UNIVERSITY BIRMINGHAM University of Birmingham Research at Birmingham

Antibiotic resistance in the commensal human gut microbiota

Lamberte, Lisa E; van Schaik, Willem

DOI: 10.1016/j.mib.2022.102150

License: Creative Commons: Attribution (CC BY)

Document Version Publisher's PDF, also known as Version of record

Citation for published version (Harvard):

Lamberte, LE & van Schaik, W 2022, 'Ántibiotic resistance in the commensal human gut microbiota', *Current Opinion in Microbiology*, vol. 68, 102150. https://doi.org/10.1016/j.mib.2022.102150

Link to publication on Research at Birmingham portal

General rights

Unless a licence is specified above, all rights (including copyright and moral rights) in this document are retained by the authors and/or the copyright holders. The express permission of the copyright holder must be obtained for any use of this material other than for purposes permitted by law.

•Users may freely distribute the URL that is used to identify this publication.

•Users may download and/or print one copy of the publication from the University of Birmingham research portal for the purpose of private study or non-commercial research.

•User may use extracts from the document in line with the concept of 'fair dealing' under the Copyright, Designs and Patents Act 1988 (?) •Users may not further distribute the material nor use it for the purposes of commercial gain.

Where a licence is displayed above, please note the terms and conditions of the licence govern your use of this document.

When citing, please reference the published version.

Take down policy

While the University of Birmingham exercises care and attention in making items available there are rare occasions when an item has been uploaded in error or has been deemed to be commercially or otherwise sensitive.

If you believe that this is the case for this document, please contact UBIRA@lists.bham.ac.uk providing details and we will remove access to the work immediately and investigate.



ScienceDirect



Antibiotic resistance in the commensal human gut microbiota

Lisa E Lamberte and Willem van Schaik



Antibiotic-resistant infections are a major threat to global public health and there is an urgent need to develop new drugs and interventions to treat and prevent infections caused by antibiotic-resistant bacteria. The human gut microbiota harbours both commensals and opportunistic pathogens which can acquire resistance to antibiotics through mutation and horizontal gene transfer. The powerful combination of modern high-throughput DNA sequencing and microbiological culture methods is providing novel insights into the mechanisms of antibiotic resistance among, up to recently poorly studied, commensal bacteria in the gut. Interventions to minimise the abundance of antibiotic-resistant commensals and opportunistic pathogens include faecal microbiota transplantation and the use of live biotherapeutics, but the efficacy of these treatments remains elusive.

Address

Institute of Microbiology and Infection, College of Medical and Dental Sciences, University of Birmingham, Birmingham B15 2TT, United Kingdom

Corresponding author: Willem van Schaik (w.vanschaik@bham.ac.uk).

Current Opinion in Microbiology 2022, 68:102150 This review comes from a themed issue on Microbiota Edited by Lindsay Hall and Melanie Schirmer

https://doi.org/10.1016/j.mib.2022.102150

1369-5274/© 2022 Elsevier Ltd. All rights reserved.

The human gut microbiota as a reservoir of antibiotic resistance genes

Antibiotic resistance is a grave threat to modern medicine and global public health. The global attributable mortality of antibiotic resistance is estimated to number around 1.3 million deaths [1]. Most of these deaths occur in low-income and middle-income countries, with the highest numbers in South Asia (an estimated 389 000 deaths) and Sub-Saharan Africa (approximately 255 000 deaths) [1]. Antibiotic resistance can be mediated by a variety of mechanisms, with the most important being the prevention of access of the antibiotic to its target, the prevention of the antibiotic binding to its target and the modification or degradation of the antibiotic [2]. Bacteria can develop resistance through mutations, which can then further spread vertically upon cell division to daughter cells. Alternatively, bacteria can acquire mobile genetic elements carrying antibiotic resistance genes in a process termed horizontal gene transfer (HGT). Additionally, genes transferred horizontally may also be inherited vertically from mother to daughter cells (Figure 1), further contributing to the spread of antibiotic resistance genes. Mechanisms of HGT include transformation, transduction, conjugation and DNA transfer via membrane vesicles [3]. Collectively, these pathways of HGT contribute to the global spread of antibiotic resistance genes in microbial ecosystems. The transfer of antibiotic resistance genes is predicted to be particularly high in ecosystems where microbial abundance and diversity are high, such as the bacterial communities found in the human gut $[4\bullet,5]$.

The term 'human gut microbiota' describes the collective of microbes that colonise the human intestinal tract [6]. Members of the gut microbiota typically have a symbiotic relationship with their human host, by supplying nutrients and providing protection from pathogenic organisms [7]. However, opportunistic pathogens can also be present in the gut microbiota. These are mostly carried asymptomatically in healthy individuals but can cause infections, particularly when the host is immunocompromised. These gut-dwelling, opportunistic pathogens include Clostridioides difficile, Escherichia coli and Enterococcus faecium [8-10]. In addition, species in the genus Bacteroides, in particular Bacteroides fragilis, are among the most prominent anaerobic causes of infection, even though they are widely regarded as commensal members of the gut microbiota [11,12]. Indeed, the human gut microbiota is now recognised as a reservoir of antibiotic resistance determinants, termed the 'gut resistome' [13,14]. Thus, there is an interest to study antibiotic resistance in the human gut microbiota and to characterise to what extent the resistome can contribute to the emergence of multidrug-resistant clones of opportunistic pathogens.

In this review, we discuss current research into the human gut resistome using high-throughput DNA sequencing and microbiological culture. We primarily focus on antibiotic resistance in gut commensals as resistance mechanisms of opportunistic pathogens that





colonise the human gut have been reviewed elsewhere [10,15,16]. We will also discuss current strategies to reduce the levels of antibiotic-resistant bacteria in the human gut by microbiota manipulation.

Antibiotic resistance in gut commensals

The human gut microbiota in healthy adults is a generally stable ecosystem that is mostly studied using highthroughput DNA sequencing. Initial studies showed that a large diversity of antibiotic resistance genes exists in the human gut microbiota with genes encoding resistance to tetracyclines, beta-lactams and macrolides being particularly prevalent across gut microbiotas of different individuals [17]. Methods to predict novel antibiotic resistance genes through machine learning approaches or on the basis of the predicted threedimensional structure of the proteins they encode suggest that gut bacteria carry over 6000 uncharacterised antibiotic resistance determinants [18•,19]. With most high-throughput sequencing methods, it remains a challenge to link an antibiotic resistance gene to its bacterial host or hosts. This challenge can be overcome through the use of metagenomic chromosome confirmation capture methods, most prominently by a technique termed Hi-C, in which regions of bacterial DNA that are in close proximity to each other are captured and sequenced [4•]. When antibiotic resistance genes are thus linked to chromosomal markers, the microbial hosts of these antibiotic resistance genes can be identified. Studies using Hi-C have suggested that HGT of resistance genes is frequent in the human gut microbiota [4•]. The taxonomic resolution of Hi-C is, however, often insufficient to identify the hosts of resistance genes down to the strain- or species-level, and may not be able to identify links between resistance genes and chromosomal markers in members of the gut microbiota that are present at low abundance [20]. For this reason, the use of microbiological culture methods to isolate resistant bacteria from the gut microbiota is an essential alternative technique to profile the gut resistome, with high-throughput approaches being used to isolate, identify and characterise the microbial hosts of resistance genes [21].

A systematic study has recently assessed the impact of 144 different antibiotics on a set of strains representing 38 species of gut bacteria [22••]. This study showed that β -lactam resistance among gut commensals is strain-specific and most likely spreads through HGT. Remarkably, both macrolides and tetracyclines selectively kill a wide range of gut commensals, which suggests that these antibiotics may disproportionately affect the gut microbiota during therapy. As the species described in this study are representative to those of the healthy human gut microbiota, we use these bacteria as a basis to

discuss some of the key members of the gut commensal community in the following paragraphs.

Among the quantitatively most prominent members of the gut microbiota, strains from the genus *Bacteroides* have high resistance rates across antibiotic drug classes, particularly β -lactams and tetracyclines [23–25]. Resistance to β -lactams in these genera is linked to the genes *cfxA*, *cfiA*, and *cepA*, while resistance to tetracyclines is linked to the gene *tetQ* [24]. The *tetQ* gene, along with the macrolide resistance gene *ermF*, is carried on a 65-kbp conjugative transposon, named CTnDOT, that is present in 80% of *Bacteroides* spp isolates. CTnDOT excision and conjugative transfer is triggered by exposure to low levels of tetracycline, thus leading to its rapid dissemination among *Bacteroides* strains [26].

The mucin-degrader Akkermansia muciniphila, a species in the phylum Verrucomicrobia, is near ubiquitously present in the adult human gut microbiota, making up approximately 3% of the bacteria in the colon [27]. Levels of A. muciniphila are lower in individuals with a variety of conditions, including obesity, metabolic syndrome and diabetes. This observation has led to research efforts to better understand the impact of A. muciniphila on human health [28]. Antibiotic resistance in A. muci*niphila* has so far been poorly studied. A recent study showed that the type strain of A. muciniphila was resistant to nearly all quinolone antibiotics $[22 \bullet \bullet]$. Genome sequence analysis of 39 Akkermansia muciniphila strains showed that a single strain among this dataset had acquired sulphonamide and aminoglycoside resistance genes through an HGT event from the Salmonella enterica plasmid pRSF1010 [29]. As A. muciniphila is proposed as a live biotherapeutic that could positively contribute to host health [30], a deeper understanding of its antibiotic resistance mechanisms and the potential of its resistance genes to spread horizontally is urgently needed.

Species in the genus *Bifidobacterium* are abundant in the infant gut, but present at lower levels in adult gut. Supplementation of infant nutrition with *Bifidobacterium* to promote health is a topic of considerable interest [31]. It is therefore important to ensure that probiotic *Bifidobacterium* strains are free of any relevant antibiotic resistance genes important to infant gut health. An exception can be made for the gene *ileS*, which confers intrinsic mupirocin resistance [32]. In a study that assessed the resistome of *Bifidobacterium* species from gut metagenome data sets of adults and infants, the tetracycline resistance gene *tetW* was predicted to be carried on a conjugative transposon, suggesting they can be acquired or disseminated via HGT [33].

C. difficile has been shown to develop resistance to metronidazole through the acquisition of a high-copy plasmid, presumably via HGT, although the donor could not be identified [34]. HGT in the gut microbiota appears to be particularly prominent among members of the phylum Firmicutes and it is thus likely that there is widespread sharing of resistance genes in this phylum, including between commensals and opportunistic pathogens, like *C. difficile* and *Enterococcus* [35••].

However, it is still unclear to what extent antibiotic resistance genes in commensals are a threat to human health. An important recent study set out a framework that can be used to assess the risks associated with finding resistance genes in microbial genome sequences [36°]. The resistance genes in the highest risk category are those that are associated with mobile genetic elements in human pathogens. The large majority (81.6%) of antibiotic resistance genes were, however, not associated with mobile genetic elements. These genes are thus likely to be intrinsic determinants of antibiotic resistance, and, if found in a commensal, may not meaningfully contribute to the burden of resistance genes among pathogens.

Interventions to reduce expansion of the gut resistome

The human gut resistome is affected by a variety of factors, including changes in diet and exposure to antibiotics [37,38]. In particular, members of the families Enterobacteriaceae and Enterococcaceae, which contain several opportunistic pathogens, were found to expand and persist during antibiotic treatment of healthy adult individuals [39,40]. Additionally, antibiotic treatment diversifies the resistome across individuals, suggesting that the resistome composition is highly individualised [37]. The impact of the resistome is well recognised in vulnerable individuals such as preterm infants and immunocompromised individuals. In particular, the gut microbiota in hospitalised patients undergoes rapid and dynamic changes, such as the loss of microbial diversity and the expansion of opportunistic pathogens, during their stay [41,42]. However, commensal anaerobes present during admission may prevent the expansion of pathogenic bacteria by suppressing their growth and colonisation [42,43].

Given the importance of the resistome in human health, methods to circumvent the expansion of the resistome by manipulating the microbiota are being explored. Currently, the most-studied methods include faecal microbiota transplantation (FMT), and the use of live biotherapeutics (probiotics) which could suppress the outgrowth of bacteria carrying antibiotic resistance genes (Figure 1). Of these, FMT is the most dramatic intervention to modulate the composition of the gut microbiota as it involves a replacement of the original gut microbiota of the host by new microbiota provided via

the stools of a healthy donor [44]. FMTs are effective in the treatment of recurrent C. difficile infections and FMTs in patients suffering from C. difficile infections have been shown to lead to the elimination of antibiotic resistance genes from the gut microbiota as well [45]. The success of FMT in the treatment of C. difficile infections has spurred several studies into the use of FMT to eradicate gut colonisation by multidrug-resistant bacteria. The authors of a recent systematic review on a total of 36 studies covering 254 patients remarked that variability in patient populations, FMT protocols and the multidrug-resistant bacteria that are being targeted by the treatment complicate the interpretation of data on the efficacy of FMTs on gut colonisation by multidrugresistant bacteria. Despite these limitations, however, FMT was associated with a moderate amount of reduction (ranging from 20% to 90%) of gut colonisation by multidrug-resistant bacteria [46•].

Evidence for the effectiveness of probiotics as a method for microbiota recovery and eradication of antibiotic-resistant bacteria after antibiotic exposure has so far been elusive [47]. Studies using lactic acid bacteria, which are traditionally used in probiotic products, even suggested that probiotics might negatively affect the reconstitution of the gut microbiota post-antibiotic exposure [48]. A recent study determined the impact of taking both antibiotics and probiotics (a commercially available probiotic supplement composed of 11 strains from the Lactobacillus, Bifidobacterium, Streptococcus, and Lactococcus genera) on the human gut resistome. In individuals where the probiotics colonised the gut, and which were not treated with antibiotics, a reduction in antibiotic resistance gene load was observed in an individual-specific way [49•]. Currently, there is significant interest in the use of novel live biotherapeutic products which contain gut commensals that have not been traditionally used as probiotics in food products [50], but no studies have so far studied the impact of these novel products on the levels of antibiotic resistance genes in the gut microbiota [47]. The use of novel live biotherapeutic products can, however, be an intriguing approach as recent studies in gut microcosms suggest that the gut microbiota can suppress growth of E. coli and its evolution towards antibiotic resistance upon exposure to an antibiotic [43]. Other promising interventions include prebiotics, postbiotics, phagemediated therapies, conjugation inhibitors, and vaccines, although only a limited number of studies that has been conducted with inconsistent outcomes [47,51]. Finally, it may be possible to redeploy existing drugs to protect commensal bacteria against exposure to antibiotics. While the precise mechanisms of these antidotes have not been characterised, the anticoagulant dicumarol provided some protection to *Bacteroides vulgatus* upon exposure to erythromycin in a mouse model [22••].

Conclusions

The spread of antibiotic-resistant pathogens is a major public health concern and there are ongoing intensive research efforts to develop new drugs and interventions to treat and prevent multidrug-resistant infections. As commensals in the human gut microbiota frequently carry antibiotic resistance genes, these bacteria may contribute to the emergence of resistant clones of opportunistic pathogens, particularly in the rare events where HGT occurs across phylogenetic barriers [35••,52]. For this reason, there is an interest to develop interventions that reduce the selection for antibiotic-resistant bacteria in the human gut microbiota (Figure 1). Both FMTs and the administration of live biotherapeutics have shown some promise to reduce carriage of multidrug-resistant bacteria in the gut, but significant variations in the success of these interventions have been observed. Due to the complex interactions between the host, the microbiota, and external factors (e.g. diet), it may be unlikely that there will be an easy 'onesize-fits-all' solution to reduce the burden of antibioticresistant bacteria in the gut microbiota. Despite this observation, there remains an urgent need for studies on unravelling the role of gut bacteria in the dissemination of antibiotic resistance genes to opportunistic pathogens. Insights from these studies can be useful to identify novel 'hubs' of resistance gene dissemination among commensal bacteria, potentially leading to the development of targeted approaches to inhibit HGT or to eradicate these strains from the gut.

Conflict of interest statement

The authors declare the following financial interests/ personal relationships which may be considered as potential competing interests: W.v.S. has received consultancy fees from Vedanta Biosciences.

Acknowledgements

L.E.L. and W.v.S. are funded through Biotechnology and Biological Sciences Research Council (BB/S017941/1). Work in the lab of W.v.S. is also supported by a Royal Society Wolfson Merit Award (WM160092).

References and recommended reading

Papers of particular interest, published within the period of review, have been highlighted as:

- of special interest
- •• of outstanding interest.
- Antimicrobial Resistance Collaborators: Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. Lancet 2022, 399:629-655.
- Blair JMA, Webber MA, Baylay AJ, Ogbolu DO, Piddock LJV: Molecular mechanisms of antibiotic resistance. Nat Rev Microbiol 2015, 13:42-51.
- McInnes RS, McCallum GE, Lamberte LE, van Schaik W: Horizontal transfer of antibiotic resistance genes in the human gut microbiome. Curr Opin Microbiol 2020, 53:35-43.
- Kent AG, Vill AC, Shi Q, Satlin MJ, Brito IL: Widespread transfer of mobile antibiotic resistance genes within individual gut

microbiomes revealed through bacterial Hi-C. Nat Commun 2020, 11:4379.

By using the metagenomic chromosomal confirmation capture technique Hi-C, the authors find evidence for pervasive HGT in the gut, microbiota including, perhaps surprisingly, between different phyla.

- Groussin M, Poyet M, Sistiaga A, Kearney SM, Moniz K, Noel M, Hooker J, Gibbons SM, Segurel L, Froment A, et al.: Elevated rates of horizontal gene transfer in the industrialized human microbiome. Cell 2021, 184:2053-2067 e18.
- 6. Marchesi JR, Ravel J: The vocabulary of microbiome research: a proposal. *Microbiome* 2015, **3**:31.
- Ducarmon QR, Zwittink RD, Hornung BVH, van Schaik W, Young VB, Kuijper EJ: Gut microbiota and colonization resistance against bacterial enteric infection. *Microbiol Mol Biol Rev* 2019, 83:e00007-19.
- Wyres KL, Hawkey J, Mirčeta M, Judd LM, Wick RR, Gorrie CL, Pratt NF, Garlick JS, Watson KM, Pilcher DV, et al.: Genomic surveillance of antimicrobial resistant bacterial colonisation and infection in intensive care patients. BMC Infect Dis 2021, 21:683.
- Gasparrini AJ, Wang B, Sun X, Kennedy EA, Hernandez-Leyva A, Ndao IM, Tarr PI, Warner BB, Dantas G: Persistent metagenomic signatures of early-life hospitalization and antibiotic treatment in the infant gut microbiota and resistome. Nat Microbiol 2019, 4:2285-2297.
- Tougas SR, Lodha N, Vandermeer B, Lorenzetti DL, Tarr PI, Tarr GAM, Chui L, Vanderkooi OG, Freedman SB: Prevalence of detection of Clostridioides difficile among asymptomatic children: a systematic review and meta-analysis. JAMA Pediatr 2021, 175:e212328.
- Cobo F, Aliaga L, Expósito-Ruiz M, Navarro-Marí JM: Anaerobic bacteraemia: a score predicting mortality. Anaerobe 2020, 64:102219.
- Liu W, Cheng M, Li J, Zhang P, Fan H, Hu Q, Han M, Su L, He H, Tong Y, et al.: Classification of the gut microbiota of patients in Intensive Care Units during development of sepsis and septic shock. Genom Proteom Bioinform 2020, 18:696-707.
- 13. van Schaik W: The human gut resistome. Philos Trans R Soc Lond B Biol Sci 2015, 370:20140087.
- Anthony WE, Burnham C-AD, Dantas G, Kwon JH: The gut microbiome as a reservoir for antimicrobial resistance. J Infect Dis 2021, 223:S209-S213.
- Miller WR, Murray BE, Rice LB, Arias CA: Resistance in vancomycin-resistant enterococci. Infect Dis Clin N Am 2020, 34:751-771.
- Ruppé É, Woerther P-L, Barbier F: Mechanisms of antimicrobial resistance in Gram-negative bacilli. Ann Intensive Care 2015, 5:21.
- Ho J, Yeoh YK, Barua N, Chen Z, Lui G, Wong SH, Yang X, Chan MC, Chan PK, Hawkey PM, et al.: Systematic review of human gut resistome studies revealed variable definitions and approaches. Gut Microbes 2020, 12:1700755.
- Ruppé E, Ghozlane A, Tap J, Pons N, Alvarez A-S, Maziers N,
 Cuesta T, Hernando-Amado S, Clares I, Martínez JL, et al.: Prediction of the intestinal resistome by a three-dimensional structure-based method. Nat Microbiol 2019, 4:112-123.

By performing homology comparative modelling of proteins that can be produced by gut bacteria, the authors suggest that many novel antibiotic resistance genes may be present in the genomes of gut bacteria, with most of them awaiting further characterisation.

- Li Y, Xu Z, Han W, Cao H, Umarov R, Yan A, Fan M, Chen H, Duarte CM, Li L, et al.: HMD-ARG: hierarchical multi-task deep learning for annotating antibiotic resistance genes. *Microbiome* 2021, 9:40.
- Yaffe E, Relman DA: Tracking microbial evolution in the human gut using Hi-C reveals extensive horizontal gene transfer, persistence and adaptation. Nat Microbiol 2020, 5:343-353.
- Forster SC, Kumar N, Anonye BO, Almeida A, Viciani E, Stares MD, Dunn M, Mkandawire TT, Zhu A, Shao Y, et al.: A human gut

bacterial genome and culture collection for improved metagenomic analyses. *Nat Biotechnol* 2019, **37**:186-192.

 Maier L, Goemans CV, Wirbel J, Kuhn M, Eberl C, Pruteanu M,
 Müller P, Garcia-Santamarina S, Cacace E, Zhang B, et al.: Unravelling the collateral damage of antibiotics on gut bacteria. Nature 2021, 599:120-124.

A landmark paper that systematically identifies resistance and susceptibility to a wide range of antibiotics among 38 species of gut bacteria. Remarkably, the authors also show, in a proof-of-principle study in a mouse model, that gut commensals can be protected from antibiotics by the administration of agonist drugs.

- Ecale F, El Houari A, Crapart S, Laparre J, Ramnath M, Berjeaud J-M, Rodier M-H, Crépin A: In vitro sensitivity of 30 anaerobic bacterial strains of the human intestinal core microbiota to antibiotics: culture and LC-MS/MS approaches. *Anaerobe* 2021, 67:102314.
- Sóki J, Wybo I, Hajdú E, Toprak NU, Jeverica S, Stingu C-S, Tierney D, Perry JD, Matuz M, Urbán E, et al.: A Europe-wide assessment of antibiotic resistance rates in *Bacteroides* and *Parabacteroides* isolates from intestinal microbiota of healthy subjects. Anaerobe 2020, 62:102182.
- 25. Kierzkowska M, Majewska A, Mlynarczyk G: Trends and impact in antimicrobial resistance among *Bacteroides* and *Parabacteroides* species in 2007–2012 compared to 2013–2017. *Microb Drug Resist* 2020, 26:1452-1457.
- Waters JL, Salyers AA: Regulation of CTnDOT conjugative transfer is a complex and highly coordinated series of events. *mBio* 2013, 4:e00569-13.
- Collado MC, Derrien M, Isolauri E, de Vos WM, Salminen S: Intestinal integrity and Akkermansia muciniphila, a mucin- degrading member of the intestinal microbiota present in infants, adults, and the elderly. Appl Environ Microbiol 2020, 73:7767-7770.
- de Vos WM: Microbe Profile: Akkermansia muciniphila: a conserved intestinal symbiont that acts as the gatekeeper of our mucosa. *Microbiol* 2017, 163:646-648.
- Guo X, Li S, Zhang J, Wu F, Li X, Wu D, Zhang M, Ou Z, Jie Z, Yan Q, et al.: Genome sequencing of 39 Akkermansia muciniphila isolates reveals its population structure, genomic and functional diversity, and global distribution in mammalian gut microbiotas. BMC Genom 2017, 18:800.
- Cheng D, Xie MZ: A review of a potential and promising probiotic candidate-Akkermansia muciniphila. J Appl Microbiol 2021, 130:1813-1822.
- Alcon-Giner C, Dalby MJ, Caim S, Ketskemety J, Shaw A, Sim K, Lawson MAE, Kiu R, Leclaire C, Chalklen L, et al.: Microbiota supplementation with *Bifidobacterium* and *Lactobacillus* modifies the preterm infant gut microbiota and metabolome: an observational study. *Cell Rep Med* 2020, 1:100077.
- 32. Serafini F, Bottacini F, Viappiani A, Baruffini E, Turroni F, Foroni E, Lodi T, van Sinderen D, Ventura M: Insights into physiological and genetic mupirocin susceptibility in Bifidobacteria. *Appl Environ Microbiol* 2011, **77**:3141-3146.
- Duranti S, Lugli GA, Mancabelli L, Turroni F, Milani C, Mangifesta M, Ferrario C, Anzalone R, Viappiani A, van Sinderen D, et al.: Prevalence of antibiotic resistance genes among human gutderived Bifidobacteria. Appl Environ Microbiol 2017, 83:e02894-16.
- Boekhoud IM, Hornung BVH, Sevilla E, Harmanus C, Bos-Sanders IMJG, Terveer EM, Bolea R, Corver J, Kuijper EJ, Smits WK: Plasmid-mediated metronidazole resistance in *Clostridioides difficile*. Nat Commun 2020, 11:598.
- Forster SC, Liu J, Kumar N, Gulliver EL, Gould JA, Escobar-Zepeda
 A, Mkandawire T, Pike LJ, Shao Y, Stares MD, et al.: Strain-level characterization of broad host range mobile genetic elements transferring antibiotic resistance from the human microbiome. Nat Commun 2022, 13:1445.

The authors show widespread horizontal antibiotic resistance gene transfer, including across different phyla, genes among gut bacteria by comparing more than 40 000 genomes of commensals and pathogens.

Broad host-range HGT is experimentally verified from gut commensals to the pathogen Klebsiella oxytoca.

36. Zhang A-N, Gaston JM, Dai CL, Zhao S, Poyet M, Groussin M, Yin
X, Li L-G, van Loosdrecht MCM, Topp E, et al.: An omics-based framework for assessing the health risk of antimicrobial resistance genes. Nat Commun 2021, 12:4765.

While antibiotic resistance genes can be easily identified in genomes and metagenomes, there is still a lack of understanding of the risks that these genes may pose to humans. This paper provides an important conceptual step forward by providing a systematic risk assessment of antibiotic resistance genes.

- Li J, Rettedal EA, van der Helm E, Ellabaan M, Panagiotou G, Sommer MOA: Antibiotic treatment drives the diversification of the human gut resistome. Genom Proteom Bioinform 2019, 17:39-51.
- Schwartz DJ, Langdon AE, Dantas G: Understanding the impact of antibiotic perturbation on the human microbiome. *Genome Med* 2020, 12:82.
- Kang K, Imamovic L, Misiakou M-A, Bornakke Sørensen M, Heshiki Y, Ni Y, Zheng T, Li J, Ellabaan MMH, Colomer-Lluch M, *et al.*: Expansion and persistence of antibiotic-specific resistance genes following antibiotic treatment. *Gut Microbes* 2021, 13:1-19.
- Palleja A, Mikkelsen KH, Forslund SK, Kashani A, Allin KH, Nielsen T, Hansen TH, Liang S, Feng Q, Zhang C, et al.: Recovery of gut microbiota of healthy adults following antibiotic exposure. Nat Microbiol 2018, 3:1255-1265.
- 41. Ravi A, Halstead FD, Bamford A, Casey A, Thomson NM, van Schaik W, Snelson C, Goulden R, Foster-Nyarko E, Savva GM, et al.: Loss of microbial diversity and pathogen domination of the gut microbiota in critically ill patients. *Microbial Genomics* 2019, 5:e000293.
- Chanderraj R, Brown CA, Hinkle K, Falkowski N, Ranjan P, Dickson RP, Woods RJ: Gut microbiota predict *Enterococcus* expansion but not vancomycin-resistant *Enterococcus* acquisition. mSphere 2020, 5:e00537-20.
- 43. Baumgartner M, Bayer F, Pfrunder-Cardozo KR, Buckling A, Hall AR: Resident microbial communities inhibit growth and antibiotic-resistance evolution of *Escherichia coli* in human gut microbiome samples. *PLoS Biol* 2020, 18:e3000465.
- Allegretti JR, Mullish BH, Kelly C, Fischer M: The evolution of the use of faecal microbiota transplantation and emerging therapeutic indications. *Lancet* 2019, 394:420-431.
- 45. Millan AS: Evolution of plasmid-mediated antibiotic resistance in the clinical context. *Trends Microbiol* 2018, **26**:978-985.
- 46. Bilsen MP, Lambregts MMC, van Prehn J, Kuijper EJ: Faecal
 microbiota replacement to eradicate antimicrobial resistant bacteria in the intestinal tract – a systematic review. Curr Opin Gastroenterol 2022, 38:15-25.

The authors of this recent systematic review provide a synthesis of the outcomes of cohort studies and case reports into the application of FMT to eradicate antibiotic-resistant bacteria from the gut.

- Wuethrich I, Pelzer B W, Khodamoradi Y, Vehreschild MJGT: The role of the human gut microbiota in colonization and infection with multidrug-resistant bacteria. *Gut Microbes* 2021, 13:1911279.
- 48. Suez J, Zmora N, Zilberman-Schapira G, Mor U, Dori-Bachash M, Bashiardes S, Zur M, Regev-Lehavi D, Ben-Zeev Brik R, Federici S, et al.: Post-antibiotic gut mucosal microbiome reconstitution is impaired by probiotics and improved by autologous FMT. Cell 2018, 174:1406-1423 e16.
- 49. Montassier E, Valdés-Mas R, Batard E, Zmora N, Dori-Bachash M,
 Suez J, Elinav E: Probiotics impact the antibiotic resistance gene reservoir along the human Gl tract in a person-specific and antibiotic-dependent manner. Nat Microbiol 2021, 6:1043-1054.

This study provides important insights into the complex, often highly individual-specific, interactions between antibiotic exposure and the use of a commercially available oral probiotic on the gut resistome.

- O'Toole PW, Marchesi JR, Hill C: Next-generation probiotics: the spectrum from probiotics to live biotherapeutics. Nat Microbiol 2017, 2:1-6.
- 51. Palencia-Gándara C, Getino M, Moyano G, Redondo S, Fernández-López R, González-Zorn B, de la Cruz F: Conjugation inhibitors

effectively prevent plasmid transmission in natural environments. *mBio* 2021, **12**:e01277-21.

 Ellabaan MMH, Munck C, Porse A, Imamovic L, Sommer MOA: Forecasting the dissemination of antibiotic resistance genes across bacterial genomes. Nat Commun 2021, 12:2435.