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Review

The effect of antibiotics on the composition of the intestinal microbiota - a systematic review

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SUMMARY

Objective: Antibiotics change the composition of the intestinal microbiota. The magnitude of the effect of antibiotics on the microbiota and whether the effects are short-term or persist long-term remain uncertain. In this review, we summarise studies that have investigated the effect of antibiotics on the composition of the human intestinal microbiota.

Methods: A systematic search was done to identify original studies that have investigated the effect of systemic antibiotics on the intestinal microbiota in humans.

Results: We identified 129 studies investigating 2076 participants and 301 controls. Many studies reported a decrease in bacterial diversity with antibiotic treatment. Penicillin only had minor effects on the intestinal microbiota. Amoxicillin, amoxcillin/clavulanate, cephalosporins, lipopolyglycopeptides, macrolides, ketolides, clindamycin, tigecycline, quinolones and fosfomycin all increased abundance of Enterobacteriaea other than *E. coli* (mainly *Citrobacter* spp., *Enterobacter* spp. and *Klebsiella* spp.). Amoxcillin, cephalosporins, macrolides, clindamycin, quinolones and sulphonamides decreased abundance of *E. coli*, while amoxcillin/clavulante, in contrast to other penicillins, increased abundance of *E. coli*. Amoxicllin, piperacillin and ticarcillin, cephalosporins (except fifth generation cephalosporins), carbapenems and lipoglycopeptides were associated with increased abundance of *Enterococcus* spp., while macrolides and doxycycline decreased its abundance. Piperacillin and ticarcillin, carbapenems, macrolides, clindamycin and quinolones strongly decreased the abundance of anaerobic bacteria. In the studies that investigated persistence, the longest duration of changes was reported after treatment with ciprofloxacin (one year), clindamycin (two years) and clarithromycin plus metronidazole (four years). Many antibiotics were associated with a decrease in butyrate or butryrate-producing bacteria.

Conclusion: Antibiotics have profound and sometimes persisting effects on the intestinal microbiota, characterised by diminished abundance of beneficial commensals and increased abundance of potentially detrimental microorganisms. Understanding these effects will help tailor antibiotic treatment and the use of probiotics to minimise this 'collateral damage'.

Introduction

The human intestine is the habitat for a rich and diverse community of microbes consisting of archaea, bacteria, eukaryota (fungi, helminths, and protozoans) and viruses. So far, more than 1000 bacterial species have been identified,[1] but it has been suggested that there might be up to 36,000 different species of bacteria living in the intestine.[2] Even though it was previously thought that 80% of the intestinal microbiota cannot be cultured,[3] the main genera (such as *Bacteroides* spp., *Bifidobacterium* spp., *Clostridium* spp., *Enterobacteriaceae, Enterococcus* spp., *Lactobacillus* spp. and *Veillonella* spp.) are regularly identified in bacterial cultures. More recently, novel methods using selective culture media have enabled the majority of species within the microbiota to be cultured.[4,5] Metagenomic shotgun sequencing provides a more in-depth analysis of the intestinal microbiota, including identification of bacterial species, resistance genes, as well as the identification of eukaroytes and viruses. Apart from being involved in various metabolic functions, the intestinal microbes are also crucial for the development of the immune system and regulation

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of immune responses. The complex interplay between a 'healthy' and 'dysbiotic' intestinal microbiota, which influences many health outcomes, remains incompletely understood.[6–8]

Antibiotics are among the most commonly prescribed drugs. Despite their benefits, their use has been associated with both short- and long-term adverse health outcomes, including increased risk of necrotising enterocolitis,[9,10] bronchial hypersensitivity and asthma,[11] obesity[12] and autoimmune diseases.[13] Antibiotic administration leads to perturbations in the intestinal microbiota through which some of these adverse health outcomes are likely mediated. This 'collateral damage' to the micobiota includes changes in abundance of certain taxa, a decrease in 'colonisation resistance' (protection against colonisation with potentially pathogenic (e.g. *Enterobacteriaceae*) or opportunistic (e.g. *Clostridium difficile, Candida* spp.)) organisms, and the development of antibiotic resistance.[14] The human intestine has the highest density of microbes of all known environments. Bacteria living in the human intestine have a 25-fold higher rate of gene transfer than bacteria in other settings,[15] and antibiotic exposure further increases horizontal gene transfer.[16–20]

The effect of antibiotics on the intestinal microbiota likely depends on the spectrum of activity (narrow vs broad spectrum), formulation, route of administration, pharmacokinetics and pharmacodynamics (e.g. biliary secretion), as well as dose and duration of administration. The extent of the effect of antibiotics on the composition of microbiota and whether the effects are only short-term or persist long-term remain uncertain. Additionally, it is uncertain whether antibiotic-resistant strains persist in the absence of selective pressure through antibiotics.

In this review, we summarise studies that have investigated the effect of antibiotics on the composition of the human intestinal microbiota. Understanding these effects will help tailor antibiotic treatment to minimise this 'collateral damage'.

Systematic review methods

In January 2019, MEDLINE (1946 to present) was searched using the Ovid interface with the following search terms: (antibacterial agents OR anti-infective agents OR anti-microbial agents OR antibiotics OR antitubercular agents OR penicillins OR amoxicillin OR carbapenems OR cephalosporins OR macrolides OR quinolones OR glycopeptides OR aminoglycosides OR tetracyclines OR tigecycline OR daptomycin OR streptogramin OR linezolid OR colistin OR trimethoprim OR sulphonamides OR nitrofurantoin OR fosfomycin) AND (bacteria OR microbio* OR faeces OR faces OR feces OR fecal OR stool OR intestin* OR intestinal mucosa OR gastrointestinal microbiome OR gastrointestinal tract OR gastrointestinal disease). All studies in humans investigating the effect of systemic antibiotic exposure on the composition of the intestinal microbiota were included. Exclusion criteria comprised studies in which: results were not reported in English; the antibiotic regime was not specified; antibiotics were not given systemically; concurrent probiotics were administered; rectal swabs rather than stool samples were analysed. Also excluded were studies which included participants with: *C. difficile* or other intestinal infections; underlying malignancies; immunosuppressive therapy; colorectal surgery. References of retrieved articles were hand-searched for additional publications. The selection of included studies is summarised in Fig. 1. The following variables were extracted from the included studies: year of study, country, study design, number and characteristics of participants, age of participants, previous antibiotic treatment, antibiotic treatment (drug, dose, frequency, route of administration, duration), microbiome analysis method, timing of stool analysis in relation to start of antibiotic treatment and key findings (including changes in diversity, abundance of microbes, short chain fatty acids (SCFAs) and antibiotic resitance). The ROBINS-1 tool was used to assess risk of bias.[21]

Systematic review results

Our search identified 24,718 studies. Of these, 100 fulfilled the inclusion criteria. Hand-searching references identified 29 further relevant studies. The 129 studies included in this review investigated 2076 participants and 301 controls. The results of these studies are summarised in Table 1 and supplementary Tables 1 and 2.[22–150] All of the studies were done in industrialised countries: Belgium 3, Denmark 1, France 8, Germany 12, Greece 1, Iceland 3, Italy 3, Japan 5, Poland 1, Spain 2, Switzerland 1, Sweden 60, the Netherlands 14, United Kingdom 7, United States 11 (three studies were done in two different countries). The number of participants in each study ranged from 1 to 84 (median 12, mean 16). The majority of studies (102) included healthy participants. The remaining studies included participants with sinusitis 1, lower respiratory tract infections 2, bronchitis 2, chronic obstructive pulmonary disease 1, skin, soft tissue or bone infections 3, urinary tract infections 5, diverse infections 3, liver cirrhosis 3, dyspeptic disorder 1, maxillo-facial surgery 1, gastric surgery 1 and *Helicobacter pylori* infection 3. In one study, participants' characteristics were not specified. Multiple methods were used to determine the bacterial intestinal microbiota, including bacterial culture 109, pulsed-field gel electrophoresis (PFGE) 2, terminal restriction fragment length polymorphism (T-RFLP) 3, temporal temperature gel electrophoresis restriction fragment length polymorphism (TTGE) 3, polymerase chain reaction (PCR) 4, matrix-assisted laser desorption ionisation-time of flight mass spectrometry (MALDI-TOF-MS) 1, 16S rRNA gene sequencing 15 (Illumina MiSeq 1, Roche 454 GS FLX Titanium 9, Roche 454 GS Junior 1, Roche 454 not further specified 2, sequencing machine not specified 2; hypervariable regions V1-V2 1, V1-V3 2, V3-V4 1, V3-V5 1, V3+V6 1, V4 2, V5-V7 3, V6 1, V6-V8 1, region not specified 2), metagenomic shotgun sequencing 1 (Illumina MiSeq). Seven studies used two different methods and one study three different methods. Bacterial diversity was assessed in 8 studies. Concentrations of SCFAs in stool were measured in 7 studies. The risk of bias in the studies included in this review is summarised in supplementary Table 3.

Tables 1 and supplementary Tables 1 and 2, as well as Fig. 2, provide a summary of the main findings of the 129 studies included in this review.

Penicillins

The effect of penicillin on the intestinal microbiota was investigated in four studies that included 38 participants and six controls.[22–25] All four studies used bacterial culture for assessment. The three studies that measured penicillin in stool did not detect the antibiotic.[22–24] In two studies, no changes in abundance of bacteria were observed.[23,24] One study reported new colonisation with *Klebsiella* spp. and an increase in abundance of *Clostridium* spp. and *E. coli* during treatment[22] and another study an increase in abundance of *Enterococcus* spp.[25] In both studies, bacterial abundance returned to pre-antibiotic levels 14 days after stopping antibiotic treatment (AT).[22,25] Penicillin was not reported to influence abundance of fungi. No increase in penicillin-resistance was observed in intestinal bacteria during or after treatment.[23,24] One study measured concentrations of SCFAs and did not find any changes in fecal concentrations during pencillin administration.[24]

The effect of amoxicillin, ampicillin and bacampicillin on the intestinal microbiota has been investigated in 13 studies including 194 participants and 41 controls.[23,25–34,143,149] Ten studies used bacterial culture and three studies 16S rRNA sequencing (plus

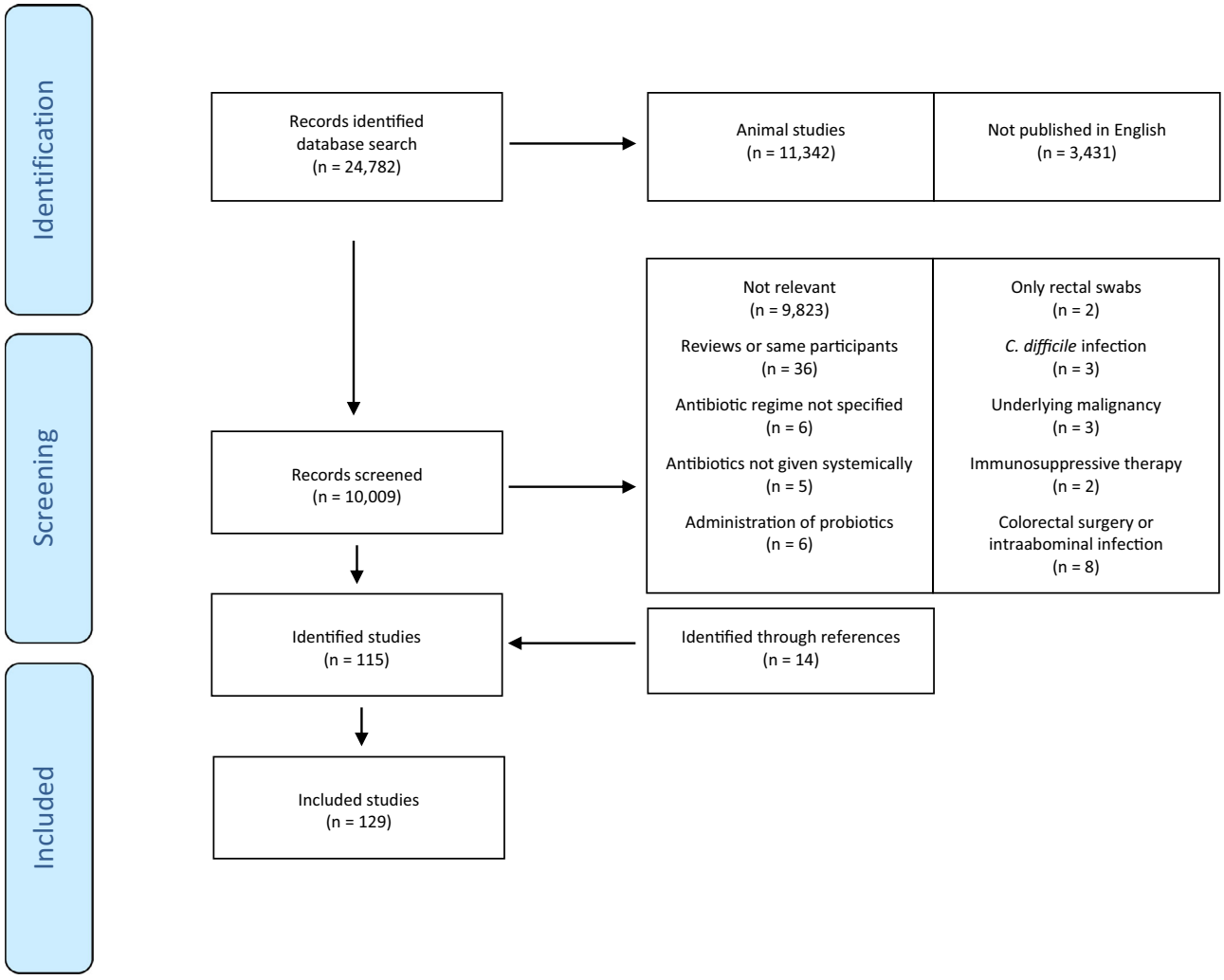


Fig. 1. Selection of studies.

TTGE and metagenomic shotgun sequencing in one study each). Four studies measured amoxicillin concentrations in stool and could not detect the antibiotic.[31,34,143,149] Only one study assessed bacterial microbiota diversity and did not find any influence of amoxicillin on bacterial diversity.[26]

Another study measured intra-individual similarity indices and reported that, three days after the start of amoxicillin treatment, a dissimilarity of 46% was reached compared to pre-treatment.[28] Similarity returned to 89% of the pre-treatment state 60 days after stopping AT.[28]

Amoxicillin was associated with decreased abundance of *E. coli*[29–32] in 12 of the 13 studies,[27] but an increased abundance of *Enterobacteriaea* other than *E. coli* (*Citrobacter* spp., *Enterobacter* spp., *Klebsiella* spp., *Morganella* spp., *Pseudomonas* spp. and *Shigella* spp.).[27,29–33] Results in relation to Gram positive aerobic bacteria were inconsistent with most studies reporting an increase in abundance of *Enterococcus* spp.,[25,29,32,33] *Staphylococcus* spp.[31] and *Streptococcus* spp.,[31,32] but some studies also reporting no influence on the abundance of these bacteria[30–33,149] or a mild decrease.[32]

During treatment with amoxicillin, an increase in abundance of *Alistipes* spp.,[26] *Bacteroides* spp.,[26,27,33] *Bifidobacterium* spp.,[32,33] *Eubacterium* spp.,[31,33] *Lactobacillus* spp.,[33] *Parabacteroides* spp.,[26] *Phascolarctobacterium* spp.[26] and *Rominococcus* spp.[28] was reported. In contrast, the abundance of *Anaerostipes* spp.,[26] *Blautia* spp.,[26] *Collinsella* spp.,[26] *Coprococcus* spp.,[26] *Dilaster* spp.,[26] *Fusobacerium* spp.,[34] *Lachnospirum* spp.,[26] *Marvinbryantia* spp.,[26] *Oscillospira* spp.,[27] *Peptostreptococcus* spp.,[34] *Roseburia* spp.,[26,27] and *Veillonella* spp.[26,29,34] decreased. Two studies reported a small increase in *Clostridium* spp. during or after treatment with amoxicillin,[28,29] while another study reported a decrease 28 days after treatment.[31] New colonisation with *C. difficile* was reported in only one study (in two participants).[33] Five studies reported that bacterial abundance returned to pre-antibiotic levels seven to 21 days after stopping AT.[25,30–32,149] However, seven studies, especially the ones including sequencing techniques for analysis, reported that bacterial abundance had not returned to pre-antibiotic levels 12 months after stopping AT.[26–29,33,34] Four studies reported an increase in yeast (*C. albicans* in one study) during treatment with amoxicillin,[29,30,32,33] which persisted 28 to 55 days after stopping AT in three studies.[28,29,33] Six studies reported an increase in amoxicillin-resistant *Enterobactericaeae, Enterococcus* spp., *E. coli* or beta-lactamase concentrations in stool.[29–32,143] The increase in amoxicillin-resistant *Enterobacteriaceae* and the increase in beta-lactamase concentrations persisted 21 to 28 days after stopping AT in all,[29-31,33] but one study.[32]

In the one study, which administered omeprazole to controls, *Enterobacteriaea* and *Enterococcus* spp. also increased during

Table 1a
Changes in the abundance of aerobic bacteria in the intestinal microbiota associated with adminstration of antibiotics (reported on genus level).

Increased abundance | Decreased abundance | Inconsisted findings
Increased abuandance or no change | Decreased abundance or no change | No change in aubundance
White boxes depict that no finfings were reported for the respective bacteria

	AEROBIC BACTERIA																		
	Total number	*ACINETOBACTER*	*BACILLUS*	*CITROBACTER*	*CORYNEBACTERIUM*	*ENTEROBACTERIACEAE**	*ENTEROBACTER*	*ENTEROCOCCUS*	*ESCHERICHIA*	*KLEBSIELLA*	*MORGANELLA*	*MICROCOCCUS*	*PROTEUS*	*PSEUDOMONAS*	*SALMONELLA*	*STAPHYLOCOCCUS*	*STREPTOCOCCUS*	Other bacteria	Normalisation (after antibiotic treatment)
PENICILLINS																			
Penicillin[22-25]	na[22-25]		na[22]			na[24]		↓[25] na[22,24]	↑[22] na[25]	↑[22]							na[22,24]		d14[22,25]
Amoxicillin[26-33,149]	↑GN[30]		na[32]	↑[29]	↑[32]	↑[29,31,33]	↑[29,31,32]	↑[29,32,33] na[30,31,149]	↓[26-32] ↑[27]	↑[26-32,149]	↑[29]			↑[33]		↑[31] na[32,33]	↑[31,32] ↓[32] na[33]	↑*Shigella*[27]	d7-d21[30-32,149] not d28-55[27-29,33] not 12m[26]
Ampicillin[25]	na[25]							↑[25]	na[25]										d14[25]
Bacampicillin[23,34]						na[34]		na[34]									na[34]		
Pivmecillinam[35]			na[35]				↑[35]	na[35]	↓[35]	↑[35]									
Mezlocillin[25]	na[25]							na[25]	na[25]								↓[35]		d14[35]
Azlocillin[36]								↓[36]	↓[36]	↑[36]							↓[36]		d14[36]
Flucloxacillin[37]				↑[37]		↑[37]			↑[37]	↑[37]			↑[37]						
Amoxicillin/clavulanate[37-40,147]				↑[37]		↑[37,39,40]	↑[38]	↑[147]	↑[37-39,147]	↑[37] na[147]									d14-d28[36,147] not d14-d60[39,40]
Piperacillin[25]	na[25]							↑[25]	↑[25]										d14[25]
Ticarcillin[25]	na[25]							↑[25]	na[25]										d14[25]
Ticarcillin/clavulanate[41]			na[41]		na[41]	↓[41]		↑[41]				na[41]				na[41]	↑[41]		d14[41]
CEPHALOSPORINS																			
Cefadroxil[22]			na[22]					na[22]	na[22]							na[22]	↓[22]		d14[22]
Cephaloridine[25]	na[25]							na[25]	na[25]										
Cephazolin[25]																			
Cefaclor[33,42,43]				↑[43]		↑[33] na[42]	↑[43]	↑[33] na[42]		↑[43]						↑[43] ↓[33]	↓[33] na[42]		not d14-42[33,43]
Cefprozil[44]						↓[44]		↑[44]								↑[44]			d4[44]
Cefuroxime axetil[45,46,50,149]			na[45]	↑[46]		↓[46] na[45]	↑[46]	↑[45,50,149]	↓[46] na[149]	↑[46]					↑[50]	↑[45] ↓[46] na[50]	↑[45]		d14[46,50,149] not d14[45]
Cefuroxime[25]	na[25]							↑[25]	na[25]										d14[25]
Cefoxitin[23,25,47]	na[25]			↑[47]		↑↓[23]	↑[23]	↑↓[23] na[25]	na[25]				↑[47]	↑[23]		↑[47]	↑[47]		d14[23]
Cefotetan[25]	↓[25]							↑[25]	↓[25]										d14[25]
Latamoxef[25]	↑[25]							↑[25]	↓[25]										d14[25]
Loracarbef[30,48]	na[30,48]		na[48]		na[48]	na[48]		↑[30,48]		↑[30]		na[48]				na[48]	↑[48]		d7[48] not d21[30]
Cefixime[43,49,50]						↓[43,50]		↑[49,50]	↓[43,49]						↑[50]	↑[50] na[50]	↓[49]		d14[49] not d14[50]
Cefoperazone[51,52]			↓[51]		↑[52] ↓[51]	↓[52]		↑[51]		↑[51]				↑[52]		↑[52] ↓[51]	↓[51]	↑Stenotrophomonas[51]	
Cefotaxime[25]	na[25]							na[25]	na[25]										

(*continued on next page*)

Table 1a (*continued*)

Ceftriaxone[25,53-58,150]	↑[25] ↑GN bacilli[54]		↑[56] na[58]			↑[57,59]		↑[25,54,56-59,150]	↓[25,56,58,59,150]							↑[56] ↓[57,59]	↓[57,59]		d12-28[25,58,150] not d9-15[54,56,57,59]
Cefpodoxime proxetil[31,50,59,149]						↓[50,149]		↑[31,149] na[50]	↓[31,149]	↓[31]						↑[31,149] na[50]	↓[31]		d14[31]
Ceftibuten[60,149]			na[60]			↑[60] ↓149		↑[60,149]	↓[60,149]								↓[60]		d14[60,149]
Ceftazidime/avibactam[61]						↓[61]		↑[61]	↑[61]										not d15[61]
Cefetamet-pivoxil[50]						↓[50]													not d14[50]
Cefepime[62]			na[62]		na[62]	na[62]		na[62]	↓[62]							na[62]	na[62]		d13[62]
Cefpirome[63]									↓[63]										d14[63]
Ceftaroline[64]				↑[64]				na[64]	↓[64]	↑[64]									not d14[64]
Ceftaroline/avibactam[65]						↓[65]		↓[65]	↓[65]	↑[65]									d18[65]
Ceftobiprole[66]							na[66]	↓[66]	↓[66]										d14[66]
CARBAPENEMS AND PENEMS																			
Meropenem[67]			na[67]		na[67]	↓[67]		↑[67]				na[67]				na[67]	↓[67]		d14[67]
Lenapenem[68]	na[68]		na[68]					na[68]						na[68]		na[68]	↓[68]		d10[68]
Ertapenem[150]								↑[150]	↓[150]										d28[150]
Ritipenem acoxil[69]																			
LIPOGLYCOPEPTIDES																			
Vancomycin[70]																↓[70]			d7[70]
Teicoplanin[70]	↑[70] ↑GN bacilli[70]							↑[70]								↓[70]	↑[70]		d7[70]
Telavancin[71]						↑[71]		na[71]	na[71]										not d14[71]
Dalbavancin[72]						↑[72]	↑[72]	↑[72]		↑[72]									not d28[72]
AMINOGLYCOSIDES																			
Paromomycin[73]									↑[73]										not d43[73]
MACROLIDES AND KETOLIDES																			
Spiramycin[74]																			
Erythromycin[76,77]					↓[76]	↑[76] ↓[77]		↓[76] ↓[77]	↓[76]							↑[76]	↓[76] ↓[77]		d14[76] not d11[77]
Clarithromycin[75,76,81,146]			na[76,146]	↑[75,146]	na[76]	↓[76,146]	↑[75,146]	↓[146] na[75,76,81]	↓[75,81,146] ↑[76]	↑[75,146]		↓[75] ↑[146] na[76]		↑[146]		↓[75] ↑[146] na[76]	↓[76] ↑[146] na[75]		d14-28[75,76,81,146]
Roxithromycin[78]						↓[78]	na[78]							na[78]		na[78]			d7[78]
Dirithromycin[79]								na[79]	↓[79]							↑[79]	↑[79]		d16[79]
Telithromycin[75]				↑[75]			↑[75]	↓[75]	↓[75]	↑[75]		↑[75]				↑[75]	na[75]		d14[75]
Solithromycin[80]						↑[80]		↓[80]	↓[80]										d7[80]
Azithromycin[81]								na[81]	↓[81]										d14[81]
LINCOSAMIDES																			
Clindamycin[24,26,83-90]	↓GP[83]			↑[88-90]		↑[24,90] ↓[88]	↑[88-90]	↑[24,90] ↓[87,89]	↓[88] na[90]	↑[88-90]						↓[90]	↑[24] ↓[90]		2m[83] not d14[89,90] not 6m[87,88]
TETRACYCLINES																			
Doxycycline[91,92]						↓[92] na[91]	↑[92]	↓[91,92]	↓[91]	↑[92]			↑[92]				↓[92]		d9-28[91,92]
Minocycline[26]																			
GLYCYLCYCLINE																			
Tigecycline[93,94]						↑[93,94] ↓[93]	↑[94]	↑[94] ↓[93,94]	↓[94]	↑[94]									d20[93] not d21[94]
STREPTOGRAMINS																			
Quinupristin/dalfopristin[95]						↑[95]	↑[95]							na[95]					d30[95]
OXAZOLIDINONES																			
Linezolid[147]								↓[147]	na[147]	↑[147]									d28[147]
QUINOLONES																			
Nalidixic acid[96]						na[96]		na[96]	↓[96]										

(*continued on next page*)

Table 1a (*continued*)

Norfloxacin[97-99,128,142]	↓GN bacilli[98]		na[97]		na[97]	↓[97-99,142]		na[97,128,142]	↓[128]								na[97]	na[97,128]		d7-14[97,99,142] not d7[128]
Ofloxacin[101,102,114,120]	↓GN bacilli[102]		↓[101]		↓[101,120]	↓[101,102,114]		↓[101,114,120]	↓[114,120]								↑[101]	↓[102] ↑[102]		d7-28[101,102,120] not d6[102]
Enoxacin[103]			na[103]			↓[103]	↑[103]	na[103]				na[103]		↑[103]			na[103]	na[103]	↑*Flavobacterium*[103]	d14[103]
Fleroxacin[104]						↓[104]		↓[104]	↓[104]											not 17d[104]
Lemofloxacin[105,106]			na[105]		na[105]	↓[105,106]		na[105]										↑[106] na[105]		d14[105] not d7[106]
Ciprofloxacin[26,82-84,96,98,107-111,113-119,148]	↓[116,117] ↓coliforms[119] ↓GN bacilli[98,148] ↓GN[83,112]			↑[112,118,119]		↓[96,98,111,113-116]	↑[119] ↓[112]	↑[83,96,111,112] ↓[108,113,114,117] na[148]	↓[83,111,112,114,118]	↓[112]			↑[118]	↓[112] na[116]		↑[111] ↓[111-113,116,117,119]	↓[113,117,119]	↑*Acinetobacter*[112] ↑*Alcaligenes*[112] ↑*Xantomonas*[112]	d3-60[83,112,115-117] not d7-60[96,108,111,113,116,118,119]
Levofloxacin[120,121]			↓[120,121]			↓[120,121]		↓[120,121]	↓[120]											d7[120] not d14[121]
Sparfloxacin[122]			na[122]					↓[122]	↓[122]								na[122]	na[122]		not d49[122]
Moxifloxacin[146]			na[146]					↓[146]	↓[146]								na[146]	na[146]		d28[146]
Gatifloxacin[123]							na[123]	↓[123]	↓[123]								↑[123]			d10[123]
Gemifloxacin[124,125]			na[124]			↓[125]		↓[124,125]	↓[124,125]								na[124,125]	↓[124]		d21[124]
Clinafloxacin[126]				↑[126]		↑[126]	↑[126]	↑[126] ↓[126]	↓[126]	↑[126]								↑[126]		not d14[126]
Pefloxacin[96,127]	↓GN bacilli[127]					↓[96]		↑[96] ↓[127]												not d14[96]
Rulfoxacin[128,151]								na[128,151]	↓[128]									na[128]		not d7[128]
Garenoxacin (BMS-284756)[129]			↓[129]		↓[129]	↓[129]		↑[129]									na[129]			d14[129]
Sitafloxacin (DU-6859a)[130]			↓[130]			↓[130]		↓[130]												not d14[130]
Trovafloxacin[125,131]				↑[125]		↓[125]		↓[125]	↓[125]	↑[125]									↑Hafnia[125]	
NITROIMIDAZOLES																				
Tinidazole[77]	na[77]																			
TRIMETHOPRIM AND SULPHONAMIDES																				
Sulphasomidine[133]									↓[133]											
Sulphalene[133]									↓[133]											
Trimethoprim[132]	↓coliforms[132]	↑[132]						↑[132]						↑[132]						not d14[132]
Trimethoprim/sulfamethoxazole[132,142]	↓coliforms[132]					↓[142]		na[142]												d14[142] not d14[132]
POLYMYXINS																				
Polymyxin E[134]						↓[134]		↓[134]												
ANTIBIOTICS BELONGING TO OTHER CLASSES																				
Nitrofurantoin[107,135,142]						↓[142]		↓[142]												
Fosfomycin[136,137]				↑[136]			↑[136,137]	↓[136]	↓[137]	↑[136,137]				↑[136]			↓[137]			d12[136] d14[137]
Rifaximin[138,139]							na[139]	na[139]										↓[138] na[139]		
MCB3837[140]						↓[140]		↓[140]	↓[140]											d14[140]
COMBINATION OF SEVERAL ANTIBIOTICS																				
Amoxicillin plus metronidazole[143]				↑[143]		↑[143]		↑[143]	na[143]	↑[143]										d28[143]
Clarithromycin plus metronidazol[143-145]						↑[143,145]		↑[143-145]	↓[143]	↑[145]										d28[143,145]
Cefuroxime axetil followed vancomycin[46]				↑[46]			↑[46]		↑[46]	↑[46]										not d21[46]
Ciprofloxacin plus clindamycin[148]				↑[148]				↑[148]												

* genus level not available

d – day
GN – Gram negative
GP – Gram positive
m – months
na – not affected
y – years

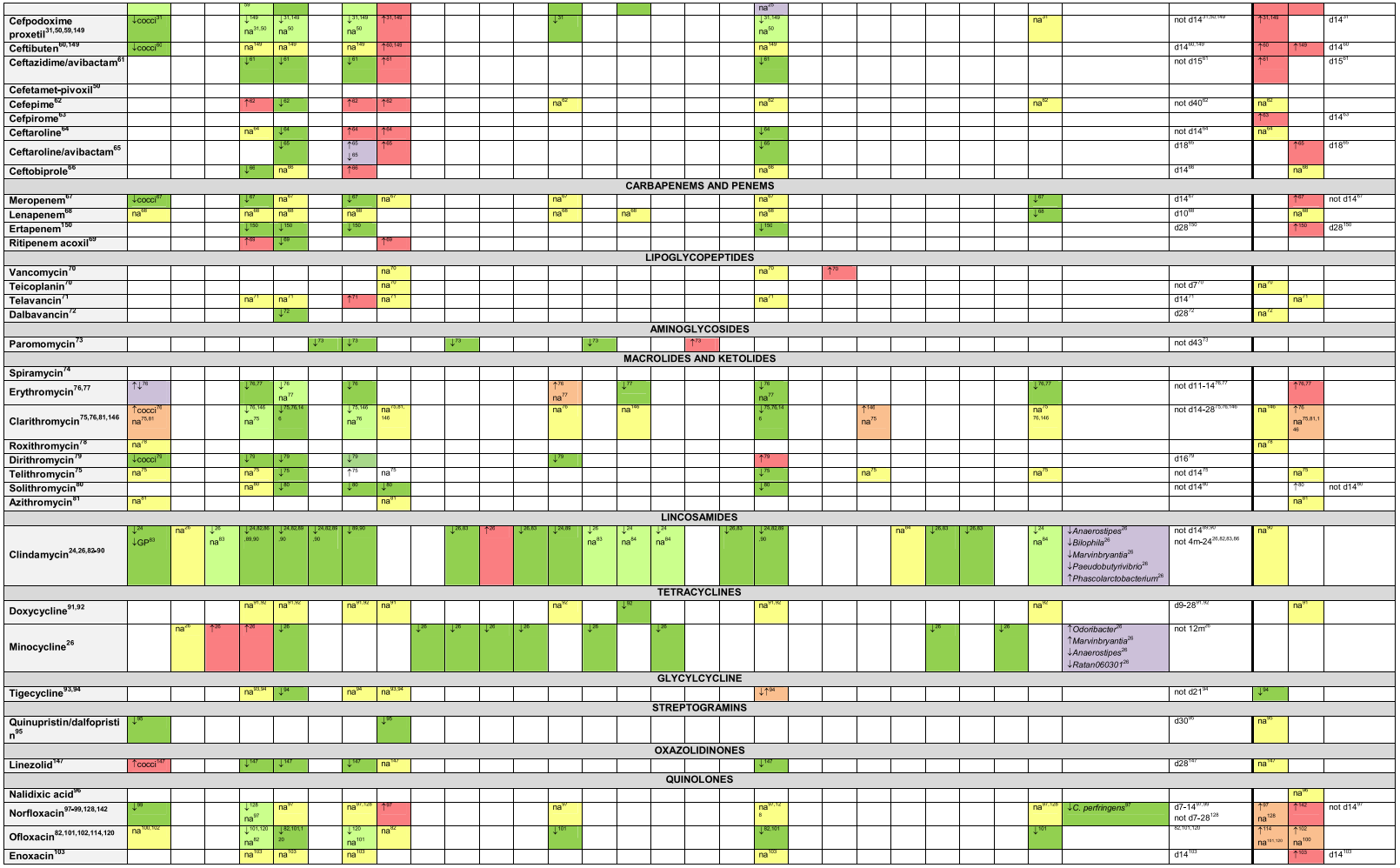
Table 1b
Changes in the abundance of anaerobic bacteria and fungi in the intestinal microbiota associated with adminstration of antibiotics (on genus level).

Increased abundance | Decreased abundance | Inconsisted findings
Increased abuandance or no change | Decreased abundance or no change | No change in aubundance
White boxes depict that no finfings were reported for the respective bacteria

	ANAEROBIC BACTERIA																												FUNGI		
	Total number	*AKKERMANSIA*	*ALISTIPES*	*BACTEROIDES*	*BIFIDOBACTERIUM*	*BLAUTIA*	*CLOSTRIDIUM*	*C. DIFFICILE*	*COLLINSELLA*	*COPROCOCCUS*	*DIALISTER*	*DOREA*	*EUBACTERIUM*	*FAECALIBACTERIUM*	*FUSOBACTERIUM*	*GARDNERELLA*	*HOLDEMANIA*	*LACHNOSPIRUM*	*LACTOBACILLUS*	*PARABACTEROIDES*	*PEDICOCCUS*	*PEPTOSTREPTOCOCCUS*	*PREVOTELLA*	*ROSEBURIA*	*RUMINOCOCCUS*	*SUTTERELLA*	*VEILLONELLA*	Other bacteria	Normalisation (after antibiotic treatment)	YEAST	*CANDIDA*	Normalisation (after antibiotic treatment)
PENICILLINS																															
Penicillin[22–25]	na[22,23]			na[22,24, 25]	na[24]		↑[22] na[24,25]						na[24]		na[24]				na[24,25]								na[24]		d14[22]			
Amoxicillin[26–33,149]	↓GP cocci[29] ↓cocci[33] na[30,149]	na[26]	↑26	↑26,27,33 na[29,31, 149]	↑32,33 na[29,31, 149]	↓26	↑28,29 ↓31 na[32,33, 149]	↑33 na[30,31, 149]	↓26	↓26	↓26,27	↓26	↑31,33 na[32]	↓27				↓26	↑33 na[29,31, 32]	↑26				↓26,27	↑28		↓26,29	↑Phascolarctobacterium[26] ↓Anaerostipes[26] ↓Oscillospira[27] ↓Marvinbryantia[26]	d14-21[30,31] not d28-55[27–29,33] not 12m[26]	↑29,30,32 na[31,149]	↑33	d7-21[30,32] not d28-55[28,29,33]
Ampicillin[25]	na[25]			na[25]			↑25												↓25									d14[25]			
Bacampicillin[23,34]				na[34]	na[34]		na[34]						na[34]		↓34				na[34]			↓34				↓34		not d7[34]			
Pivmecillinam[35]	na[35]			na[35]	na[35]		na[35]												na[35]							na[35]					
Mezlocillin[25]	na[25]			na[25]			↓25												na[25]									d14[25]			
Azlocillin[36]				↓36			↓36	na[36]					↓36						↓36									d14[36]		↑36	
Flucloxacillin[37]																															
Amoxicillin/clavulanate[37–40,147]	↑cocci[147]			↑40 na[147]	↓39,40,147		↓40,147												↓147	↑38				↓38	na[39]			d28[147] not d14-60[38–40]	↑37		
Piperacillin[25]	na[25]			↓25			na[25]											↓25										d14[25]			
Ticarcillin[25]	na[25]			↓25			↓25												↓25									d14[25]			
Ticarcillin/clavulanate[41]				na[41]	↓41		↓41						↓41						↓41									d14[41]	na[41]		
CEPHALOSPORINS																															
Cefadroxil[22]				na[22]			na[22]																					d14[22]			
Cephaloridine[25]																															
Cephazolin[25]	na[25]			na[25]			na[25]	na[25]											na[25]												
Cefaclor[33,42,43]	↓cocci[42]			↑33 na[42]	↓43 na[33,42]		↓43 na[33,42]	↑43					na[33,42]						na[33,42]									d7[42] not d14-42[33,43]	na[42]	↑33,43	not d14-42[33,43]
Cefprozil[44]	↓cocci[44]			↑44																								d4[44]			
Cefuroxime axetil[45,50,149]				↑149 na[45]	↓45,46 na[50,149]		↓45,46,149	↑45,50,149					na[45]						↓46 na[50,149]		↑46					na[50]	↑C. perfringens[50]	d14[46,50,149] not d14[45]		↑45,149	not d14[45]
Cefuroxime[25]	na[25]			na[25]			na[25]	↑25											na[25]												
Cefoxitin[23,25,47]	na[25]			↓23 ↑47 na[25]	na[23,47]		↓25 ↑47 na[23]	↑25					na[23,47]		↓23 na[47]				↓47 ↑ na[25]									d14[23,25]	na[46]		
Cefotetan[25]	↓25			↓25			na[25]	↑25											na[25]									d14[25]			
Latamoxef[49]	na[25]			na[25]			na[25]	↑25											↓48									d14[25]			
Loracarbef[30,48]	na[30,48]			na[48]	↓48		na[48]	↑30 na[48]					↓48						↓48										↑30		d21[30]
Cefixime[49,50]				↓49 na[50]	↓49,50 na[50]		↓49,50	↑49,50											na[50]							na[50]	↑C. perfringens[50]	d14[49,50] not d14[50]	↑54	↓50	not d14[50]
Cefoperazone[51,52]	↓52			↓51	↓51		na[51]	↑51 ↓52					↓51		↓51				↓51											↑52	
Cefotaxime[25]	na[25]			na[25]			na[25]	↑25											na[25]												
Ceftriaxone[25,53–58,150]	↓53,55 na[25]			↓53,55-57,150 na[25,58]	↓53,55-58,150		↓58,150 na[25,59]	↑25,53,57 59					↓57		↓57				↓56 ↓58,59,150									d5-28[25,53,55,56,150] not d9-15[54,56,57,59]	↑57,59	↑56,58,150	d11-28[54,56,150] not d9-15[54,56,57,59]

(continued on next page)

Table 1b (*continued*)



(*continued on next page*)

Table 1b (*continued*)

Fleroxacin[104]					na[104]														na[104]									not d17[104]		↑[104]	not 17[104]
Lemofloxacin[105,106]	↓[106] na[106]			↓[105]	na[105]		na[105]						na[105]		na[105]				na[105]							↓[105]		d14[105]	na[105,106]		
Ciprofloxacin[26,82-84,96,98,107-119,148]	↓cocci[117] ↓GP[83] na[116,119]	na[26]	↓[26,83,109]	↓[113,116,117] ↑[26,107] na[112,118]	↓[107,113,117,118] ↑[83]	↑[107]	↓[113,116,117] na[107,112]	na[118]		↓[26] na[83]	↓[107]	na[83]	↑[107] ↓[117]	na[107]	↓[117] na[84]	↓[26]	↓[26]	na[83]	↓[113,117] na[111,112]				↓[26] na[84]	↑[107] na[83]	↓[26,107] na[83]	↓[109]	↓[113] na[84]	↑*Pseudobutyrivibrio*[26] ↓*Anaerotruncues*[26] ↓*Bilophila*[26] ↓*Christensenella*[26] ↓*Oscillospira*[107] ↓*Subdoligranulum*[26] ↓*Thalassospira*[109] ↓*Turicibacter*[26]	d14[113] 12m[83] not d14[111,113] not 6-12m[26,109,110]	↑[114] na[113,115,116,118,119,148]	↑[96,98,111,112]	d14[117] not d14[96,111]
Levofloxacin[120,121]				na[120,121]	↓[120,121]		↓[120,121]	na[121]					na[121]						↓[121] na[120]		↓[121]					↓[121]		d7[120] not d14[121]	↑[121] na[120]		not d14[121]
Sparfloxacin[122]				na[122]	↓[122]		↓[122]	na[122]					na[122]						na[122]							na[122]		na[122]			
Moxifloxacin[146]				na[146]	na[146]		↓[146]	na[146]							na[146]				na[146]		na[146]							d28[146]		na[146]	
Gatifloxacin[123]				na[123]	na[123]		↓[123]								↓[123]											na[166]		d30[123]	na[123]		
Gemifloxacin[125]				↓[125] na[124]	na[124]		na[124]												↓[124] na[125]							na[124]		d21[124]	na[125]	na[124]	
Clinafloxacin[126]				↓[126]	↓[126]		↓[126] ↑[126]	↑[126]											↓[126]									not d14[126]		↑[126]	not d14[126]
Pefloxacin[96,127]																													↑[127]	↑[96]	not d14[96]
Rulfoxacin[128,151]				↓[128,151]			na[128,151]																								
Garenoxacin (BMS-284756)[129]				↓[129]	↓[129]		↓[129]						↑[129]						↓[129]									d14[129]		↑[129]	d14[129]
Sitafloxacin (DU-6859a)[130]				↓[130]	↓[130]		↓[130]						↓[130]						↓[130]		↓[130]					↓[130]		not d14[130]	↑[130]		not d14[130]
Trovafloxacin[125,131]				↓[125]																											
NITROIMIDAZOLES																															
Tinidazole[77]	na[77]																												na[77]		
TRIMETHOPRIM AND SULPHONAMIDES																															
Sulphasomidine[133]																															
Sulphalene[133]																															
Trimethoprim[132]	na[132]																														
Trimethoprim/sulfamethoxazole[132,142]	na[132]																												na[142]		
POLYMYXINS																															
Polymyxin E[134]																															
ANTIBIOTICS BELONGING TO OTHER CLASSES																															
Nitrofurantoin[107,135,142]		na[107]	na[107]	na[107]	↑[135] na[107]	↑[107]				na[107]		na[107]	↓[107]										na[107]	na[107]				d31-43[135]			
Fosfomycin[136,137]				na[136]			na[136]												na[136]											na[136,137]	
Rifaximin[138,139]				na[139]	na[139]		na[139]						↑[139]		na[139]				na[138,139]		na[139]	na[138,139]		na[139]		↓[138,139]					
MCB3837[140]				na[140]	↓[140]		↓[140]												↓[140]											na[140]	d14[140]
COMBINATION OF SEVERAL ANTIBIOTICS																															
Amoxicillin plus metronidazole[143]				na[143]	↓[143]		↓[143]	na[143]											na[143]		↑[143]					na[143]		d28[143]	↑[143]	↑[145]	d28[143]
Clarithromycin plus metronidazole[143-145]				↓[143,145]	↓[143-145]		↓[143,145]	↑[145] na[143]	↓[144]										↓[143,145]		na[143]			↑[144]		na[143]	↓*Actinomyces*[145]	not d28[143,145] not 4y[144]	na[143]	↑[145]	d28[145]
Cefuroxime axetil than vancomycin[46]				↓[46]	↓[46]		↓[46]												↑[46]	↑[46]											not d21[46]
Ciprofloxacin plus clindamycin[148]																														↑[148]	

d – day
GN – Gram negative
GP – Gram positive
m – months
na – not affected
y – years

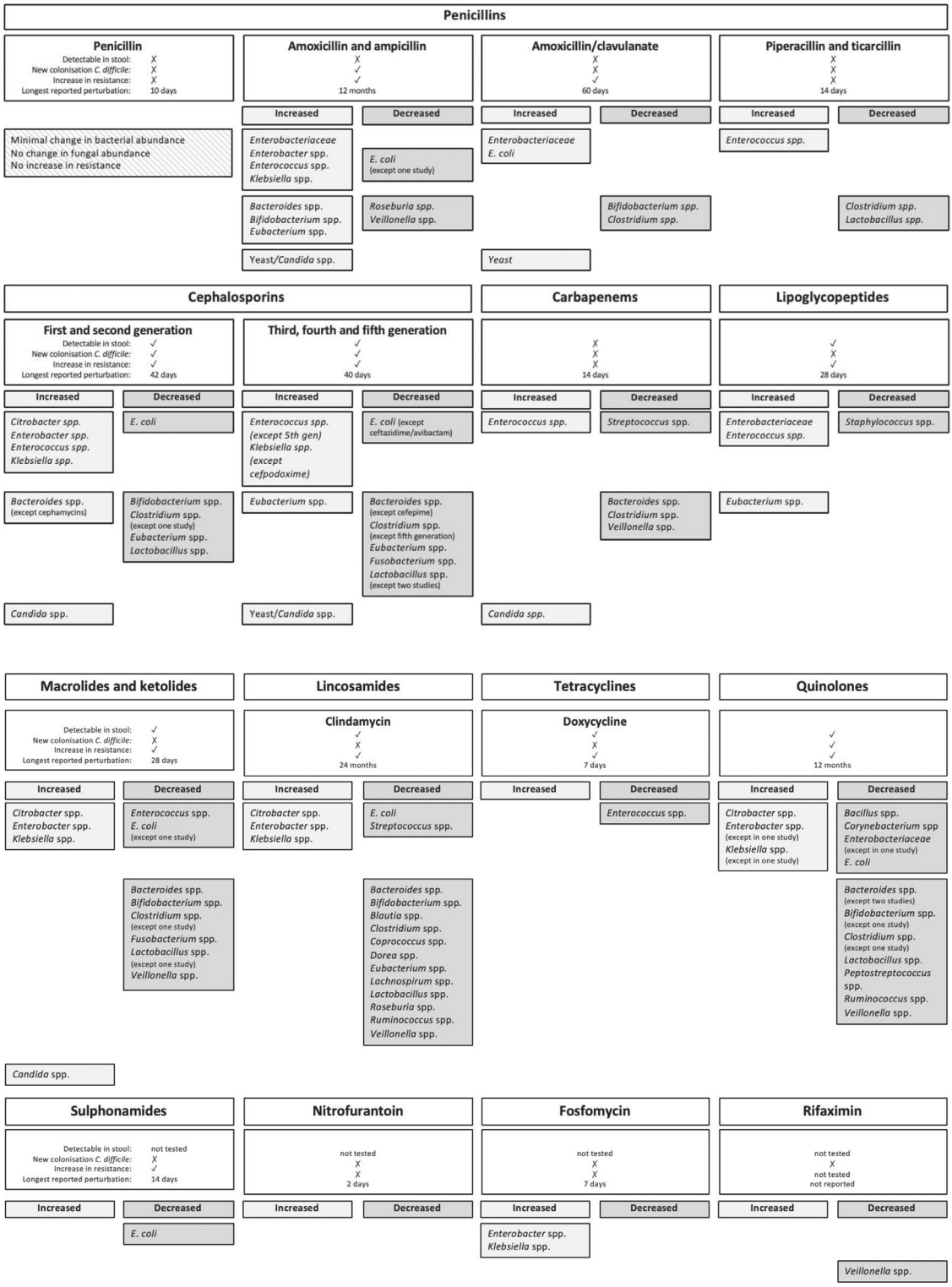


Fig. 2. Summary of findings from studies that have investigated the effect of antibiotics on the intestinal microbiota (findings included only for those reported in two or more studies).

treamtent, but returned to pre-treatment numbers four weeks after stopping the drug.[29]

The effect of other pencillins (pivmecillinam,[35] mezlocillin,[25] azlocillin,[36] flucloxacillin,[37] amoxicillin/clavulanate,[37–40,147] piperacillin,[25] ticarcillin,[25] and ticarcillin/clavulanate[41]) was investigated in nine studies including 131 participants and 30 controls. Bacterial culture was used in six studies, 16S rRNA in two studies and PCR plus TTGE in one study. Only three studies measured antibiotic concenctrations in stool.[35,41,147] Pivemecillinam was the only antibiotic that could be detected (in concentrations of up to 16 mg/kg).[35]

Amoxicillin/clavulante was associated with a decrease in bacterial diversity.[38] The results in relation to changes in abundance of aerobic bacteria were similar to results from studies using

older penicllins with an increase in *Enterobacteriaceae,*[37,39,40] including *Citrobacter* spp.,[37] *Klebsiella* spp.[35-37] and *Proteus* spp.[35-37] Amoxicillin/clavulanate, piperacillin, ticarcillin and ticarcillin/clavulanate were reported to increase the abundance of *Enterococcus* spp.[25,41,147] Additionally (and dissimilar to amoxicillin), flucloxacillin, amoxicillin/clavulanate and piperacillin were associated with an increased abundance of *E. coli.*[37–39,147] In contrast to aerobic bacteria, the abundance of anaerobic bacteria decreased with almost all of these antibiotics (*Clostridium* spp. with mezlocillin;[25] *Bacteroides* spp., *Clostridium* spp., *Eubacterium* spp. and *Lactobacillus* spp. with azlocillin,[36] *Bifidobacterium* spp., *Clostridium* spp., *Lactobacillus* spp. and *Roseburia*. spp. with amoxicillin/clavulanate,[38–40,147] *Bacteroides* spp., *Bifidobacterium* spp., *Clostridium* spp., *Lachnospirum* spp. and *Lactobacillus* spp. with piperacillin, ticarcillin and ticeracillin/clavulante[25,41]). The only exception was an increase in *Bacteroides* spp. and *Parabacteroides* spp. with amoxicillin/clavulanate treatment.[38,40] However, flucloxacillin did not change abundance of anaerobic bacteria.[37] No new colonisation with *C. difficile* was observed in any of the studies. Many studies reported bacterial abundance to return to pre-antibiotic levels 14 to 28 days after stopping AT.[25,35,36,38,41,147] Nevertheless, in three studies, bacterial abundance had not returned to pre-antibiotic levels seven to 60 days after stopping AT.[38–40] An increase in abundance of yeast or *Candida* spp. was reported with azlocillin,[36] flucloxacillin[37] and amoxicillin/clavulanate[37] and persisted 14 days after stopping AT.[37] As with amoxicillin, an increase in resistance was reported for *Enterobacteriacaea*[35,36] and *Enterococcus* spp.[147] Follow-up testing was only done in one study after administration of amoxicillin/clavulanate and resistance persisted in *Enterococcus* spp. on last follow-up testing 28 days after stopping AT.[147]

Cephalosporins

The effect of cephalosporins on the intestinal microbiota was studies in 33 studies that included 510 participants and 53 controls.[22,23,25,30,31,33,42-66,149,150] All studies used bacterial culture. Cefadroxil,[22] cefaclor,[42] ceftaroline[64] and ceftobiprole[66] were not detected in stool, while the other cephalosporins were detected in maximal mean concentrations of 0.4 to 430 mg/kg.[31,45,48,49,54,56,60,61,64,65,149] The highest concentrations were observed for ceftriaxone,[54,56] cefpodoxime proxetil[31,149] and ceftazidime/avibactam.[61]

Most studies using cephalosporins reported a decreased abundance of *Enterobacteriacaea.*[23,43,44,46,50,52,61,65,149] However, four studies reported an increase.[33,57,59,60] All, but one study (using ceftazidime/avibactam),[61] reported a decreased abundance of *E. coli.*[25,31,43,46,49,56,58-60,62-66,149,150] In contrast, the abundance of *Citrobacter* spp.,[43,46,47,64] *Klebsiella* spp.[30,43,46,51,64,65] and *Pseudomonas* spp.[50] increased. *Enterococcus* spp. abundance increased in all studies that used cephalosporins,[23,25,30,31,33,44,45,48-51,54,56–61,149,150] except the ones using ceftaroline/avibactam[65] or ceftobiprole[66] (for which a decreased abundance of *Enterococcus* spp. was reported). Changes in the abundance of *Staphylococcus* spp. and *Streptococcus* spp. were reported in both directions.[22,31,33,43-52,56,57,59,60,149]

The abundance of *Bacteroides* spp. increased with first and second generation cephalosporins,[25,33,44,149] while it decreased with cephamycins[23,47] and higher generation cephalosporins[49,51,53,55-57,61,66,149,150] (the only exception being cefepime for which the abundance of *Bacteroides* spp. also increased).[62] Most studies reported a decrease in the abundance of *Clostridium* spp.,[31,43,45–47,49,50,58,61,149,150] except studies using high-generation cephalosporins (cefepime,[62] ceftaroline,[64] ceftaroline/avibactam[65] and ceftobiprole),[66] for which an increased abundance of *Clostridium* spp. was reported. New colonisation or an increase in *C. difficile* was reported in many studies using cephalosporins.[25,30,31,43,45,49-51,53,57,59-62,64,65,149] The abundance of other anaerobic bacteria was either not affected or (for *Bifidobacterium* spp.,[31,43,45,46,48-51,53,55-59,61,62,64,65,149,150] *Eubacterium* spp.,[31,48,51,57] and *Lactobacillus* spp.[31,46,47,51,58,59,61,64,65,149,150]) decreased. Some studies reported bacterial abundance returned to pre-antibiotic levels 4 to 14 days after stopping AT.[22,23,25,42,44,46,48-50,53,55,58,60,65,66,149,150] However, in many studies, bacterial abundance had not 'normalised' on last testing 14 to 42 days after stopping AT.[31,33,43,45,50,54,56,57,59,61,62,64,149] The abundance of yeast (unkown[30,31,54,57,59-61,63,149] and *Candida* spp.[33,40,43,52,56,58,65,149,150]) increased in many of the studies. The increased abundance of yeast was reported to persist for a shorter duration with higher-generation cephalosporins compared to first- or second-generations cephalosporins.[61,63,65]

An increase in resistance was reported after treatment with cefoxitin (*Bacteroides* spp.,[47] *Clostridium* spp.,[23] *Enterococcus* spp.,[23] *E. agglomerans,*[23] *P. aeruginosa*[23]), cefpodoxime proxetil (*E. cloacae,*[31] non-fermentative Gram negative rods[31]), ceftazidime/avibactam (*Clostridium* spp.,[61] *Enterococcus* spp.,[61] *Lactobacillus* spp.[61]) and ceftaroline/avibactam (*Bacteroides* spp.[65]).

SCFAs in stool were only measured in one study: ceftriaxone decreased concentrations of acetic, butyric, i-butyric, i-valeric, n-valeric, propionic and pyruvic acid and increased the concentration of lactic acid.[55]

Carbapenems and penems

The effect of carbapenems and penems on the intestinal microbiota was investigated in four studies including 37 participants and 10 controls.[67–69,150] All studies used bacterial culture. With meropenem treatment, a decrease in the abundance of *Enterobacteriacaea* was observed.[67] *Enterococcus* spp. increased in abundance with meropenem[67] and ertapenem (the later was also associated with a decreased abundance of *E. coli).*[150] The abundance of *Streptococcus* spp. decreased with meropenem and lenapenem.[67,68] Carbapenems also decreased the abundance of anaerobic bacteria (*Bacteroides* spp., *Clostridium* spp. with meropenem[67] and ertapenem,[150] *Bifidobacterium* spp. and *Lactobacillus* only with ertapenem[150] and *Veillonella* spp. with meropenem[67] and lenapenem[68]). Bacterial abundance returned to pre-antibiotic levels within 28 days after stopping AT in all three studies.[67,68,150] The abundance of *Candida* spp. increased with meropenem and ertapenem treatment and was reported to be persistently elevated 14 days after stopping AT in one study, but not 28 days after stopping AT in another other study.[67,150]

The penem ritipenem acoxil increased the abundance of *Bacteroides* spp., but decreased the abundance of *Bifidobacterium* spp.[69] Five participants became newly colonised with *C. difficile.*[69] An increase in resistance was observed in *Clostridium* spp.[69] In this study an increase in total faecal SCFAs and acetic acid concentrations was reported during treatment with ritipenem acoxil, while concentrations of i-butyric, i-caproic, i-valeric, n-butyric, n-caproic, n-valeric and propionic acid did not change.[69]

Lipopolyglycopeptides

The influence of lipopolyglycopeptides on the intestinal microbiota was investigated in four studies that included 63 participants and 10 controls.[46,70-72] All studies used bacterial culture, and one study additionally used PFGE. Fecal concentrations of orally administiered lipopolyglycopeptides were very high (mean concentrations around 500 mg/kg and maximal concentrations greater than 1800 mg/kg).[46,70] After intravenous administration, mean concentrations of dalbavancin in stool varied between 0.8 and 22 mg/kg[72]

and telavancin could not be detected in stool.[71] Administration of telavancin and dalbavancin led to an increased abundance of *Enterobacteriacaea*[71,72] and administration of teicoplanin and dalbavancin to an increased abundance of *Enterococcus* spp.[70,72] Additionally, dalbavacin also increased the abundance of *Citrobacter* spp. and *Klebsiella* spp. In contrast, the abundance of *Staphylococcus* spp. decreased with oral administration of vancomycin and teicoplanin.[70] Abundance of anaerobic bacteria was reported to increase with lipopolyglycopeptides treatment (*Clostridium* spp. with telavancin,[71] *Lactobacillus* spp. with vancomycin and teicoplanin[70] and *Pepdicoccus* spp. with vancomycin[70]). One study reported bacterial abundance had returned to pre-antibiotic levels seven days after stopping oral vancomycin or teicoplanin.[70] However, in the other studies, bacterial abundance did not returned to pre-antibiotic levels 14 to 28 days after stopping intravenous administration of telavancin and dalbavanvin.[71,72] The abundance of fungi was not affected by lipopolyglycopeptides.[70–72] Administration of vancomycin and teicoplanin led to an increase in resistant bacteria (*Enterococcus* spp.,[46,70] coagulase-negative staphylococci[70] and *Pedicoccus*[46,70]), while no increase in resistance was observed after administration of telavancin or dalbavancin.[71,72]

Aminoglycocides

The effect of aminoglycocides on the intestinal microbiota was investigated in only one study that included five participants and one control.[73] The study used 16S rRNA sequencing. Paromomycin given orally decreased bacterial diversity, increased the abundance of *Escherichia* spp. and *Holdermania* spp., but decreased the abundance of *Ruminococcaceae, Lachnospiraceae, Bautia* spp., *Coprococcus* spp., *C. hiranonis* and *Faecalibacterium prausnitzii.* Pretreatment diversity was reached six to eight weeks after stopping AT.[73] Paromomycin concentration in stool was not measured and resistance was not tested in this study.[73]

Macrolides and ketolides

The effect of macrolides on the intestinal microbiota was investigated in 12 studies that included 188 participants and 36 controls.[74–81,143-146] All studies used bacterial cultures. In all studies that measured antibiotic concentrations in stool, macrolides or ketolides could be detected in high concentrations. Mean concentrations of dirithromycin and solithromycin were lower (30 and 48 mg/kg)[79,80] than concentrations of other macrolides (146 to 978 mg/kg).[74–77,146]

Spiramycin did not have an effect on the abundance of bacteria or fungi.[74] The other macrolides decreased the abundance of *Enterococcus* spp.[75–77,80,146] and *E. coli*[75,76,79–81,146] and increased the abundance of *Citrobacter* spp.,[75,146] *Klebsiella* spp.[75,146] and *Pseudomonas* spp.[146] Changes in abdunance of *Enterobacteriacaea,*[76–78,80,146] *Micrococcus* spp.,[75,146] *Streptococcus* spp.[75,76,79,146] and *Staphylococcus* spp.[76,77,79,146] were observed in both directions. For anaerobic bacteria, macrolides and ketolides decreased the abundance of *Bacteroides* spp.[76,77,79,146] *Bifidobacterium* spp.,[75,76,79,80,146] *Fusobacterium* spp.,[77] *Lactobacillus* spp.[75,76,80,146] (except in one study)[79] and *Veillonella* spp.[76,77] Erthryomycin, clarithromycin and solithromycin decreased the abundance of *Clostridium* spp.,[75,76,80,146] while dirithromycin and telithromycin increased it.[75,79] The abundance of *Eubacterium* spp. was altered in both directions (increased with erythromycin[76] and decreased with dirithromycin[79]).

All, but one study,[77] reported abundance of aerobic bacteria had returned to pre-antibiotic levels seven to 28 days after stopping AT.[75,76,78-81,146] In contrast, for anaerobic bacteria, abundance returned to pre-antibiotic levels 16 days after stopping AT in one study,[79] while in the other studies abundance had not returned to pre-antibiotic levels on last testing 11 to 28 days after stopping AT.[75–77,80,146] An increase in the abundance of *Candida* spp. was reported with erythromycin,[76,77] clarithromycin[76] and solithromycin treatment.[80] Notably, an increase in macrolide-reistance was observerd in almost all of the studies (aerobic bacteria,[77] *Bacteroides* spp.,[75] *Citrobacter* spp.,[79,146] *Clostridium* spp.,[76,77] *Enterobacteriaceae,*[75] *Enterobacter* spp.,[79] *Enterococcus* spp.,[75] Group D streptococci,[74] *Klebsiella* spp.,[79,146] *Proteus* spp.,[79,146] *Pseudomonas* spp.,[79,146] *Serratia* spp.[79] and yeast[77]).

Erythromycin led to a large decrease in fecal concentrations of valeric, isovaleric, 2-methyl-butyric and propionic acids and a minor decrease in acetic, isobutyric and butyric acids.[77]

Lincosamides

The effect of clindamycin on the intestinal microbiota was investigated in 13 studies that included 47 participants and 24 controls.[24,26,83–90,148] Four studies used 16S rRNA sequencing[26,82–84] three studies used PCR, T-RFLP and PFGE,[85,86,88] one study bacterial culture plus T-RFLP[89] and three studies bacterial cultures only.[24,90,148] All studies that measured clindamycin in stool could detect the antibiotic, the mean concentrations varying between 102 and 148 mg/kg.[24,82,83,86] Clindamycin increased the abundance of *Citrobacter* spp.,[88–90] *Enterobacter* spp.[88-90] and *Klebsiella* spp.[88–90] In constrast, the abundance of *E. coli* and *Streptococcus* decreased.[88,90] Changes in abundance of *Enterobacteriaceae,*[24,88,90] *Enterococcus* spp.[24,87,89,90] and *Staphylococcus* spp.[24,90] were reported in both directions.

Clindamycin strongly decreased the abundance of anaerobic bacteria (*Alistipes* spp.,[26] *Anaerostipes* spp.,[26] *Bacteroides* spp.,[24,82,86,89,90] *Bilophila* spp.,[26] *Bifidobacterium* spp.,[24,82,89,90] *Blautia* spp.,[26] *Clostridium* spp.,[89,90] *Coprococcus* spp.,[26,83] *Dorea* spp.,[26,83] *Eubacterium* spp.,[24,89] *Faecalibacterium* spp.,[24] *Fusobacterium* spp.,[26] *Holdemania* spp.,[26,83] *Lachnospirium* spp.,[24,82,89,90] *Marvinbryantia* spp.,[26] *Paeudobutyrivibrio* spp.,[26] *Phascolarctobacterium* spp.,[26] *Prevotella* spp.,[26,83] *Roseburia* spp.,[26,83] and *Veillonella* spp.[24] Notably, no new colonisation or increased colonisation with *C. difficile* was reported. The abundance of fungi was not influenced. Return to pre-antibiotic levels was reported for aerobic bacteria two months after stopping AT in one study,[83] while in all other studies bacterial abundance had not returned to pre-antibiotic levels the time of last testing (14 days,[89,90] 4,[26,82] 12,[83] 6,[87,88] 12[83] and 24 months[86] after stopping AT[87,88]).

Increased resistance to clindamycin was observered in many studies (*Bacteroides* spp.,[86] *Clostridium* spp.,[24] *Enterococcus* spp.,[87] *E. coli,*[88] and *Enterobacteriaceae* other than *E. coli*[89]). One study reported that after seven days of clindamycin therapy, the proportion of clindamycin-resistant strains of *Bacteroides* spp. increased from 3% to 76%. These resistance rates were persistently high 18 months (59%) and 24 months (34%) after stopping AT.[86] Clindamycin decreased fecal concentrations of acetic, valeric, isovaleric, butyric, isobutyric and propionic acids.[24,90]

Tetracyclines

The effect of tetracyclines was investigated in three studies that included 37 participants and 30 controls.[26,91,92] One study used 16S rRNA gene sequencing[26] and the other two studies used bacterial cultures.[91,92] Doxycycline was detected in stool at mean concentrations of 0.5 to 22 mg/kg.[91,92] Doxycycline decreased the abundance of *Enterobacteriaceae, Enterococcus* spp., *E. coli,*

Fusobacterium spp. and *Streptococcus* spp.[91,92] Minocycline was associated with a decrease in bacterial diversity and changes in abundance of many anaerobic bacteria (increased abundance of *Alistipes* spp., *Bacteroides* spp., *Marvinbryantia* spp. and *Odoribacter* spp., decreased abundance of *Anaerostipes* spp., *Bifidoabacterium* spp., *Collinsella* spp., *Coprococcus* spp., *Dialister* spp., *Dorea* spp., *Faecalibacterium* spp., *Gardnerella* spp, *Ratan060301, Roseburia* spp. and *Sutterella* spp.)[26] After doxycycline administration, bacterial abundance was reported to have returned to pre-antibiotic levels nine to 28 days after stopping AT.[91,92] However, the study using minocycline reported that bacterial abundance did not return to pre-antibiotic levels 12 months after stopping AT.[26] No changes in fungal abundance was observed with tetracyclines.

Doxycycline was associated with increased resistance in anaerobic cocci, *Bacteroides* spp., *Bifidobacterium* spp., Enterobactericaeae, *Enterococcus* spp., Gram positive rods and *Lactobacillus* spp.[91,92] Doxycycline was associated with a marked decrease in fecal isobutyric acid (40%) and slight decrease in butyric, propionic and acetic acids.[92]

Glycylcycline

The effects of tigecycline on the intestinal microbiota was investigated in two studies that included 79 participants and 24 controls.[93,94] Both studies used bacterial culture. Mean tigecycline concentrations in stool varied between 2 and 112 mg/kg.[93,94] Tigecycline decreased the total number of *Enterobacteriaceae* and *E. coli*, while the abundance of *Enterobacteriaceae* other than *E. coli* (*Klebsiella* spp. and *Enterobacter* spp.) increased.[93,94] The abundance of *Bifidobacterium* spp., *Enterococcus* spp. and *Lactobacillus* spp. decreased during AT.[93,94] However, 21 days after stopping AT, the abundance of *Enterococcus* spp. and *Lactobacillus* spp. was higher compared to pre-treatment.[94] In one study, bacterial abundance had returned to pre-antibiotic levels 20 days after stopping AT.[93] However, this was not the case in another study where changes were still evident 21 days after stopping AT.[94] One study reported a decrease in the abundance of yeast with administration of tigecycline.[94] Treatment with tigecycline led to an increase in resistant bacteria (*B. fragilis, B. thetaiotaomicron, B. vulgaris, E. cloacae, E. coli* and *K. pneumoniae*).[93,94]

Streptogramins

The effect of quinupristin/dalfopristin on the intestinal microbiota was studied in one study that included 20 participants and four controls.[95] The study used bacterial culture. The mean concentration of quinupristin/dalfopristin in stool was 291/42 mg/kg. Abundance of *Enterobacteriaceae* and *Enterococcus* spp. increased during AT.[95] One participant became newly colonised with *C. difficile*.[95] The abundance of *Enterobacteriaceae* had returned to pre-antibitoic levels 10 days and the abundance of *Enterococcus* spp. 30 days after stopping AT. There was no change in abundance of fungi. The prevalence of erythromycin and quinupristin/dalfopristin-resistant anaerobic bacteria and *Enterococcus* spp increased under treatment with quinupristin/dalfopristin.[95]

Quinolones

The effect of quinolones was studied in 42 studies that included 520 participants and 69 controls.[26,82–84,96–131,142,146,148] Bacterial culture was used in 36 studies (plus MALDI-TOF-MS and 16S rRNA sequencing in one study each) and 16S rRNA sequencing in six studies (plus metagenomic shotgun sequencing in one study). Quinolones in stool were detected in all studies that measured fecal concentrations. Mean concentrations ranged from 6 to 953 mg/kg and maximal concentrations reached 2271 mg/kg.[82,83,97,99,100,102,103,105,111,119,120,122,124-126,128–130,148] The highest fecal concentrations were observed with norfloxacin and ciprofloxacin.[97,99,128]

Four studies investigated bacterial diversity with ciprofloxacin treatment and all four reported decreased diversity.[26,82,109,110]

With quinolones treatment, the abundance of *Enterobacteriaceae*,[96-99,101–106,111,113-116,120,121,125,129,130,142] *E. coli*[83,96,104,111,112,114,118,120,122-126,128,146] *Bacillus* spp.[101,120,121,129,130] and *Corynebacterium* spp.[101,120,129] decreased. In contrast, abundance of *Citrobacter* spp.,[112,118,119,125,126] *Enterobacter* spp.[103,119,126] and *Klebsiella* spp.[125,126] increased (except in one study in which a decrese in abundance was observed for the latter two[112]). Changes in the abundance of *Enterococcus* spp.,[83,96,101,104,108,111–114,117,120–127,129,130,146] *Pseudomonas* spp.,[103,112] *Staphylococcus* spp.[101,111-113,116,117,119,123] and *Streptococcus* spp.[102,106,113,117,119,124,126] were reported in both directions.

For anaerobic bacteria, quinolones were almost always associated with decreased abundance. A decrease was reported for *Bacteroides* spp.[101,105,113,116,117,120,123,125,126,128,129,151] (the only exception were two studies which used ciprofloxacin and reported an increase),[26,107] *Bifidobacterium* spp.[82,101,107,113,117,118,120-122,126,129,130] (except one study which using ciprofloxacin),[83] *Clostridium* spp.[113,116,117,120-123,126,129,130,146] (except one study using clindafloxacin),[126] *Lactobacillus* spp.,[82,101,113,117,121,124,126,129,130] *Peptostreptococcus* spp.[121,130] and *Veillonella* spp.[97,101,105,113,121,130] Ciprofloxacin was associated with a decreased abundance of many more anaerobic bacteria (detailed in supplementary Table 1).[26,107,109] Changes in *Eubacterium* spp. were reported in both directions.[101,107,117,129,130] New colonisation with *C. difficile* was only observed in two studies (one each using norfloxacin[97] and clindafloxacin).[126]

Several studies reported persistently disturbed bacterial abundance on last testing 6–12 months after stopping AT.[26,109,110] The abundance of fungi and yeast increased with the majority of quinolones.[96-98,102–104,111,112,114,121,126,127,129,130,142] An increase in resistance was observerd with norfloxacin, ciprofloxacin, levofloxacin, gemifloxacin, clinafloxacin, garenoxacin, sitafloxacin and trovafloxacin in *Acinetobacter* spp.,[112] *Alcaligenes* spp.,[112] *Bacteroides* spp.,[121,126,130] *Bifidobacterium* spp.,[82] *Candida* spp.,[97] *C. freundii*,[112] *C. difficile*,[97] coagulase-negative staphylococci,[116] *Corynebacterium* spp.,[116] *Enterobacteriaceae*,[129] *Enterococcus* spp.,[108,129] *E. coli*,[112,125,142] and *Xantomonas* spp.[112] Increase in resistance was not observed with nalidixic acid,[96] olfoxacin,[100,102,120] enoxacin,[103] lemofloxaxin[106] and gatifloxacin treatment.[123]

Nitroimidazoles

The effect of tinidazole on the intestinal microbiota was investigated in one study that included 10 participants.[77] Tinidazole was not detectable in stool. There was no change in bacterial abundance and no increase in resistance.[77]

Trimethoprim and sulphonamides

The effect of trimethoprim and sulphonamides (sulphasomidine, sulphalene) on the intestinal microbiota was investigated in three studies that included 95 participants and 12 controls.[132,133,142] All three studies used bacterial cultures. Antibiotic concentration in stool was not measured. Two studies used either trimethoprim or trimethoprim/sulfamethoxazole[132,142] and one study sulphasomidine and sulphalene.[133] In both studies, a reduced abundance of coliform bacteria, *Enterobacteriaceae* or *E. coli* was reported.[132,133,142] Bacterial abundance was reported to have returned to pre-antibiotic levels 14 days after stopping AT.[142] There was an increased in abundance of resistant *E. coli*,[132,133,142] *Acinetobacter* spp. and *Pseudomonas* spp.[132]

Polymyxins

There was only one study involving 6 participants which investigated the influence of polymyxin E on the intestinal microbiota.[134] The study used bacterial culture. Antibiotic concentration in stool was not measured. Polymycin led to a decrease in the abundance of *Enterobacteriaceae* and *E. faecalis.* The abundance of fungi was not influenced.[134] Resistance was not tested.

Antibotics belonging to other classes

There were three studies which investigated the effect of nitrofurantoin on the abundance of the intestinal microbiota in 22 participants and 24 controls.[107,135,142] Nitrofurantoin in stool was not measured. Two studies used 16S rRNA gene sequencing and one study bacterial culture. One study reported an increase in abundance of Actinobacteria and *Bifidobacterium* spp. and one study an increase in abundance of *Clostridium* spp. and a decrease in the abundance of *Faecalibacterium* spp.[107,135] The third study did not find any changes in the abundance of microbiota.[135] In one study bacterial abundance had returned to pre-antibiotic levels 31 to 43 days after stopping AT, while the other one did not do follow-up testing.[107,135,142] Resistance was only tested in one study, which did not report an increase in resistance.[142]

Two studies involving 16 participants investigated the influence of fosfomycin on the intestinal microbiota.[136,137] Both studies used bacterial culture. Antibiotic concentrations in stool were not measured. Fosfomycin led to a decrease in abundance of *Enterococcus* spp. and *E. coli.* However, while the abundance of *E. faecalis* decreased, there was an increase in abundance of *E. feacium.*[136] There was also an increase in abundance of *Citrobacter* spp., *Enterobacter* spp., *Klebsiella* spp. and *Pseudomonas* spp.[136,137] The abundance of anaerobic bacteria of fungi was not influenced. Bacterial abundance returned to pre-antibiotic levels 12 to 14 days after stopping AT.[136,137] There was no increase in fosfomycin-resistant bacteria.

There were two studies which investigated the influence of rifaximin on the intestinal microbiota in 40 participants.[138,139] Both studies used 16S rRNA gene sequencing. The antibiotic concentration in stool was not measured. Rifaximin did not decrease bacterial diversity, but led to a decrase in abundance of *Streptococcus* spp. and *Veillonella* spp., while the abundance of *Eubacterium* spp. increased. Neither of the studies did resistance testing.

There was one study which investigated the influence of MCB3837, a combination of a oxazolidinone and quinolone antibiotic, on the intestinal microbiota of 12 participants.[172] The mean fecal concentration of MCB3837 varied between 117 and 171 mg/kg. The antibiotic decreased the abundance of *Bifidobacterium* spp., *Clostridium* spp., *Enterococcus* spp. and *Lactobacillus* spp. Bacterial abundance had returned to pre-antibiotic levels 14 days after stopping AT. There was no increase in resistant bacteria.

Combinations of several antibiotics

There were 10 studies that included 210 participants and 40 controls that investigated either the effect of a combination of antibiotcs or successive treatment on the intestinal microbiota.[46,142–150] The results of these studies are detailed in Table 1 and supplementary Tables 1 and 2.

Discussion

This review shows that antibiotics have profound effects on the intestinal microbiota. Amoxicillin/clavulante, ciprofloxacin, minocycline, clindamycin, paromomycin and clarithromycin plus metronidazol were associated with decreased bacterial diversity,[26,38,73,82,109,110,144] while amoxcillin and rifaximin did not influence bacterial diversity.[26,138,139] Penicillin only had minor effects on the abundance of different taxa in the intestinal microbiota and did not increase resistance.[22–24] Amoxicillin, amoxcillin/clavulanate, cephalosporins, lipopolyglycopeptides, macrolides, ketolides, clindamycin, tigecycline, quinolones and fosfomycin all increased abundance of *Enterobacteriaea* other than *E. coli* (mainly *Citrobacter* spp., *Enterobacter* spp. and *Klebsiella* spp.).[27,29-33,37,39,40,71,72,75,88-90,93,94,103,112,118,119,125,126,136,137,146] Amoxcillin, cephalosporins, macrolides, clindamycin, quinolones and sulphonamides decreased abundance of *E. coli,*[25,29-32,43,46,49,56,58-60,62–66,75,76,79-81,83,96,104,111,112,114,118,120,122-126,128,132,133,142,146,149,150] while amoxcillin/clavulante, in contrast to other penicillins, increased abundance of *E. coli.*[37-39,147] Doxycycline influenced aerobic bacteria more than anaerobic bacteria and decreased the abundance of *Enterobacteriae* including *E. coli.*[91,92] Amoxicllin, piperacillin and ticarcillin, cephalosporins (except fifth generation), carbapenems and lipoglycopeptides were associated with increased abundance of *Enterococcus* spp.,[23,25,29–33,41,44,45,48-51,54,56-61,67,70,72,149,150] while macrolides and doxycycline decreased its abundance.[75–77,80,91,92,146] Amoxicillin, amoxicillin/clavulanate, cephalosporins, lipopolyglycopeptides and macrolides had varying effects on anaerobic bacteria,[26,27,33,34,38–40,70,71,76,77,79,146,147] while piperacillin and ticarcillin, carbapenems, macrolides, clindamycin and quinolones strongly decreased the abundance of anaerobic bacteria.[24–26,41,67,75–77,79,80,82,86,89,90,101,105,113,116,117,120,125,126,128,129,146,150,151] New or increased colonisation with *C. difficile* was observed with amoxcillin,[33] cephalosporins,[25,30,31,43,45,49–51,53,57,59,61,62,64,65,149] ritipenem acoxil,[69] quinupristin/dalfopristin,[95] norfloxacin[97] and clindafloxacin.[126] Amoxcillin, amoxcillin/clavulanate, cephalosporins, carbapenems and macrolides increased abundance of yeast.[29–33,37,43,52,54,56–61,63,65,67,76,77,80,149,150] Changes in the intestinal microbiota were observed within 24 h after the start of antibiotic administration and were reported to persist longest after treatment with ciprofloxacin (one year),[26] clindamycin (two years)[86] and clarithromycin plus metronidazole plus (four years).[144] However, these results are of course strongly influenced by the timing of follow-up samples.

Even though the effect of different classes of antibiotics on the abundance of microbial taxa was consistent across multiple studies, the effect of antibiotics on the intestinal microbiota, is likely modified/shaped many factors. For example, cephalosporins typically first decreases the abundance of Enterobacteriacae, mainly *E. coli* and then increases the abundance of Enterobactericae other than *E. coli,* such as *Citrobacter* spp., *Enterobacter* spp., *Klebsiella* spp. and *Pseudomonas* spp.,[59] This shows that the duration of antibiotic treatment has both a quantitative and qualitative influence on the instinal microbiota. Furthermore, some studies report temporal variations in the direction of changes in the abundance of certain bacteria. For example, with cefoxitin treatment, the abundance of *Enterococcus* spp. increased during the first few days and then decreased, while, conversely, the abundance of Enterobacteriaeae first decreased and then increased.[23] Similarly, with ceftriaxone treatment, the abundance of *Enterococcus* spp.,[54] with amoxicillin treatment the abundance of *Streptococcus* spp.[32] and with ceftaroline/avibactam treatment the abundance of *Clostridium* spp.[65] first decreased, but ceasing AT increased compared to pre-treatment numbers. Hence, the timing of stool sampling will strongly influence results: testing stool samples taken only at one time point might distort findings. A further important point, which has to date only been investigated in animal studies, is that changes in the intestinal microbiota induced antibiotics might vary according to the pre-treatment composition of the microbiota.[152] Moreover, several studies have shown that the effect of antibiotics on the intestinal microbiota is dose dependent, with stronger changes occurring with higher doses of antibiotics.[129,132]

Likewise, pharmacodynamics of the drug also influence the effect of the antibiotic on the intestinal microbiota. For example, the effect of ceftriaxone on the instintal microbiota is positively associated with its biliary clearance.[56,57] The influence of antibiotics might also depend on the forumulation of the drug. For example, one study included in this review, showed that changes in bacterial abundance only occurred in participants who were given bacampicillin as a syrup and not in these who were given tablets.[34]

Importantly, the clinical consequences of changes in the intestinal microbiota with antibiotic treatment is largely unknown. Many studies show that antibiotics increase the abundance of Enterobacteriaceae. These Gram negative bacteria are often resistant to beta-lactam and other antibiotics, meaning an increased abundance might render the host more susceptible to infections with antibiotic-resistant bacteria. This phenomenon has been observed in infants in neonatal intensive care units, who are more often clonised with *Klebsiella* spp., *Enterobacter* spp. and *Citrobacter* spp., when treated with antibiotics.[153]

Blautia spp., *Coprococcus* spp. and *Faecalibacterium* spp. have been associated with anti-inflammatory qualities.[73,154,155] Therefore, a decreased abundance of these bacteria might change the intestinal milieu to a more pro-inflammatory state. Consistent with this, a decreased abundance of *Blautia* spp. and *Faecalibacterium* spp. has been associated with colorectal cancer,[156] a decreased abundance of *Faecalibacterium* spp. with chronic inflammatory bowel diseases[154,155] and a decreased abundance of *Coprococcus* spp. with irritable bowel syndrome.[157] A decrease in *Blautia* spp. has been reported with amoxcillin,[26] paromycin[73] and clindamycin[24,82,89,90] treatment; a decrease in *Coprococcus* spp. with amoxcillin,[26] minocycline[26] and clarithromycin plus metronidazole[144] treatment; and a decrease in *Faecalibacterium* spp. with amoxcillin,[27] paromycin[73] clindamycin[26] and minocycline treatment.[26]

Antibiotic-associated diarrhoea (AAD) is defined as diarrhoea associated with administration of antibiotics and no other obvious cause. AAD is the most common adverse event related to antibiotic use and affects up to 34% of patients receiving antibiotics.[158] Bacteria in the colon, especially anaerobic bacteria, metabolise undigested carbohydrates into lactic acid and SCFAs.[159] The loss of these bacteria can lead to osmotic diarrhoea.[160] Butyrate is an important source of energy for the mucosa and a lack of this SCFA can disrupt the integrity of colonic epithelial cells, function of the mucosa and the regulation of T cells.[161-163] A decrease in butyrate-producting bacteria has been linked to diabetes type 2,[164] obesity[165] and cardiovascular disease.[166] In contrast, butyrate has been reported to be protective against colon cancer[167] and improve insulin sensitivity in animal studies.[168,169] The relative abundance of butyrate-producting bacteria is strongly affected by antibiotics (particularly a decrease in the families *Lachnospiraceae, Porphyromonadaceae* and *Ruminococcaceae,* and the genera *Alistipes, Faecalibacterium* spp., *Sutterella* spp. and *Thalassospira* spp.).[26,27,73,82,83,107,109,110] Most of the butyrate-producting bacteria have been identified in the *Clostridum* clusters IV and XIVa,[170,171] which are reduced during AT.[40,73] These bacteria are also involved in the lipid metabolism, as they have bile acid activity.[172] A decrease of butyrate in stool was found with ceftriaxone,[55] erythromycin,[77] clindamycin[24,90] and doxycline treatment,[92] but not with phenoxymethylpenicillin,[24] ritipenem acoxil[69] or norfloxacin.[97]

A further important issue with antibiotic treatment is increased antibiotic resistance. This was observered with almost all antibiotics, except penicillin,[23,24] some cephalosporins,[30,42,43,45,48,54,60,63,64,66,149] meropenem,[67] telavancin[71] and dalbavancin.[72] A broad variety of bacteria with increased resistance was observed with macrolide,[74–81,143–146] clindamycin,[24,86–89] doxycycline,[91,92] tigecycline[93,94] and ciprofloxacin treatment[82,108,112,116,119] Several studies have shown that increased resistance can still be evident two to four years after treatment.[85-87,144,173,174] For example, after treatment with clindamycin for seven days, increased numbers of clindamycin-resistant *B. thetaiotaomicron* persisted two years after treatment.[85,86] Similarly, after treatment with clarithromycin, metronidazole and omeprazole for *H. pylori* eradication, clarithromycin-resistant *Bacteroides* spp., *Enterococcus* spp. (carrying the erm(B) gene), *Staphylococcus* spp. and *Streptococcus* spp. persisted for up to three years.[173,174] After treatment with clindamycin, increased abundance of macrolide-resistant *Enterococcus* spp. (carrying the erm(A), erm(B) and mef(A) gene) was still found two years after treatment.[87] Importantly, antibiotics do not only increase specific resistance to the antibiotic being used for treatment, but also increase resistance to other classes of antibiotics. This has been observed for amoxcillin,[26] clindamycin,[26,86,87] ciprofloxacin[26] and quinupristin/dalfopristin.[95] The risk of inducing resistance is an important consideration when choosing antibiotics, especially for long-term administration. For example, low-dose prophylaxtic treatment with nitrofurantoin led to resistant *E. coli* in only 2% of samples analysed, while trimethoprim/sulfamethoxazole (TMP/SMX) led to resistant *E. coli* in 8%.[175] Treatment with TMP/SMX led to a smaller increase in sulphonamide-resistant *E. coli* than treatment with trimethoprim alone.[132,176]

Only one study has investigated the effect of antibiotics on the abundance of viruses in the intestinal microbiota.[177] This study was not included in our review, because the antibiotic regime was not specified. In this study, antibiotics did not change the overall viral diversity in fecael viromes. However, there was an expansion of the of viral genes putatively involved in resistance to numerous classes of antibiotics, suggesting that viruses play an important role in the resilience of human microbial communities to antibiotic disturbances.

The strengths of our review are the comprehensive literature search and the clearly definded inclusion criteria. The main limitation is that many of the included studies were limited by small sample sizes and short follow-up, which limits assertions about the presistance of changes induced by antibiotics. It was notable that a large number of studies were done by the same research group in Sweden. Also, many of the studies used only a short time interval from previous antibiotics as an exclusion criteria. None of the studies corrected for potential confounding factors, such as geographic location, previous antibiotic use, age, diet, hospitalisation. Additionally, different techniques were uses to analyse stool samples and many studies use cultivation-based rather than molecular-based methods. Stool samples were analysed at different taxonomic levels (phyla, family, genus, species) and only bacterial (and not archaeal, viral or eukaryotal abundance) was investigated. Even though some studies, used 16s RNA sequencing, it only allows for determination on genus levels and also does not identify antibiotic resistance genes.

Because of this heterogenicity in study design a meta-analysis was not feasible. Also, since the combinations and durations of antibiotic administration varied widely between studies, it was not possible to compare the effect of combination therapy vs single antibiotic treatment on the intestinal microbiota.

In the future, advanced sequencing techniques will provide a more in-depth analysis of the microbiota and allow for analysis of the bacterial microbiota down to a species-level, as well as identification of eukoaryotes (fungi and parasites), viruses and resistance genes. The relative abundance of certain species, or specific microbial signatures might be more important for health outcomes than changes on class or family level, which were reported in many of the studies included in this review. Further research is necessary to find out what the optimal microbes and especially combination

of microbes are for humans, before evidence-based interventions to prevent adverse outcomes in situations where antibiotics cannot be avoided, including modifying the intestinal microbiota with directed pre- and probiotics or bacteriophages can be developed.

In summary, antibiotics have profound effects on the intestinal microbiota by diminishing the abundance of beneficial commensals and increasing the abundance of detrimental pathogens or commensals. Understanding these effects will help tailor antibiotic treatment for different clinical situations and to minimise 'collateral damage'. Further research should focus on the impact of potential confounding factors, including the influence of the pre-treatment composition of the intestinal microbiota, co-morbidities, age and diet. Also, further studies are needed that investigate antibiotic-induced changes of arachea, eukaryote and virues, have long-term follow-up over several years, and correlate changes in the intestinal microbiota with clinical outcomes.

Declaration of Competing Interest

The authors declare no conflict of interest.

CRediT authorship contribution statement

Petra Zimmermann: Writing - original draft. **Nigel Curtis:** Writing - review & editing.

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Supplementary material

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References

1. Rajilic-Stojanovic M, de Vos WM. The first 1000 cultured species of the human gastrointestinal microbiota. *FEMS Microbiol Rev* 2014:996–1047.
2. Frank DN, St Amand AL, Feldman RA, Boedeker EC, Harpaz N, Pace NR. Molecular-phylogenetic characterization of microbial community imbalances in human inflammatory bowel diseases. *Proc Natl Acad Sci U S A* 2007:13780–5.
3. Eckburg PB, Bik EM, Bernstein CN, Purdom E, Dethlefsen L, Sargent M, et al. Diversity of the human intestinal microbial flora. *Science* 2005:1635–8.
4. Forster SC, Kumar N, Anonye BO, Almeida A, Viciani E, Stares MD, et al. A human gut bacterial genome and culture collection for improved metagenomic analyses. *Nat Biotechnol* 2019:186–92.
5. Lagier JC, Khelaifia S, Alou MT, Ndongo S, Dione N, Hugon P, et al. Culture of previously uncultured members of the human gut microbiota by culturomics. *Nat Microbiol* 2016:16203.
6. Zeevi D, Korem T, Segal E. Talking about cross-talk: the immune system and the microbiome. *Genome Biol* 2016:50.
7. Zimmermann P, Messina N, Mohn WW, Finlay BB, Curtis N. Association between the intestinal microbiota and allergic sensitization, eczema, and asthma: A systematic review. *J Allergy Clin Immunol* 2018.
8. Zimmermann P, Curtis N. The influence of the intestinal microbiome on vaccine responses. *Vaccine* 2018:4433–9.
9. Kuppala VS, Meinzen-Derr J, Morrow AL, Schibler KR. Prolonged initial empirical antibiotic treatment is associated with adverse outcomes in premature infants. *J Pediatr* 2011:720–5.
10. Cotten CM, Taylor S, Stoll B, Goldberg RN, Hansen NI, Sanchez PJ, et al. Prolonged duration of initial empirical antibiotic treatment is associated with increased rates of necrotizing enterocolitis and death for extremely low birth weight infants. *Pediatrics* 2009:58–66.
11. Metsala J, Lundqvist A, Virta LJ, Kaila M, Gissler M, Virtanen SM. Prenatal and post-natal exposure to antibiotics and risk of asthma in childhood. *Clin Exp Allergy* 2015:137–45.
12. Azad MB, Moossavi S, Owora A, Sepehri S. Early-Life Antibiotic Exposure, Gut Microbiota Development, and Predisposition to Obesity. *Nestle Nutr Inst Workshop Ser* 2017:67–79.
13. Strzepa A, Lobo FM, Majewska-Szczepanik M, Szczepanik M. Antibiotics and autoimmune and allergy diseases: Causative factor or treatment? *Int Immunopharmacol* 2018:328–41.
14. van der Waaij D, Nord CE. Development and persistence of multi-resistance to antibiotics in bacteria; an analysis and a new approach to this urgent problem. *Int J Antimicrob Agents* 2000:191–7.
15. Smillie CS, Smith MB, Friedman J, Cordero OX, David LA, Alm EJ. Ecology drives a global network of gene exchange connecting the human microbiome. *Nature* 2011:241–4.
16. Lester CH, Frimodt-Moller N, Sorensen TL, Monnet DL, Hammerum AM. In vivo transfer of the vanA resistance gene from an Enterococcus faecium isolate of animal origin to an E. faecium isolate of human origin in the intestines of human volunteers. *Antimicrob Agents Chemother* 2006:596–9.
17. Salyers AA, Gupta A, Wang Y. Human intestinal bacteria as reservoirs for antibiotic resistance genes. *Trends Microbiol* 2004:412–16.
18. Scott KP. The role of conjugative transposons in spreading antibiotic resistance between bacteria that inhabit the gastrointestinal tract. *Cell Mol Life Sci* 2002:2071–82.
19. Doucet-Populaire F, Trieu-Cuot P, Dosbaa I, Andremont A, Courvalin P. Inducible transfer of conjugative transposon Tn1545 from Enterococcus faecalis to Listeria monocytogenes in the digestive tracts of gnotobiotic mice. *Antimicrob Agents Chemother* 1991:185–7.
20. Goerke C, Koller J, Wolz C. Ciprofloxacin and trimethoprim cause phage induction and virulence modulation in Staphylococcus aureus. *Antimicrob Agents Chemother* 2006:171–7.
21. Sterne JA, Hernan MA, Reeves BC, Savovic J, Berkman ND, Viswanathan M, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *Bmj* 2016:i4919.
22. Adamsson I, Edlund C, Sjostedt S, Nord CE. Comparative effects of cefadroxil and phenoxymethylpenicillin on the normal oropharyngeal and intestinal microflora. *Infection* 1997:154–8.
23. Heimdahl A, Kager L, Malmborg AS, Nord CE. Impact of different betalactam antibiotics on the normal human flora, and colonization of the oral cavity, throat and colon. *Infection* 1982:120–4.
24. Heimdahl A, Nord CE. Effect of phenoxymethylpenicillin and clindamycin on the oral, throat and faecal microflora of man. *Scand J Infect Dis* 1979:233–42.
25. Ambrose NS, Johnson M, Burdon DW, Keighley MR. The influence of single dose intravenous antibiotics on faecal flora and emergence of Clostridium difficile. *J Antimicrob Chemother* 1985:319–26.
26. Zaura E, Brandt BW, Teixeira de Mattos MJ, Buijs MJ, Caspers MP, Rashid MU, et al. Same Exposure but Two Radically Different Responses to Antibiotics: Resilience of the Salivary Microbiome versus Long-Term Microbial Shifts in Feces. *MBio* 2015:e01693 615 e01601.
27. Pallav K, Dowd SE, Villafuerte J, Yang X, Kabbani T, Hansen J, et al. Effects of polysaccharopeptide from Trametes versicolor and amoxicillin on the gut microbiome of healthy volunteers: a randomized clinical trial. *Gut Microbes* 2014:458–67.
28. De La Cochetiere MF, Durand T, Lepage P, Bourreille A, Galmiche JP, Dore J. Resilience of the dominant human fecal microbiota upon short-course antibiotic challenge. *J Clin Microbiol* 2005:5588–92.
29. Stark CA, Adamsson I, Edlund C, Sjosted S, Seensalu R, Wikstrom B, et al. Effects of omeprazole and amoxycillin on the human oral and gastrointestinal microflora in patients with Helicobacter pylori infection. *J Antimicrob Chemother* 1996:927–39.
30. Floor M, van Akkeren F, Rozenberg-Arska M, Visser M, Kolsters A, Beumer H, et al. Effect of loracarbef and amoxicillin on the oropharyngeal and intestinal microflora of patients with bronchitis. *Scand J Infect Dis* 1994:191–7.
31. Brismar B, Edlund C, Nord CE. Impact of cefpodoxime proxetil and amoxicillin on the normal oral and intestinal microflora. *Eur J Clin Microbiol Infect Dis* 1993:714–19.
32. Black F, Einarsson K, Lidbeck A, Orrhage K, Nord CE. Effect of lactic acid producing bacteria on the human intestinal microflora during ampicillin treatment. *Scand J Infect Dis* 1991:247–54.
33. Christensson B, Nilsson-Ehle I, Ljungberg B, Nömm I, Oscarsson G, Nordström L, et al. Swedish Study Group. A randomized multicenter trial to compare the influence of cefaclor and amoxycillin on the colonization resistance of the digestive tract in patients with lower respiratory tract infection. *Infection* 1991:208–15.
34. Heimdahl A, Nord CE, Weilander K. Effect of bacampicillin on human mouth, throat and colon flora. *Infection* 1979:S446–51.
35. Sullivan A, Edlund C, Svenungsson B, Emtestam L, Nord CE. Effect of perorally administered pivmecillinam on the normal oropharyngeal, intestinal and skin microflora. *J Chemother* 2001:299–308.
36. Nord CE, Bergan T, Aase S. Impact of azlocillin on the colon microflora. *Scand J Infect Dis* 1986:163–6.
37. Vlaspolder F, de Zeeuw G, Rozenberg-Arska M, Egyedi P, Verhoef J. The influence of flucloxacillin and amoxicillin with clavulanic acid on the aerobic flora of the alimentary tract. *Infection* 1987:241–4.
38. Kabbani TA, Pallav K, Dowd SE, Villafuerte-Galvez J, Vanga RR, Castillo NE, et al. Prospective randomized controlled study on the effects of Saccharomyces boulardii CNCM I-745 and amoxicillin-clavulanate or the combination on the gut microbiota of healthy volunteers. *Gut Microbes* 2017:17–32.
39. Mangin I, Leveque C, Magne F, Suau A, Pochart P. Long-term changes in human colonic Bifidobacterium populations induced by a 5-day oral amoxicillin-clavulanic acid treatment. *PLoS One* 2012:e50257.
40. Young VB, Schmidt TM. Antibiotic-associated diarrhea accompanied by large-scale alterations in the composition of the fecal microbiota. *J Clin Microbiol* 2004:1203–6.

41. Nord CE, Bergan T, Thorsteinsson SB. Impact of ticarcillin/clavulanate on the intestinal microflora. *J Antimicrob Chemother* 1989:221–6.
42. Nord CE, Heimdahl A, Lundberg C, Marklund G. Impact of cefaclor on the normal human oropharyngeal and intestinal microflora. *Scand J Infect Dis* 1987:681–5.
43. Finegold SM, Ingram-Drake L, Gee R, Reinhardt J, Edelstein MA, MacDonald K, et al. Bowel flora changes in humans receiving cefixime (CL 284,635) or cefaclor. *Antimicrob Agents Chemother* 1987:443–6.
44. Lode H, Muller C, Borner K, Nord CE, Koeppe P. Multiple-dose pharmacokinetics of cefprozil and its impact on intestinal flora of volunteers. *Antimicrob Agents Chemother* 1992:144–9.
45. Edlund C, Brismar B, Sakamoto H, Nord CE. Impact of Cefuroxime-axetil on the Normal Intestinal Microflora. *Microbial Ecology in Health and Disease* 1993:185–9.
46. Edlund C, Barkholt L, Olsson-Liljequist B, Nord CE. Effect of vancomycin on intestinal flora of patients who previously received antimicrobial therapy. *Clin Infect Dis* 1997:729–32.
47. Mulligan ME, Citron D, Gabay E, Kirby BD, George WL, Finegold SM. Alterations in human fecal flora, including ingrowth of Clostridium difficile, related to cefoxitin therapy. *Antimicrob Agents Chemother* 1984:343–6.
48. Nord CE, Grahnen A, Eckernas SA. Effect of loracarbef on the normal oropharyngeal and intestinal microflora. *Scand J Infect Dis* 1991:255–60.
49. Nord CE, Movin G, Stalberg D. Impact of cefixime on the normal intestinal microflora. *Scand J Infect Dis* 1988:547–52.
50. Novelli A, Mazzei T, Fallani S, Dei R, Cassetta MI, Conti S. Betalactam therapy and intestinal flora. *J Chemother* 1995:25–31.
51. Alestig K, Carlberg H, Nord CE, Trollfors B. Effect of cefoperazone on faecal flora. *J Antimicrob Chemother* 1983:163–7.
52. Mulligan ME, Citron DM, McNamara BT, Finegold SM. Impact of cefoperazone therapy on fecal flora. *Antimicrob Agents Chemother* 1982:226–30.
53. Welling GW, Meijer-Severs GJ, Helmus G, van Santen E, Tonk RH, de Vries-Hospers HG, et al. The effect of ceftriaxone on the anaerobic bacterial flora and the bacterial enzymatic activity in the intestinal tract. *Infection* 1991:313–16.
54. de Vries-Hospers HG, Tonk RH, van der Waaij D. Effect of intramuscular ceftriaxone on aerobic oral and faecal flora of 11 healthy volunteers. *Scand J Infect Dis* 1991:625–33.
55. Meijer-Severs GJ, Van Santen E, Meijer BC. Short-chain fatty acid and organic acid concentrations in feces of healthy human volunteers and their correlations with anaerobe cultural counts during systemic ceftriaxone administration. *Scand J Gastroenterol* 1990:698–704.
56. Arvidsson A, Leijd B, Nord CE, Angelin B. Interindividual variability in biliary excretion of ceftriaxone: effects on biliary lipid metabolism and on intestinal microflora. *Eur J Clin Invest* 1988:261–6.
57. Nilsson-Ehle I, Nord CE, Ursing B. Ceftriaxone: pharmacokinetics and effect on the intestinal microflora in patients with acute bacterial infections. *Scand J Infect Dis* 1985:77–82.
58. Vogel F, Ochs HR, Wettich K, Kalich S, Nilsson-Ehle I, Odenholt I, et al. Effect of step-down therapy of ceftriaxone plus loracarbef versus parenteral therapy of ceftriaxone on the intestinal microflora in patients with community-acquired pneumonia. *Clin Microbiol Infect* 2001:376–9.
59. Orrhage K, Sjostedt S, Nord CE. Effect of supplements with lactic acid bacteria and oligofructose on the intestinal microflora during administration of cefpodoxime proxetil. *J Antimicrob Chemother* 2000:603–12.
60. Brismar B, Edlund C, Nord CE. Effect of ceftibuten on the normal intestinal microflora. *Infection* 1993:373–5.
61. Rashid MU, Rosenborg S, Panagiotidis G, Lofdal KS, Weintraub A, Nord CE. Ecological effect of ceftazidime/avibactam on the normal human intestinal microbiota. *Int J Antimicrob Agents* 2015:60–5.
62. Bacher K, Schaeffer M, Lode H, Nord CE, Borner K, Koeppe P. Multiple dose pharmacokinetics, safety, and effects on faecal microflora, of cefepime in healthy volunteers. *J Antimicrob Chemother* 1992:365–75.
63. Knothe H, Schafer V, Sammann A, Badian M, Shah PM. Influence of cefpirome on pharyngeal and faecal flora after single and multiple intravenous administrations of cefpirome to healthy volunteers. *J Antimicrob Chemother* 1992:81–6.
64. Panagiotidis G, Backstrom T, Asker-Hagelberg C, Jandourek A, Weintraub A, Nord CE. Effect of ceftaroline on normal human intestinal microflora. *Antimicrob Agents Chemother* 2010:1811–14.
65. Rashid MU, Rosenborg S, Panagiotidis G, Soderberg-Lofdal K, Weintraub A, Nord CE. Ecological Effect of Ceftaroline-Avibactam on the Normal Human Intestinal Microbiota. *Antimicrob Agents Chemother* 2015:4504–9.
66. Backstrom T, Panagiotidis G, Beck O, Asker-Hagelberg C, Rashid MU, Weintraub A, et al. Effect of ceftobiprole on the normal human intestinal microflora. *Int J Antimicrob Agents* 2010:537–41.
67. Bergan T, Nord CE, Thorsteinsson SB. Effect of meropenem on the intestinal microflora. *Eur J Clin Microbiol Infect Dis* 1991:524–7.
68. Nakashima M, Uematsu T, Kosuge K, Nakagawa S, Hata S, Sanada M. Pharmacokinetics and safety of BO-2727, a new injectable 1-beta-methyl carbapenem antibiotic, and its effect on the faecal microflora in healthy male volunteers. *J Antimicrob Chemother* 1994:987–98.
69. Meijer-Severs GJ, van Santen E, Puister SM, Boersma WG. The effect of FCE 22891, a new oral penem, on faecal flora anaerobes and their fermentation end products in patients with chronic obstructive pulmonary disease. *Infection* 1993;**21**:311–17.
70. Van der Auwera P, Pensart N, Korten V, Murray BE, Leclercq R. Influence of oral glycopeptides on the fecal flora of human volunteers: selection of highly glycopeptide-resistant enterococci. *J Infect Dis* 1996:1129–36.
71. Rashid MU, Weintraub A, Nord CE. Effect of telavancin on human intestinal microflora. *Int J Antimicrob Agents* 2011:474–9.
72. Nord CE, Rasmanis G, Wahlund E. Effect of dalbavancin on the normal intestinal microflora. *J Antimicrob Chemother* 2006:627–31.
73. Heinsen FA, Knecht H, Neulinger SC, Schmitz RA, Knecht C, Kuhbacher T, et al. Dynamic changes of the luminal and mucosa-associated gut microbiota during and after antibiotic therapy with paromomycin. *Gut Microbes* 2015:243–54.
74. Andremont A, Trancrede C, Desnottes JF. Effect of oral spiramycin on the faecal and oral bacteria in human volunteers. *J Antimicrob Chemother* 1991:355–60.
75. Edlund C, Alvan G, Barkholt L, Vacheron F, Nord CE. Pharmacokinetics and comparative effects of telithromycin (HMR 3647) and clarithromycin on the oropharyngeal and intestinal microflora. *J Antimicrob Chemother* 2000:741–9.
76. Brismar B, Edlund C, Nord CE. Comparative effects of clarithromycin and erythromycin on the normal intestinal microflora. *Scand J Infect Dis* 1991:635–42.
77. Heimdahl A, Nord CE. Influence of erythromycin on the normal human flora and colonization of the oral cavity, throat and colon. *Scand J Infect Dis* 1982:49–56.
78. Pecquet S, Chachaty E, Tancrede C, Andremont A. Effects of roxithromycin on fecal bacteria in human volunteers and resistance to colonization in gnotobiotic mice. *Antimicrob Agents Chemother* 1991:548–52.
79. Eckernas SA, Grahnen A, Nord CE. Impact of dirithromycin on the normal oral and intestinal microflora. *Eur J Clin Microbiol Infect Dis* 1991:688–92.
80. Rashid MU, Rosenborg S, Panagiotidis G, Holm J, Soderberg Lofdal K, Weintraub A, et al. Ecological Effect of Solithromycin on Normal Human Oropharyngeal and Intestinal Microbiota. *Antimicrob Agents Chemother* 2016:4244–51.
81. Matute AJ, Schurink CA, Krijnen RM, Florijn A, Rozenberg-Arska M, Hoepelman IM. Double-blind, placebo-controlled study comparing the effect of azithromycin with clarithromycin on oropharyngeal and bowel microflora in volunteers. *Eur J Clin Microbiol Infect Dis* 2002:427–31.
82. Rashid MU, Weintraub A, Nord CE. Development of antimicrobial resistance in the normal anaerobic microbiota during one year after administration of clindamycin or ciprofloxacin. *Anaerobe* 2015:72–7.
83. Rashid MU, Zaura E, Buijs MJ, Keijser BJ, Crielaard W, Nord CE, et al. Determining the Long-term Effect of Antibiotic Administration on the Human Normal Intestinal Microbiota Using Culture and Pyrosequencing Methods. *Clin Infect Dis* 2015:S77–84.
84. Card RM, Mafura M, Hunt T, Kirchner M, Weile J, Rashid MU, et al. Impact of Ciprofloxacin and Clindamycin Administration on Gram-Negative Bacteria Isolated from Healthy Volunteers and Characterization of the Resistance Genes They Harbor. *Antimicrob Agents Chemother* 2015:4410–16.
85. Jernberg C, Lofmark S, Edlund C, Jansson JK. Long-term ecological impacts of antibiotic administration on the human intestinal microbiota. *Isme j* 2007:56–66.
86. Lofmark S, Jernberg C, Jansson JK, Edlund C. Clindamycin-induced enrichment and long-term persistence of resistant Bacteroides spp. and resistance genes. *J Antimicrob Chemother* 2006:1160–7.
87. Lindgren M, Lofmark S, Edlund C, Huovinen P, Jalava J. Prolonged impact of a one-week course of clindamycin on Enterococcus spp. in human normal microbiota. *Scand J Infect Dis* 2009:215–19.
88. Nyberg SD, Osterblad M, Hakanen AJ, Lofmark S, Edlund C, Huovinen P, et al. Long-term antimicrobial resistance in Escherichia coli from human intestinal microbiota after administration of clindamycin. *Scand J Infect Dis* 2007:514–20.
89. Jernberg C, Sullivan A, Edlund C, Jansson JK. Monitoring of antibiotic-induced alterations in the human intestinal microflora and detection of probiotic strains by use of terminal restriction fragment length polymorphism. *Appl Environ Microbiol* 2005:501–6.
90. Orrhage K, Brismar B, Nord CE. Effect of Supplements with Bifidobacteriurn longum and Lactobacillus acidophilus on the Intestinal Microbiota during Administration of Clindamycin. *Microbial Ecology in Health and Disease* 1994:17–25.
91. Rashid MU, Panagiotidis G, Backstrom T, Weintraub A, Nord CE. Ecological impact of doxycycline at low dose on normal oropharyngeal and intestinal microflora. *Int J Antimicrob Agents* 2013:352–7.
92. Heimdahl A, Nord CE. Influence of doxycycline on the normal human flora and colonization of the oral cavity and colon. *Scand J Infect Dis* 1983:293–302.
93. Yamashita N, Matschke K, Gandhi A, Korth-Bradley J. Tigecycline pharmacokinetics, tolerability, safety, and effect on intestinal microflora in healthy Japanese male subjects. *J Clin Pharmacol* 2014:513–19.
94. Nord CE, Sillerstrom E, Wahlund E. Effect of tigecycline on normal oropharyngeal and intestinal microflora. *Antimicrob Agents Chemother* 2006:3375–80.
95. Scanvic-Hameg A, Chachaty E, Rey J, Pousson C, Ozoux ML, Brunel E, et al. Impact of quinupristin/dalfopristin (RP59500) on the faecal microflora in healthy volunteers. *J Antimicrob Chemother* 2002:135–9.
96. Van Saene JJ, Van Saene HK, Geitz JN, Tarko-Smit NJ, Lerk CF. Quinolones and colonization resistance in human volunteers. *Pharm Weekbl Sci* 1986:67–71.
97. Edlund C, Bergan T, Josefsson K, Solberg R, Nord CE. Effect of norfloxacin on human oropharyngeal and colonic microflora and multiple-dose pharmacokinetics. *Scand J Infect Dis* 1987:113–21.
98. de Vries-Hospers HG, Welling GW, van der Waaij D. Influence of quinolones on throat- and faecal flora of healthy volunteers. *Pharm Weekbl Sci* 1987:S41–4.
99. Pecquet S, Andremont A, Tancrede C. Selective antimicrobial modulation of the intestinal tract by norfloxacin in human volunteers and in gnotobiotic mice associated with a human fecal flora. *Antimicrob Agents Chemother* 1986:1047–52.

100. Leigh DA, Walsh B, Harris K, Hancock P, Travers G. Pharmacokinetics of ofloxacin and the effect on the faecal flora of healthy volunteers. *J Antimicrob Chemother* 1988:115–25.
101. Edlund C, Kager L, Malmborg AS, Sjostedt S, Nord CE. Effect of ofloxacin on oral and gastrointestinal microflora in patients undergoing gastric surgery. *Eur J Clin Microbiol Infect Dis* 1988:135–43.
102. Pecquet S, Andremont A, Tancrede C. Effect of oral ofloxacin on fecal bacteria in human volunteers. *Antimicrob Agents Chemother* 1987:124–5.
103. Edlund C, Lidbeck A, Kager L, Nord CE. Effect of enoxacin on colonic microflora of healthy volunteers. *Eur J Clin Microbiol* 1987:298–300.
104. Shah PM, Sammann A, Schafer V, Seczendi M, Knothe H. Fleroxacin: safety, tolerance and effect on the faecal flora of healthy volunteers. *J Antimicrob Chemother* 1988:209–13.
105. Edlund C, Brismar B, Nord CE. Effect of lomefloxacin on the normal oral and intestinal microflora. *Eur J Clin Microbiol Infect Dis* 1990:35–9.
106. Leigh DA, Harris C, Tait S, Walsh B, Hancock P. Pharmacokinetic study of lomefloxacin and its effect on the faecal flora of volunteers. *J Antimicrob Chemother* 1991:655–62.
107. Stewardson AJ, Gaia N, Francois P, Malhotra-Kumar S, Delemont C, Martinez de Tejada B, et al. Collateral damage from oral ciprofloxacin versus nitrofurantoin in outpatients with urinary tract infections: a culture-free analysis of gut microbiota. *Clin Microbiol Infect* 2015;**344**:e341 e311.
108. de Lastours V, Maugy E, Mathy V, Chau F, Rossi B, Guerin F, et al. Ecological impact of ciprofloxacin on commensal enterococci in healthy volunteers. *J Antimicrob Chemother* 2017:1574–80.
109. Dethlefsen L, Relman DA. Incomplete recovery and individualized responses of the human distal gut microbiota to repeated antibiotic perturbation. *Proc Natl Acad Sci U S A* 2011:4554–61.
110. Dethlefsen L, Huse S, Sogin ML, Relman DA. The pervasive effects of an antibiotic on the human gut microbiota, as revealed by deep 16S rRNA sequencing. *PLoS Biol* 2008:e280.
111. Krueger WA, Ruckdeschel G, Unertl K. Influence of intravenously administered ciprofloxacin on aerobic intestinal microflora and fecal drug levels when administered simultaneously with sucralfate. *Antimicrob Agents Chemother* 1997:1725–30.
112. Borzio M, Salerno F, Saudelli M, Galvagno D, Piantoni L, Fragiacomo L. Efficacy of oral ciprofloxacin as selective intestinal decontaminant in cirrhosis. *Ital J Gastroenterol Hepatol* 1997:262–6.
113. Ljungberg B, Nilsson-Ehle I, Edlund C, Nord CE. Influence of ciprofloxacin on the colonic microflora in young and elderly volunteers: no impact of the altered drug absorption. *Scand J Infect Dis* 1990:205–8.
114. van Saene HK, Lemmens SE, van Saene JJ. Gut decontamination by oral ofloxacin and ciprofloxacin in healthy volunteers. *J Antimicrob Chemother* 1988:127–34.
115. Esposito S, Barba D, Galante D, Gaeta GB, Laghezza O. Intestinal microflora changes induced by ciprofloxacin and treatment of portal-systemic encephalopathy (PSE). *Drugs Exp Clin Res* 1987:641–6.
116. Holt HA, Lewis DA, White LO, Bastable SY, Reeves DS. Effect of oral ciprofloxacin on the faecal flora of healthy volunteers. *Eur J Clin Microbiol* 1986:201–5.
117. Bergan T, Delin C, Johansen S, Kolstad IM, Nord CE, Thorsteinsson SB. Pharmacokinetics of ciprofloxacin and effect of repeated dosage on salivary and fecal microflora. *Antimicrob Agents Chemother* 1986:298–302.
118. Enzensberger R, Shah PM, Knothe H. Impact of oral ciprofloxacin on the faecal flora of healthy volunteers. *Infection* 1985:273–5.
119. Brumfitt W, Franklin I, Grady D, Hamilton-Miller JM, Iliffe A. Changes in the pharmacokinetics of ciprofloxacin and fecal flora during administration of a 7-day course to human volunteers. *Antimicrob Agents Chemother* 1984:757–61.
120. Edlund C, Sjostedt S, Nord CE. Comparative effects of levofloxacin and ofloxacin on the normal oral and intestinal microflora. *Scand J Infect Dis* 1997:383–6.
121. Inagaki Y, Nakaya R, Chida T, Hashimoto S. The effect of levofloxacin, an optically-active isomer of ofloxacin, on fecal microflora in human volunteers. *Jpn J Antibiot* 1992:241–52.
122. Ritz M, Lode H, Fassbender M, Borner K, Koeppe P, Nord CE. Multiple-dose pharmacokinetics of sparfloxacin and its influence on fecal flora. *Antimicrob Agents Chemother* 1994:455–9.
123. Edlund C, Nord CE. Ecological effect of gatifloxacin on the normal human intestinal microflora. *J Chemother* 1999:50–3.
124. Barker PJ, Sheehan R, Teillol-Foo M, Palmgren AC, Nord CE. Impact of gemifloxacin on the normal human intestinal microflora. *J Chemother* 2001:47–51.
125. Garcia-Calvo G, Molleja A, Gimenez MJ, Parra A, Nieto E, Ponte C, et al. Effects of single oral doses of gemifloxacin (320 milligrams) versus trovafloxacin (200 milligrams) on fecal flora in healthy volunteers. *Antimicrob Agents Chemother* 2001:608–11.
126. Oh H, Nord CE, Barkholt L, Hedberg M, Edlund C. Ecological disturbances in intestinal microflora caused by clinafloxacin, an extended-spectrum quinolone. *Infection* 2000:272–7.
127. Vollaard EJ, Clasener HA, Janssen AJ. Influence of pefloxacin on microbial colonization resistance in healthy volunteers. *Eur J Clin Microbiol Infect Dis* 1992:257–60.
128. Marco F, Gimenez MJ, Jimenez de Anta MT, Marcos MA, Salva P, Aguilar L. Comparison of rufloxacin and norfloxacin effects on faecal flora. *J Antimicrob Chemother* 1995:895–901.
129. Nord CE, Gajjar DA, Grasela DM. Ecological impact of the des-F(6)-quinolone, BMS-284756, on the normal intestinal microflora. *Clin Microbiol Infect* 2002:229–39.
130. Inagaki Y, Yamamoto N, Chida T, Okamura N, Tanaka M. The effect of DU-6859a, a new potent fluoroquinolone, on fecal microflora in human volunteers. *Jpn J Antibiot* 1995:368–79.
131. van Nispen CH, Hoepelman AI, Rozenberg-Arska M, Verhoef J, Purkins L, Willavize SA. A double-blind, placebo-controlled, parallel group study of oral trovafloxacin on bowel microflora in healthy male volunteers. *Am J Surg* 1998:27–31.
132. Guerrant RL, Wood SJ, Krongaard L, Reid RA, Hodge RH. Resistance among fecal flora of patients taking sulfamethoxazole-trimethoprim or trimethoprim alone. *Antimicrob Agents Chemother* 1981:33–8.
133. Lidin-Janson G. Sulphonamides in the treatment of acute Escherichia coli infection of the urinary tract in women. Clinical and ecological effects of sulphasomidine and sulphalene. *Scand J Infect Dis* 1977:211–17.
134. van Saene JJ, van Saene HK, Tarko-Smit NJ, Beukeveld GJ. Enterobacteriaceae suppression by three different oral doses of polymyxin E in human volunteers. *Epidemiol Infect* 1988:407–17.
135. Vervoort J, Xavier BB, Stewardson A, Coenen S, Godycki-Cwirko M, Adriaenssens N, et al. Metagenomic analysis of the impact of nitrofurantoin treatment on the human faecal microbiota. *J Antimicrob Chemother* 2015:1989–92.
136. Knothe H, Schafer V, Sammann A, Shah PM. Influence of fosfomycin on the intestinal and pharyngeal flora of man. *Infection* 1991:18–20.
137. Hendlin D, Celozzi E, Weissberger B, Foltz EL. Effect of fosfomycin on the fecal microflora of man. *Chemotherapy* 1977:117–26.
138. Kaji K, Takaya H, Saikawa S, Furukawa M, Sato S, Kawaratani H, et al. Rifaximin ameliorates hepatic encephalopathy and endotoxemia without affecting the gut microbiome diversity. *World J Gastroenterol* 2017:8355–66.
139. Bajaj JS, Heuman DM, Sanyal AJ, Hylemon PB, Sterling RK, Stravitz RT, et al. Modulation of the metabiome by rifaximin in patients with cirrhosis and minimal hepatic encephalopathy. *PLoS One* 2013:e60042.
140. Rashid MU, Dalhoff A, Backstrom T, Bjorkhem-Bergman L, Panagiotidis G, Weintraub A, et al. Ecological impact of MCB3837 on the normal human microbiota. *Int J Antimicrob Agents* 2014:125–30.
141. Dalhoff A, Rashid MU, Kapsner T, Panagiotidis G, Weintraub A, Nord CE. Analysis of effects of MCB3681, the antibacterially active substance of prodrug MCB3837, on human resident microflora as proof of principle. *Clin Microbiol Infect* 2015;**767**:e761–4.
142. Mavromanolakis E, Maraki S, Samonis G, Tselentis Y, Cranidis A. Effect of norfloxacin, trimethoprim-sulfamethoxazole and nitrofurantoin on fecal flora of women with recurrent urinary tract infections. *J Chemother* 1997:203–7.
143. Adamsson I, Nord CE, Lundquist P, Sjostedt S, Edlund C. Comparative effects of omeprazole, amoxycillin plus metronidazole versus omeprazole, clarithromycin plus metronidazole on the oral, gastric and intestinal microflora in Helicobacter pylori-infected patients. *J Antimicrob Chemother* 1999:629–40.
144. Jakobsson HE, Jernberg C, Andersson AF, Sjolund-Karlsson M, Jansson JK, Engstrand L. Short-term antibiotic treatment has differing long-term impacts on the human throat and gut microbiome. *PLoS One* 2010:e9836.
145. Buhling A, Radun D, Muller WA, Malfertheiner P. Influence of anti-Helicobacter triple-therapy with metronidazole, omeprazole and clarithromycin on intestinal microflora. *Aliment Pharmacol Ther* 2001:1445–52.
146. Edlund C, Beyer G, Hiemer-Bau M, Ziege S, Lode H, Nord CE. Comparative effects of moxifloxacin and clarithromycin on the normal intestinal microflora. *Scand J Infect Dis* 2000:81–5.
147. Lode H, Von der Hoh N, Ziege S, Borner K, Nord CE. Ecological effects of linezolid versus amoxicillin/clavulanic acid on the normal intestinal microflora. *Scand J Infect Dis* 2001:899–903.
148. van de Leur JJ, Vollaard EJ, Janssen AJ, Dofferhoff AS. Influence of low dose ciprofloxacin on microbial colonization of the digestive tract in healthy volunteers during normal and during impaired colonization resistance. *Scand J Infect Dis* 1997:297–300.
149. Edlund C, Stark C, Nord CE. The relationship between an increase in beta-lactamase activity after oral administration of three new cephalosporins and protection against intestinal ecological disturbances. *J Antimicrob Chemother* 1994:127–38.
150. Pletz MW, Rau M, Bulitta J, De Roux A, Burkhardt O, Kruse G, et al. Ertapenem pharmacokinetics and impact on intestinal microflora, in comparison to those of ceftriaxone, after multiple dosing in male and female volunteers. *Antimicrob Agents Chemother* 2004:3765–72.
151. D'Antonio D, Pizzigallo E, Lacone A, Violante B, Di Marzio A, Lombardo M, et al. The impact of rufloxacin given as prophylaxis to patients with cancer on their oral and faecal microflora. *J Antimicrob Chemother* 1996:839–47.
152. Ju T, Shoblak Y, Gao Y, Yang K, Fouhse J, Finlay BB, et al. Initial Gut Microbial Composition as a Key Factor Driving Host Response to Antibiotic Treatment, as Exemplified by the Presence or Absence of Commensal Escherichia coli. *Appl Environ Microbiol* 2017.
153. Goldmann DA, Leclair J, Macone A. Bacterial colonization of neonates admitted to an intensive care environment. *J Pediatr* 1978:288–93.
154. Sokol H, Pigneur B, Watterlot L, Lakhdari O, Bermudez-Humaran LG, Gratadoux JJ, et al. Faecalibacterium prausnitzii is an anti-inflammatory commensal bacterium identified by gut microbiota analysis of Crohn disease patients. *Proc Natl Acad Sci U S A* 2008:16731–6.
155. Fujimoto T, Imaeda H, Takahashi K, Kasumi E, Bamba S, Fujiyama Y, et al. Decreased abundance of Faecalibacterium prausnitzii in the gut microbiota of Crohn's disease. *J Gastroenterol Hepatol* 2013:613–19.
156. Chen W, Liu F, Ling Z, Tong X, Xiang C. Human intestinal lumen and mucosa-associated microbiota in patients with colorectal cancer. *PLoS One* 2012:e39743.

157. Kassinen A, Krogius-Kurikka L, Makivuokko H, Rinttila T, Paulin L, Corander J, et al. The fecal microbiota of irritable bowel syndrome patients differs significantly from that of healthy subjects. *Gastroenterology* 2007:24–33.
158. McFarland LV. Antibiotic-associated diarrhea: epidemiology, trends and treatment. *Future Microbiol* 2008:563–78.
159. Koh A, De Vadder F, Kovatcheva-Datchary P, Backhed F. From Dietary Fiber to Host Physiology: Short-Chain Fatty Acids as Key Bacterial Metabolites. *Cell* 2016:1332–45.
160. Hogenauer C, Hammer HF, Krejs GJ, Reisinger EC. Mechanisms and management of antibiotic-associated diarrhea. *Clin Infect Dis* 1998:702–10.
161. Bhaskaran N, Quigley C, Paw C, Butala S, Schneider E, Pandiyan P. Role of Short Chain Fatty Acids in Controlling Tregs and Immunopathology During Mucosal Infection. *Front Microbiol* 2018:1995.
162. Schilderink R, Verseijden C, Seppen J, Muncan V, van den Brink GR, Lambers TT, et al. The SCFA butyrate stimulates the epithelial production of retinoic acid via inhibition of epithelial HDAC. *Am J Physiol Gastrointest Liver Physiol* 2016:G1138–46.
163. Topping DL, Clifton PM. Short-chain fatty acids and human colonic function: roles of resistant starch and nonstarch polysaccharides. *Physiol Rev* 2001:1031–64.
164. Qin J, Li Y, Cai Z, Li S, Zhu J, Zhang F, et al. A metagenome-wide association study of gut microbiota in type 2 diabetes. *Nature* 2012:55–60.
165. Le Chatelier E, Nielsen T, Qin J, Prifti E, Hildebrand F, Falony G, et al. Richness of human gut microbiome correlates with metabolic markers. *Nature* 2013:541–6.
166. Karlsson FH, Fak F, Nookaew I, Tremaroli V, Fagerberg B, Petranovic D, et al. Symptomatic atherosclerosis is associated with an altered gut metagenome. *Nat Commun* 2012:1245.
167. Smith JG, Yokoyama WH, German JB. Butyric acid from the diet: actions at the level of gene expression. *Crit Rev Food Sci Nutr* 1998:259–97.
168. Khan S, Jena GB. Protective role of sodium butyrate, a HDAC inhibitor on beta-cell proliferation, function and glucose homeostasis through modulation of p38/ERK MAPK and apoptotic pathways: study in juvenile diabetic rat. *Chem Biol Interact* 2014:1–12.
169. Gao Z, Yin J, Zhang J, Ward RE, Martin RJ, Lefevre M, et al. Butyrate improves insulin sensitivity and increases energy expenditure in mice. *Diabetes* 2009:1509–17.
170. Pryde SE, Duncan SH, Hold GL, Stewart CS, Flint HJ. The microbiology of butyrate formation in the human colon. *FEMS Microbiol Lett* 2002:133–9.
171. Barcenilla A, Pryde SE, Martin JC, Duncan SH, Stewart CS, Henderson C, et al. Phylogenetic relationships of butyrate-producing bacteria from the human gut. *Appl Environ Microbiol* 2000:1654–61.
172. Kitahara M, Takamine F, Imamura T, Benno Y. Clostridium hiranonis sp. nov., a human intestinal bacterium with bile acid 7alpha-dehydroxylating activity. *Int J Syst Evol Microbiol* 2001:39–44.
173. Jakobsson H, Wreiber K, Fall K, Fjelstad B, Nyren O, Engstrand L. Macrolide resistance in the normal microbiota after Helicobacter pylori treatment. *Scand J Infect Dis* 2007:757–63.
174. Sjolund M, Wreiber K, Andersson DI, Blaser MJ, Engstrand L. Long-term persistence of resistant Enterococcus species after antibiotics to eradicate Helicobacter pylori. *Ann Intern Med* 2003:483–7.
175. Stamey TA, Condy M, Mihara G. Prophylactic efficacy of nitrofurantoin macrocrystals and trimethoprim-sulfamethoxazole in urinary infections. Biologic effects on the vaginal and rectal flora. *N Engl J Med* 1977:780–3.
176. Toivanen A, Kasan A, Sundquist H, Toivanen P. Effect of trimethoprim on the occurrence of drug-resistant coliform bacteria in the faecal flora. *Chemotherapy* 1976:97–103.
177. Abeles SR, Ly M, Santiago-Rodriguez TM, Pride DT. Effects of Long Term Antibiotic Therapy on Human Oral and Fecal Viromes. *PLoS One* 2015:e0134941.