More detailed phylogenetic analysis (Aminov 2009) suggested that the ancestral clade of flavoprotein monooxygenase genes, from which the presently known *tet*(X) had diverged, is localized within the genome of a fish pathogen, *Flavobacterium psychrophilum* (Duchaud et al. 2007). At the time of our original analysis, the nucleotide sequences highly similar (≥99%) to *tet*(X) formed a close-fitting cluster consisting of genes found in commensal and environmental bacteria such as *Bacteroides* spp. (Speer et al. 1991; Whittle et al. 2001) and environmental *Sphingobacterium* sp. (Ghosh et al. 2009) as well as in metagenomic libraries constructed from the human gut microbiome (Kurokawa et al. 2007) and the microbiome of biological phosphorus removal sludge (García Martín et al. 2006). Although the tigecycline-resistant phenotype is experimentally confirmed only for the *tet*(X) gene from Tn*4351* (Moore et al. 2005), the high similarity of nucleotide sequences in the clade (≥99%) is indicative of shared functionality. For more distant sequences, the phenotypic expression of minocycline resistance is confirmed for an opportunistic pathogen *P. aeruginosa* (GenBank accession number AB097942), and tetracycline resistance for an environmental plasmid (GenBank accession number FJ012881), when cloned into *E. coli*.

23.12 Ecological Aspects of *tet*(X)

No penetration of *tet*(X) into the clinical microbiota was detected at the time of the first analysis, and the gene was mainly encountered in commensal and environmental bacteria (Aminov 2009). Interesting is the case with the *Bacteroides* where it has been originally detected (Speer et al. 1991). These bacteria are anaerobic, but the corresponding tetracycline-degrading activity of the flavin-dependent monooxygenase requires the presence of oxygen. Thus, the gene cannot be expressed phenotypically in *Bacteroides*, and, therefore, it was not selected as conferring tetracycline resistance. Probably it is a result of co-selection by aminoglycosides and macrolides due to the genetic linkage with *addS* and *ermF* in the *Bacteroides* transposon (Whittle et al. 2001). In aerobic bacteria, it could be potentially selected directly as conferring resistance against the tetracyclines used.

At the later dates, *tet*(X) has been detected in several other ecosystems including human gut bacteria (de Vries et al. 2011), intestinal *Bacteroides* strains (Bartha et al. 2011), sewage treatment plants (Zhang and Zhang 2011), and an oxytetracycline production wastewater treatment system (Liu et al. 2012). A recent screening of soil functional metagenomes for tetracycline resistance has suggested that the occurrence of genes conferring high-level tetracycline resistance by enzymatic inactivation in natural ecosystems may be greater than previously anticipated (Forsberg et al. 2016). Some of the purified