among the most prevalent antibiotic classes applied in animal production: an estimated 16 336 823 kg is used annually for swine production alone (Krishnasamy et al. 2015). Cumulative data for 26 EU/EEA countries (expressed in milligrams per kilogram of estimated biomass of animals) also exposed tetracyclines as the most common antibiotic class used in animal production in Europe (CIPARS 2013).

Besides, the nonclinical use of tetracyclines also includes aquaculture and horticulture (Chopra and Roberts 2001). Thus, the production and use of tetracyclines for nontherapeutic purposes are truly overwhelming. Probably because of the large-scale and extensive use of tetracyclines in agriculture, resistance against them is widespread, which made the first-generation tetracyclines essentially unusable for the therapy of human infectious diseases.

23.5 Tetracycline Resistance Mechanisms

Presumably because of the extensive use of tetracyclines in human medicine, food animals, aquaculture, and horticulture, the emergence and dissemination of tetracycline resistance among pathogens were very rapid. The two key mechanisms of resistance to tetracycline consist of target modification due to the production of alternative elongation factors, which prevent the binding of tetracyclines to the ribosomes, and the efflux of tetracyclines from the cell (Roberts 1996; Chopra and Roberts 2001; Roberts 2005). Production of ribosomal protection proteins is common among both Gram-positive and Gram-negative bacteria. The tetracycline efflux pumps differ in their structure depending on the cell wall architecture and thus are specific either for Gram-positive or Gram-negative bacteria. The less common mechanisms of resistance to tetracyclines are the enzymatic degradation of tetracyclines (Speer et al. 1991) and resistances with unclear mechanisms (Nonaka and Suzuki 2002; Kazimierczak et al. 2009). The former mechanism, which is encoded by the *tet*(X) gene, however, may have a potential to compromise the efficiency of therapy by recently introduced third-generation tetracyclines such as tigecycline (Aminov 2013a). This resistance mechanism seems to be rapidly penetrating potentially pathogenic microbiota due to the agricultural and clinical use of older tetracyclines.

23.6 Phylogeny of Tetracycline Resistance Genes

The clear majority of tetracycline resistance genes are located on mobile genetic elements (MGEs) and can be acquired by a variety of microbiota via HGT processes. But what are the original reservoirs of antibiotic resistance genes from which they are continuously mobilized? If the source of these genes