Appendix1- Criteria for assessment of multidrug resistance (MDR) in eligible bacteria.

Note- There is currently a lack of harmonised standards at international level to assess MDR in commensal and pathogenic bacteria. Recommendations for experts and international organisations (EFSA) have been compiled for the purpose of this systematic review to aid the researchers to assist their interpretation of findings in the eligible studies. These recommendations may change in the meanwhile, which is outside the control of the researchers in this study.

Table 1- *Enterococcus* spp: antimicrobial categories and agents used to define MDR (adapted from Magiorakos et el 2012 and EFSA, 2015). Please bear in mind that for the purpose of MDR assessment, resistance to other AM groups that were not included in the eligibility criteria was also conducted**.**

Antimicrobial class or category	Antimicrobial substance or agent	Species with intrinsic resistance to AM categories[a]
Aminoglycosides (except streptomycin)	Gentamicin (high level)[b]	
Streptomycin	Streptomycin (high level)[b]	
Carbapenems	Imipenem Meropenem Doripenem	*Enterococcus faecium*
Fluoroquinolones	Ciprofloxacin Levofloxacin Moxifloxacin	
Glycopeptides (not tigecycline)	Vancomycin[c]	
Glycopeptides (tigecycline only)	Tigecycline	
Lipopeptides	Daptomycin	
Macrolides	Erythromycin[c]	
Oxazolidinones	Linezolid[c]	
Penicillins	Ampicillin	
Phenicol	Chloramphenicol[c]	
Streptogramins	Quinopristin-dalfopristin[b]	*Enterococcus faecalis*
Tetracycline	Doxycycline Minocycline Tetracycline[c]	

Criteria for defining MDR in *Enterococcus* spp:

- **MDR- non-susceptible to ≥ 1 agent in ≥ 3 AM categories (listed above)**

[a] When a species has intrinsic resistance to an AM category, that category must be removed from the list in this table prior to applying the criteria for the definitions and should not be counted when calculating the number of categories to which the bacterial isolate is non-susceptible.

[b] Common antimicrobial agents/substances recommended by both Magiorakos et al (2012) and EFSA (2015).

[c] As recommended by EFSA- harmonised set of antimicrobials for MDR testing (2015).

Table 2- Enterobacteriaeceae (*Escherichia coli*)- antimicrobial categories/ classes and antimicrobial agents/substances used to define MDR (worksheet for categorising isolates)- Note: does not apply to *Salmonella* spp. (adapted from Magiorakos et el 2012 and EFSA 2015). Please bear in mind that for the purpose of MDR assessment, resistance to other AM groups that were not included in the eligibility criteria was also conducted**.**

Antimicrobial category or class	Antimicrobial agent or substance	Species with intrinsic resistance to antimicrobial agents or categories)[a]
Aminoglycosides	Gentamicin[b]	*Providencia rettgeri*, *Providencia stuartii*
	Tobramycin	*P rettgeri*, *P stuartii*
	Amikacin	
	Netilmicin	*P rettgeri*, *P stuartii*
	Streptomycin[c]	
Anti-MRSA cephalosporins	Ceftaroline (Note: approved only for *E coli*, *Klebsiella pneumoniae*, *K oxytoca*)	
Antipseudomonal penicillins + B-lactamase inhibitors	Ticarcillin-clavulanic acid	*Escherichia hermannii*
	Piperacillin-tazobactam	*E hermannii*
Carbapenems	Ertapenem	
	Imipenem	
	Meropenem	
	Doripenem	
Non-extended spectrum cephalosporins: 1st and 2nd generation cephalosporins	Cefazolin	*Citrobacter freundii*, *Enterobacter aerogenes*, *Enterobacter cloacae*, *Hafnia alvei*, *Morganella morganii*, *Proteus penneri*, *Proteus vulgaris*, *P rettgeri*, *P stuartii*, *Serratia marcescens*
	Cefuroxime	*M morganii*, *P penneri*, *P vulgaris*, *S marcescens*
Extended-spectrum cephalosporins: 3rd and 4th generation cephalosporins	Cefotaxime[b] or ceftriaxone	
	Ceftazidime	
	Cefepime	
Cephamycins	Cephalotin	*C freundii*, *E aerogenes*, *E cloacae*, *H alvei*
	cefotetan	*C freundii*, *E aerogenes*, *E cloacae*, *H alvei*
Fluoroquinolones	Ciprofloxacin[b]	
	Nalidixic acid[c]	
Folate pathway inhibitors	Trimethoprim- sulphamethoxazole	
Glycylcyclines	Tigecycline	*M morganii*, *Proteus mirabilis*, *P penneri*, *P*

Antimicrobial category or class	Antimicrobial agent or substance	Species with intrinsic resistance to antimicrobial agents or categories)[a]
		vulgaris, *P rettgeri*, *P stuartii*
Monobactams	Aztreonam	
Penicillins	Ampicillin[b]	*Citrobacter koseri*, *C freundii*, *E aerogenes*, *E cloacae*, *E hermanii*, *H alvei*, *Klebsiella* spp, *M morganii*, *P penneri, P vulgaris*, *P rettgeri*, *P stuartii*, *S marcescens*
Penicillins + B-lactamase inhibitors	Amoxicillin-clavulanic acid	*C freundii*, *E aerogenes*, *E cloacae*, *H alvei*, *M morganii*, *P rettgeri*, *P stuartii*, *S marcescens*
	Ampicillin-sulbactam	*C freundii*, *C koseri*, *E aerogenes*, *E cloacae*, *H alvei*, *P rettgeri*, *S marcescens*
Phenicols	Chloramphenicol[b]	
Phosphonic acids	Fosfomycin	
Polymyxins	Colistin	*M morganii*, *P mirabilis*, *P penneri*, *P vulgaris*, *P rettgeri*, *P stuartii*, *S marcescens*
Sulphonamides	Not specified[c]	
Tetracyclines	Tetracycline[b]	*M morganii*, *P mirabilis*, *P penneri*, *P vulgaris*, *P rettgeri*, *P stuartii*
	Doxycycline	*M morganii*, *P penneri*, *P vulgaris*, *P rettgeri*, *P stuartii*
	Minocycline	*M morganii*, *P penneri*, *P vulgaris*, *P rettgeri*, *P stuartii*
Trimethoprim	Trimethoprim	

Criteria for defining MDR in Enterobacteriaceae (including *Escherichia coli* but excluding S*almonella* spp):
MDR: non-susceptible to ≥ 1 agent/substance in ≥3 more categories/classes (as listed above)

[a] when a species has intrinsic resistance to an antimicrobial agent/substance or to a whole category/ class, that agent or category must be removed from the list in this table prior to applying the criteria for the definitions and should not be counted when calculating the number of agents or categories to which the bacterial isolate is non-susceptible.

Table 3- Assessment of MDR in *Salmonella* spp (EFSA, 2015). Please bear in mind that for the purpose of MDR assessment, resistance to other AM groups that were not included in the eligibility criteria was also conducted**.**

Antimicrobial category or class	Antimicrobial agent or substance recommended to be tested for the assessment
Aminoglycosides	Gentamicin
	Streptomycin
Extended-spectrum cephalosporins: 3rd and 4th generation cephalosporins	Cefotaxime or ceftriaxone
Fluoroquinolones	Ciprofloxacin
	Nalidixic acid
Folate pathway inhibitors	Trimethoprim
Penicillins	Ampicillin
Phenicols	Chloramphenicol
Tetracyclines	Tetracycline
Sulphonamides	Not specified
Criteria for defining MDR in Escherichia coli (EFSA 2011): **MDR: non-susceptible to ≥ 1 agent/substance in ≥3 more categories/classes (as described above)**	

Table 4- Assessment of MDR in *Campylobacter coli* and *Campylobacter jejuni* (EFSA, 2015)- Note the same criteria will be extrapolated for *Campylobacter lari* for the purpose of this systematic review. Please bear in mind that for the purpose of MDR assessment, resistance to other AM groups that were not included in the eligibility criteria was also conducted**.**

Antimicrobial category or class	**Antimicrobial agent or substance recommended to be tested for the assessment**
Aminoglycosides	Gentamicin
	Streptomycin
Fluoroquinolones	Ciprofloxacin
Macrolides	Erythromycin
Tetracyclines	Tetracycline
Criteria for defining MDR in *Campylobacter spp* (EFSA 2011): **MDR: non-susceptible to ≥ 1 agent/substance in ≥3 more categories/classes**	

Specific MDR bacteria- definition:

ESBLs (Extended Spectrum Beta-Lactamase producers) producing Gram-negative bacteria- the production of these beta-lactamase confers resistance to 3rd generation cephalosporins (as well as to penicillins and 1st and 2nd generation cephalosporins) but ESBL bacteria are often also resistant to substances in other antimicrobial classes. Cefotaxime is the substance recommended for the testing of ESBLs by EFSA. The EFSA states that: "Cefotaxime is likely to detect the presence of most cefotaximases (i.e. CTX-M enzymes), which currently appear to be the most prevalent type of ESBL enzymes in bacteria isolated from food-producing animals in the EU. The use of cefotaxime will also detect the presence of AmpC enzymes in *Salmonella* or *E. coli*. Some ESBLs are ceftazidimases rather than cefotaximases (particularly enzymes in the TEM and SHV families of ESBLs). Although testing both cefotaxime and ceftazidime is therefore optimal for the detection of all ESBLs and AmpC enzymes, EFSA's guidelines have recommended testing cefotaxime to detect all CTX-M enzymes mainly for reasons of affordability". Please note that EFSA has recommended that both cefotaxime and ceftazidime are included in future harmonised mandatory monitoring to ensure optimal detection of all ESBLs, as surveillance procedures should anticipate possible changes in the status of different ESBL enzymes.

Vancomycin-resistant Enterococcus (VRE)- bacteria from the genus Enterococcus that are resistant to vancomycin. Six different types of vancomycin resistance are shown by enterococcus: Van-A, Van-B, Van-C, Van-D, Van-E and Van-G. The significance is that Van-A VRE is resistant to both vancomycin and teicoplanin. Van-B VRE is resistant to vancomycin but susceptible to teicoplanin, and Van-C is only partly resistant to vancomycin, and susceptible to teicoplanin. Cephalosporin use is a risk factor for colonization and infection by VRE, and restriction of cephalosporin usage has been associated with decreased VRE infection and transmission in hospitals.