug inactivation	Efflux Pumps
<b><math>\beta</math>-Lactams</b>	Decreased numbers of porins, no outer cell wall	Gram pos—alterations in PBPs	Gram pos, gram neg— $\beta$ -lactamases	Resistance-nodulation-division (RND)
<b>Cephalosporins</b>	Changed selectivity of porin			
<b>Penicillins</b>	Thickened cell wall,	Modified peptidoglycan		
<b>Glycopeptides</b>	no outer cell wall			
<b>Lipopeptides</b>		Modified net cell surface charge		
<b>Aminoglycosides</b>	Cell wall polarity	Ribosomal mutation, methylation	Aminoglycoside modifying enzymes, acetylation, phosphorylation,	RND

			adenylation	
<b>Tetracyclines</b>	Decreased numbers of porins	Ribosomal protection	Antibiotic modification, oxidation	Major facilitator superfamily (MFS), RND
<b>Macrolides</b>		Ribosomal mutation methylation		ATP-binding cassette (ABC) MFS

The human microbiome's commensal bacteria serve as the primary reservoir and route of transmission for clinical ARGs (Surette & Wright, 2017). Several researches (Forsberg et al., 2012; Raymond et al., 2019; Sommer et al., 2009) have unravelled the role of gut resistome and compared its similarity with those of pathogens. Rarely does commensal bacteria transfer ARG to pathogens. Pathogenic bacteria and the human gut have nearly comparable ARGs and genetic settings, indicating the significance of GM in the formation of clinical ARGs (Sommer et al., 2009). Geographical location, chemotherapeutics (such as antibiotics), and dietary modifications have all been linked to associations between the animal gut and environmental and human gut resistomes (Pehrsson et al., 2016; Sun et al., 2020; Van Gompel et al., 2020).

### ASD and Microbiome

Early-life antibiotic exposure can alter the composition of the microbiota, which may be a factor in ASD (Whelan, 2000). GI problems in ASD are explained by the fact that children with ASD are treated with a greater quantity of antibiotics than healthy children (Kovtun et al., 2020). Moreover, oral antibiotics promote the growth of anaerobic bacteria in the gut, including *Desulfovibrio*, *Clostridium*, and phylum Bacteroidetes, which may exacerbate GI symptoms and autistic behaviours in people with ASD (Bolte, 1998). Compared to broad-spectrum and moderate-spectrum antibiotics, which increased the effect of ASD, the effect of using narrow-spectrum antibiotics was limited in relation to autism (Wimberley et al., 2018). It has been demonstrated that using several antibiotic classes while pregnant may marginally raise the incidence of ASD (Kovtun et al., 2020). In the second and third trimesters of pregnancy, penicillin use was documented in 50% of instances of oASD. It has been demonstrated that taking sulfonamides when pregnant increases the likelihood that the child would become infantile (Murray et al., 2022). Antibiotic use and ASD have not yet been proven to be related (Kovtun et al., 2020).

### References

- (CDC), C. f. d. c. a. p. (2018). Autism spectrum disorders. Retrieved from <https://www.cdc.gov/>
- (CDC), C. f. d. c. a. p. (2021). Autism spectrum disorder  
Retrieved from <https://www.cdc.gov/>
- Agrawal, S., Rao, S. C., Bulsara, M. K., & Patole, S. K. (2018). Prevalence of autism spectrum disorder in preterm infants: a meta-analysis. *Pediatrics*, 142(3).
- Almandil, N. B., Alkuroud, D. N., AbdulAzeez, S., AlSulaiman, A., Elaissari, A., & Borgio, J. F. (2019). Environmental and genetic factors in autism spectrum disorders: Special

- emphasis on data from Arabian studies. *International journal of environmental research and public health*, 16(4), 658.
- Alpizar-Rodriguez, D., Lesker, T. R., Gronow, A., Gilbert, B., Raemy, E., Lamacchia, C., . . . Strowig, T. (2019). Prevalence of *Prevotella copri* in individuals at risk for rheumatoid arthritis. *Annals of the rheumatic diseases*, 78(5), 590-593.
- Atladóttir, H. Ó., Thorsen, P., Østergaard, L., Schendel, D. E., Lemcke, S., Abdallah, M., & Parner, E. T. (2010). Maternal infection requiring hospitalization during pregnancy and autism spectrum disorders. *Journal of autism and developmental disorders*, 40(12), 1423-1430.
- Bébéar, C., & Pereyre, S. (2005). Mechanisms of drug resistance in *Mycoplasma pneumoniae*. *Current Drug Targets-Infectious Disorders*, 5(3), 263-271.
- Beceiro, A., Tomás, M., & Bou, G. (2013). Antimicrobial resistance and virulence: a successful or deleterious association in the bacterial world? *Clinical microbiology reviews*, 26(2), 185-230.
- Belkaid, Y., & Hand, T. W. (2014). Role of the microbiota in immunity and inflammation. *Cell*, 157(1), 121-141.
- Bevan, E. R., Jones, A. M., & Hawkey, P. M. (2017). Global epidemiology of CTX-M  $\beta$ -lactamases: temporal and geographical shifts in genotype. *Journal of Antimicrobial Chemotherapy*, 72(8), 2145-2155.
- Bittker, S. S., & Bell, K. R. (2018). Acetaminophen, antibiotics, ear infection, breastfeeding, vitamin D drops, and autism: an epidemiological study. *Neuropsychiatric disease and treatment*, 14, 1399.
- Blair, J. M., Richmond, G. E., & Piddock, L. J. (2014). Multi-drug efflux pumps in Gram-negative bacteria and their role in antibiotic resistance. *Future microbiology*, 9(10), 1165-1177.
- Blázquez, J., Couce, A., Rodríguez-Beltrán, J., & Rodríguez-Rojas, A. (2012). Antimicrobials as promoters of genetic variation. *Current opinion in microbiology*, 15(5), 561-569.
- Bolte, E. (1998). Autism and *Clostridium tetani*. *Medical hypotheses*, 51(2), 133-144.
- Bruce-Keller, A. J., Salbaum, J. M., & Berthoud, H.-R. (2018). Harnessing gut microbes for mental health: getting from here to there. *Biological psychiatry*, 83(3), 214-223.
- Bush, K. (2013). Proliferation and significance of clinically relevant  $\beta$ -lactamases. *Annals of the New York Academy of Sciences*, 1277(1), 84-90.
- Bush, K., & Bradford, P. A. (2016).  $\beta$ -Lactams and  $\beta$ -lactamase inhibitors: an overview. *Cold Spring Harbor perspectives in medicine*, 6(8).
- Bush, K., & Jacoby, G. A. (2010). Updated functional classification of  $\beta$ -lactamases. *Antimicrobial agents and chemotherapy*, 54(3), 969-976.
- Chancey, S. T., Zähler, D., & Stephens, D. S. (2012). Acquired inducible antimicrobial resistance in Gram-positive bacteria. *Future microbiology*, 7(8), 959-978.

- Chen, J., Wright, K., Davis, J. M., Jeraldo, P., Marietta, E. V., Murray, J., . . . Taneja, V. (2016). An expansion of rare lineage intestinal microbes characterizes rheumatoid arthritis. *Genome medicine*, 8(1), 1-14.
- Christensen, J., Grønborg, T. K., Sørensen, M. J., Schendel, D., Parner, E. T., Pedersen, L. H., & Vestergaard, M. (2013). Prenatal valproate exposure and risk of autism spectrum disorders and childhood autism. *Jama*, 309(16), 1696-1703.
- Collins, S. M., Kassam, Z., & Bercik, P. (2013). The adoptive transfer of behavioral phenotype via the intestinal microbiota: experimental evidence and clinical implications. *Current opinion in microbiology*, 16(3), 240-245.
- Cox, G., & Wright, G. D. (2013). Intrinsic antibiotic resistance: mechanisms, origins, challenges and solutions. *International Journal of Medical Microbiology*, 303(6-7), 287-292.
- Crits-Christoph, A., Hallowell, H. A., Koutouvalis, K., & Suez, J. (2022). Good microbes, bad genes? The dissemination of antimicrobial resistance in the human microbiome. *Gut Microbes*, 14(1), 2055944.
- Cuadrat, R. R., Sorokina, M., Andrade, B. G., Goris, T., & Davila, A. M. (2020). Global ocean resistome revealed: Exploring antibiotic resistance gene abundance and distribution in TARA Oceans samples. *GigaScience*, 9(5), g1aa046.
- D'Costa, V. M., McGrann, K. M., Hughes, D. W., & Wright, G. D. (2006). Sampling the antibiotic resistome. *Science*, 311(5759), 374-377.
- De Angelis, M., Francavilla, R., Piccolo, M., De Giacomo, A., & Gobbetti, M. (2015). Autism spectrum disorders and intestinal microbiota. *Gut microbes*, 6(3), 207-213.
- Donohoe, D. R., Wali, A., Brylawski, B. P., & Bultman, S. J. (2012). Microbial regulation of glucose metabolism and cell-cycle progression in mammalian colonocytes.
- Fajardo, A., Martínez-Martín, N., Mercadillo, M., Galan, J. C., Ghysels, B., Matthijs, S., . . . Baquero, F. (2008). The neglected intrinsic resistome of bacterial pathogens. *PloS one*, 3(2), e1619.
- First, M. B. (2010). Paradigm shifts and the development of the diagnostic and statistical manual of mental disorders: past experiences and future aspirations. *The Canadian Journal of Psychiatry*, 55(11), 692-700.
- Fjalstad, J. W., Esaiassen, E., Juvet, L. K., van den Anker, J. N., & Klingenberg, C. (2018). Antibiotic therapy in neonates and impact on gut microbiota and antibiotic resistance development: a systematic review. *Journal of Antimicrobial Chemotherapy*, 73(3), 569-580.
- Floris, D. L., Wolfers, T., Zabihi, M., Holz, N. E., Zwiers, M. P., Charman, T., . . . Banaschewski, T. (2021). Atypical brain asymmetry in autism—a candidate for clinically meaningful stratification. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*, 6(8), 802-812.
- Forsberg, K. J., Reyes, A., Wang, B., Selleck, E. M., Sommer, M. O., & Dantas, G. (2012). The shared antibiotic resistome of soil bacteria and human pathogens. *science*, 337(6098), 1107-1111.

- Forsyth, A., Herrman, E., Raslan, K., Ortiz, S., Lee, C., & Galhano, A. (2018). Autism Spectrum Disorder in Children: Behavioral, Sensory and Gastrointestinal Considerations and Assessment of Oral Health. *J Dent Oral Biol.* 2018; 3 (4), 1138.
- Ghoshal, U. C., Shukla, R., Ghoshal, U., Gwee, K.-A., Ng, S. C., & Quigley, E. M. (2012). The gut microbiota and irritable bowel syndrome: friend or foe? *International journal of inflammation*, 2012.
- Gibson, M. K., Wang, B., Ahmadi, S., Burnham, C.-A. D., Tarr, P. I., Warner, B. B., & Dantas, G. (2016). Developmental dynamics of the preterm infant gut microbiota and antibiotic resistome. *Nature microbiology*, 1(4), 1-10.
- Guerreiro, C. S., Calado, Â., Sousa, J., & Fonseca, J. E. (2018). Diet, microbiota, and gut permeability—the unknown triad in rheumatoid arthritis. *Frontiers in Medicine*, 5, 349.
- Half, E., Keren, N., Reshef, L., Dorfman, T., Lachter, I., Kluger, Y., . . . Stein, A. (2019). Fecal microbiome signatures of pancreatic cancer patients. *Scientific reports*, 9(1), 1-12.
- Hayat, A. A., Meny, A. H., Salahuddin, N., Alnemary, F. M., Ahuja, K.-R., & Azeem, M. W. (2019). Assessment of knowledge about childhood autism spectrum disorder among healthcare workers in Makkah-Saudi Arabia. *Pakistan journal of medical sciences*, 35(4), 951.
- Hemmati, M., Yousefi, B., Bahar, A., & Eslami, M. (2021). Importance of heme oxygenase-1 in gastrointestinal cancers: functions, inductions, regulations, and signaling. *Journal of Gastrointestinal Cancer*, 52(2), 454-461.
- Hewitt, A., Hall-Lande, J., Hamre, K., Esler, A. N., Punyko, J., Reichle, J., & Gulaid, A. A. (2016). Autism spectrum disorder (ASD) prevalence in Somali and non-Somali children. *Journal of Autism and Developmental Disorders*, 46(8), 2599-2608.
- Hsiao, E. Y., McBride, S. W., Hsien, S., Sharon, G., Hyde, E. R., McCue, T., . . . Petrosino, J. F. (2013). Microbiota modulate behavioral and physiological abnormalities associated with neurodevelopmental disorders. *Cell*, 155(7), 1451-1463.
- Hu, Y., Gao, G. F., & Zhu, B. (2017). The antibiotic resistome: gene flow in environments, animals and human beings. *Frontiers of Medicine*, 11(2), 161-168.
- Hughes, H. K., Rose, D., & Ashwood, P. (2018). The gut microbiota and dysbiosis in autism spectrum disorders. *Current neurology and neuroscience reports*, 18(11), 1-15.
- Huovinen, P., Sundström, L., Swedberg, G., & Sköld, O. (1995). Trimethoprim and sulfonamide resistance. *Antimicrobial agents and chemotherapy*, 39(2), 279-289.
- Jassim, N., Baron-Cohen, S., & Suckling, J. (2021). Meta-analytic evidence of differential prefrontal and early sensory cortex activity during non-social sensory perception in autism. *Neuroscience & Biobehavioral Reviews*, 127, 146-157.
- Khan, A. S., AlGhadeer, H. A., Mohammed, A., Al-Qassimi, T. M. A.-J., Al-Momen, H. H., & Al-Nazzal, M. Y. (2020). Autism in Saudi Arabia, a challenge to Saudi families: a cross-sectional study. *International Journal of Medicine in Developing Countries*, 4(9), 1453-1458.

- Kovtun, A. S., Averina, O. V., Alekseeva, M. G., & Danilenko, V. N. (2020). Antibiotic resistance genes in the gut microbiota of children with autistic spectrum disorder as possible predictors of the disease. *Microbial Drug Resistance*, 26(11), 1307-1320.
- Krajmalnik-Brown, R., Lozupone, C., Kang, D.-W., & Adams, J. B. (2015). Gut bacteria in children with autism spectrum disorders: challenges and promise of studying how a complex community influences a complex disease. *Microbial Ecology in Health and Disease*, 26(1), 26914.
- Kral, T. V., Eriksen, W. T., Souders, M. C., & Pinto-Martin, J. A. (2013). Eating behaviors, diet quality, and gastrointestinal symptoms in children with autism spectrum disorders: a brief review. *Journal of pediatric nursing*, 28(6), 548-556.
- Kumar, A., & Schweizer, H. P. (2005). Bacterial resistance to antibiotics: active efflux and reduced uptake. *Advanced drug delivery reviews*, 57(10), 1486-1513.
- Kurokawa, S., Kishimoto, T., Mizuno, S., Masaoka, T., Naganuma, M., Liang, K.-c., . . . Suda, W. (2018). The effect of fecal microbiota transplantation on psychiatric symptoms among patients with irritable bowel syndrome, functional diarrhea and functional constipation: an open-label observational study. *Journal of affective disorders*, 235, 506-512.
- Liu, B., & Pop, M. (2009). ARDB—antibiotic resistance genes database. *Nucleic acids research*, 37(suppl\_1), D443-D447.
- Lord, C., Elsabbagh, M., Baird, G., & Veenstra-Vanderweele, J. (2018). Autism spectrum disorder. *The lancet*, 392(10146), 508-520.
- MacFabe, D. F. (2015). Enteric short-chain fatty acids: microbial messengers of metabolism, mitochondria, and mind: implications in autism spectrum disorders. *Microbial ecology in health and disease*, 26(1), 28177.
- Marchesi, J. R., & Ravel, J. (2015). The vocabulary of microbiome research: a proposal. In (Vol. 3, pp. 1-3): Springer.
- Martinez, J. L. (2014). General principles of antibiotic resistance in bacteria. *Drug Discovery Today: Technologies*, 11, 33-39.
- Mead, J., & Ashwood, P. (2015). Evidence supporting an altered immune response in ASD. *Immunology letters*, 163(1), 49-55.
- Moore, A. M., Patel, S., Forsberg, K. J., Wang, B., Bentley, G., Razia, Y., . . . Dantas, G. (2013). Pediatric fecal microbiota harbor diverse and novel antibiotic resistance genes. *PloS one*, 8(11), e78822.
- Munita, J. M., & Arias, C. A. (2016). Mechanisms of antibiotic resistance. *Virulence mechanisms of bacterial pathogens*, 481-511.
- Murray, C. J., Ikuta, K. S., Sharara, F., Swetschinski, L., Aguilar, G. R., Gray, A., . . . Wool, E. (2022). Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. *The Lancet*, 399(10325), 629-655.
- Özcan, E., & Hsiao, E. Y. (2022). Are changes in the gut microbiome a contributor or consequence of autism—why not both? *Cell Reports Medicine*, 3(1), 100505.

- Pehrsson, E. C., Tsukayama, P., Patel, S., Mejía-Bautista, M., Sosa-Soto, G., Navarrete, K. M., . . . Bertoli, M. T. (2016). Interconnected microbiomes and resistomes in low-income human habitats. *Nature*, *533*(7602), 212-216.
- Pfeifer, Y., Cullik, A., & Witte, W. (2010). Resistance to cephalosporins and carbapenems in Gram-negative bacterial pathogens. *International Journal of Medical Microbiology*, *300*(6), 371-379.
- Pourmohamadreza-Tajrishi, M., & Azadfallah, P. (2019). The Effectiveness of Therapeutic Exercise on Motor Skills and Attention of Male Students with Autism Spectrum Disorder. *International Journal of Psychological and Behavioral Sciences*, *13*(7), 354-358.
- Pulikkan, J., Mazumder, A., & Grace, T. (2019). Role of the gut microbiome in autism spectrum disorders. *Reviews on Biomarker Studies in Psychiatric and Neurodegenerative Disorders*, 253-269.
- Randall, C. P., Mariner, K. R., Chopra, I., & O'Neill, A. J. (2013). The target of daptomycin is absent from *Escherichia coli* and other gram-negative pathogens. *Antimicrobial agents and chemotherapy*, *57*(1), 637-639.
- Raymond, F., Boissinot, M., Ouameur, A. A., Déraspe, M., Plante, P.-L., Kpanou, S. R., . . . Ouellette, M. (2019). Culture-enriched human gut microbiomes reveal core and accessory resistance genes. *Microbiome*, *7*(1), 1-13.
- Ren, Z. (2017). Gut microbial profile analysis by MiSeq sequencing of pancreatic carcinoma patients in China. *Oncotarget*. *8*, 95176–95191. In.
- Reygaert, W. (2009). Methicillin-resistant *Staphylococcus aureus* (MRSA): molecular aspects of antimicrobial resistance and virulence. *Clinical Laboratory Science*, *22*(2), 115.
- Reygaert, W. C. (2018). An overview of the antimicrobial resistance mechanisms of bacteria. *AIMS microbiology*, *4*(3), 482.
- Rogers, G., Keating, D. J., Young, R. L., Wong, M.-L., Licinio, J., & Wesselingh, S. (2016). From gut dysbiosis to altered brain function and mental illness: mechanisms and pathways. *Molecular psychiatry*, *21*(6), 738-748.
- Rossignol, D. A., Genuis, S. J., & Frye, R. E. (2014). Environmental toxicants and autism spectrum disorders: a systematic review. *Translational psychiatry*, *4*(2), e360-e360.
- Sabbagh, H. J., Al-Jabri, B. A., Alsulami, M. A., Hashem, L. A., Aljubour, A. A., & Alamoudi, R. A. (2021). Prevalence and characteristics of autistic children attending autism centres in 2 major cities in Saudi Arabia: A cross-sectional study. *Saudi medical journal*, *42*(4), 419.
- Sarkar, C., Basu, B., Chakroborty, D., Dasgupta, P. S., & Basu, S. (2010). The immunoregulatory role of dopamine: an update. *Brain, behavior, and immunity*, *24*(4), 525-528.
- Scher, J. U., Sczesnak, A., Longman, R. S., Segata, N., Ubeda, C., Bielski, C., . . . Abramson, S. B. (2013). Expansion of intestinal *Prevotella copri* correlates with enhanced susceptibility to arthritis. *elife*, *2*, e01202.

- Schmidt, T. S., Raes, J., & Bork, P. (2018). The human gut microbiome: from association to modulation. *Cell*, *172*(6), 1198-1215.
- Schulfer, A. F., Battaglia, T., Alvarez, Y., Bijmens, L., Ruiz, V. E., Ho, M., . . . Rogers, A. B. (2018). Intergenerational transfer of antibiotic-perturbed microbiota enhances colitis in susceptible mice. *Nature microbiology*, *3*(2), 234-242.
- Schultsz, C., & Geerlings, S. (2012). Plasmid-mediated resistance in Enterobacteriaceae: changing landscape and implications for therapy. *Drugs*, *72*, 1-16.
- Sharma, V. K., Johnson, N., Cizmas, L., McDonald, T. J., & Kim, H. (2016). A review of the influence of treatment strategies on antibiotic resistant bacteria and antibiotic resistance genes. *Chemosphere*, *150*, 702-714.
- Singh, S., Verma, N., & Taneja, N. (2019). The human gut resistome: Current concepts & future prospects. *The Indian journal of medical research*, *150*(4), 345.
- Sommer, M. O., Dantas, G., & Church, G. M. (2009). Functional characterization of the antibiotic resistance reservoir in the human microflora. *science*, *325*(5944), 1128-1131.
- Stecher, B., & Hardt, W.-D. (2011). Mechanisms controlling pathogen colonization of the gut. *Current opinion in microbiology*, *14*(1), 82-91.
- Stefani, S., Campanile, F., Santagati, M., Mezzatesta, M. L., Cafiso, V., & Pacini, G. (2015). Insights and clinical perspectives of daptomycin resistance in Staphylococcus aureus: a review of the available evidence. *International journal of antimicrobial agents*, *46*(3), 278-289.
- Stinear, T. P., Olden, D. C., Johnson, P. D., Davies, J. K., & Grayson, M. L. (2001). Enterococcal vanB resistance locus in anaerobic bacteria in human faeces. *The lancet*, *357*(9259), 855-856.
- Sun, J., Liao, X.-P., D'Souza, A. W., Boolchandani, M., Li, S.-H., Cheng, K., . . . Fang, L.-X. (2020). Environmental remodeling of human gut microbiota and antibiotic resistome in livestock farms. *Nature communications*, *11*(1), 1-11.
- Surette, M. D., & Wright, G. D. (2017). Lessons from the environmental antibiotic resistome. *Annual Review of Microbiology*, *71*, 309-329.
- Tavassoli, T., Miller, L. J., Schoen, S. A., Nielsen, D. M., & Baron-Cohen, S. (2014). Sensory over-responsivity in adults with autism spectrum conditions. *Autism*, *18*(4), 428-432.
- Van Gompel, L., Luiken, R. E., Hansen, R. B., Munk, P., Bouwknecht, M., Heres, L., . . . Tersteeg-Zijderfeld, M. H. (2020). Description and determinants of the faecal resistome and microbiome of farmers and slaughterhouse workers: a metagenome-wide cross-sectional study. *Environment international*, *143*, 105939.
- Villagra, N. A., Fuentes, J. A., Jofré, M. R., Hidalgo, A. A., García, P., & Mora, G. C. (2012). The carbon source influences the efflux pump-mediated antimicrobial resistance in clinically important Gram-negative bacteria. *Journal of Antimicrobial Chemotherapy*, *67*(4), 921-927.
- Wells, P. M., Adebayo, A. S., Bowyer, R. C., Freidin, M. B., Finckh, A., Strowig, T., . . . Kirkham, B. (2020). Associations between gut microbiota and genetic risk for rheumatoid

- arthritis in the absence of disease: a cross-sectional study. *The Lancet Rheumatology*, 2(7), e418-e427.
- Whelan, J. (2000). Antibiotics: a possible treatment for regressive-onset autism. *Drug Discovery Today*, 5(11), 487-488.
- Widiger, T. A., & Costa Jr, P. T. (2013). *Personality disorders and the five-factor model of personality: Rationale for the third edition*: American Psychological Association.
- Wimberley, T., Agerbo, E., Pedersen, C. B., Dalsgaard, S., Horsdal, H. T., Mortensen, P. B., . . . Yolken, R. H. (2018). Otitis media, antibiotics, and risk of autism spectrum disorder. *Autism Research*, 11(10), 1432-1440.
- Wood, T. K., Knabel, S. J., & Kwan, B. W. (2013). Bacterial persist cell formation and dormancy. *Applied and environmental microbiology*, 79(23), 7116-7121.
- Wright, G. D. (2019). Environmental and clinical antibiotic resistomes, same only different. *Current opinion in microbiology*, 51, 57-63.
- Xavier, B. B., Das, A. J., Cochrane, G., De Ganck, S., Kumar-Singh, S., Aarestrup, F. M., . . . Malhotra-Kumar, S. (2016). Consolidating and exploring antibiotic resistance gene data resources. *Journal of clinical microbiology*, 54(4), 851-859.
- Yang, S.-J., Kreiswirth, B. N., Sakoulas, G., Yeaman, M. R., Xiong, Y. Q., Sawa, A., & Bayer, A. S. (2009). Enhanced expression of dltABCD is associated with the development of daptomycin nonsusceptibility in a clinical endocarditis isolate of *Staphylococcus aureus*. *The Journal of infectious diseases*, 200(12), 1916-1920.
- Yang, X., Zhang, N., & Schrader, P. (2022). A study of brain networks for autism spectrum disorder classification using resting-state functional connectivity. *Machine Learning with Applications*, 8, 100290.
- Yi, X., Li, Y., Liu, H., Liu, X., Yang, J., Gao, J., . . . Chen, D. (2022). Inflammatory Endotype-Associated Airway Resistome in Chronic Obstructive Pulmonary Disease. *Microbiology Spectrum*, 10(2), e02593-02521.
- Zeidan, J., Fombonne, E., Scolah, J., Ibrahim, A., Durkin, M. S., Saxena, S., . . . Elsabbagh, M. (2022). Global prevalence of autism: a systematic review update. *Autism Research*, 15(5), 778-790.
- Zhang, X.-S., Li, J., Krautkramer, K. A., Badri, M., Battaglia, T., Borbet, T. C., . . . Li, Y. (2018). Antibiotic-induced acceleration of type 1 diabetes alters maturation of innate intestinal immunity. *Elife*, 7.
- Zhang, X.-X., Zhang, T., & Fang, H. H. (2009). Antibiotic resistance genes in water environment. *Applied microbiology and biotechnology*, 82, 397-414.