are no longer under patent protection, remains less well defined—doxycycline, fosfomycin, and artesunate being some notable examples (Muller *et al.*, 2015). In comparison, many of the newer antibiotics and some antiretroviral and antihepatitis drugs are better understood because it was recognized early in their development that this issue was important for drug efficacy and tolerability (Günthard *et al.*, 2016; Smolders *et al.*, 2016; Raffe and Fisher, 2015; Stockmann *et al.*, 2015; Pau and George, 2014; Barreiro *et al.*, 2014; de Kanter *et al.*, 2014; Carpenter *et al.*, 2000). A summary of the PK-PD indices of various drug classes is shown in Table 1.2.

The emergence of drug resistance is a natural evolutionary function of most microbes but is aided by exposure to sublethal drug concentrations. Thus a drug's PK-PD indices are important for defining optimal dosing, but these can become irrelevant if there is poor patient adherence to the prescribed dosing regimen or when there is frequent inadvertent clumsy subtherapeutic drug administration, as is found in some agricultural sectors such as food animals and aquaculture. For humans, the practicality of a drug's dosing (e.g. once or twice daily) and its tolerability are critical features to ensure adherence and hence avoidance of emergence of resistance. A key example is the requirement for strict dosing adherence (≥ 97%) for antiretroviral agents if resistance is to be avoided (Günthard *et al.*, 2016; Carpenter *et al.*, 2000). Yet human factors such as forgetfulness, social isolation/depression, undereducation, ill-health, and chaotic lifestyles challenge clinicians to employ the simplest practical regimens that maximize adherence, even if it may be at the price of some perceived efficacy advantage (Carpenter *et al.*, 2000; Nathanson *et al.*, 2010; Laxminarayan, 2014). Some diseases such as tuberculosis (TB), particularly multidrug resistant (MDR) and extensively drug resistant (XDR) strains, which require complex, multidosing regimens to achieve any chance of cure, are therefore innately difficult to treat effectively and encourage researchers to improve drug formulations to minimize pill burden. Furthermore, the structure of drug treatment programs, as well as their establishment and maintenance, becomes critical for diseases such as TB and HIV infection, especially in underresourced countries where the disease burden is also often high (Nathanson *et al.*, 2010; Schaecher , 2013; Brennan *et al.*, 2014; Laxminarayan, 2014). Critical features of appropriate antimicrobial availability and delivery have been reviewed by the WHO and others (WHO, 2001; WHO, 2012; WHO, 2015; Davies, 2013; Laxminarayan *et al.*, 2016a; Laxminarayan *et al.*, 2016b; O'Neill, 2016).

Thus the importance and need for good so-called antimicrobial stewardship (AMS) has never been greater, both for human and nonhuman use, particularly for antibiotics and antifungal agents. In human health, there remains a paradox between poorer nations, where there is inadequate availability to quality antimicrobials, and other regions, where there is ready access to inexpensive (some would argue, too cheap) antibiotics, such that there is gross inappropriate overusage (Laxminarayan, 2014; Van Boeckel *et al.*, 2014; Laxminarayan *et al.*, 2013; Gelband *et al.*, 2015; Laxminarayan *et al.*, 2016a; Laxminarayan *et al.*, 2016b; see Figure 1.1). For many nations, the establishment of AMS programs, to improve both in-hospital and community-based antibiotic prescribing has therefore become a key priority. However, changing

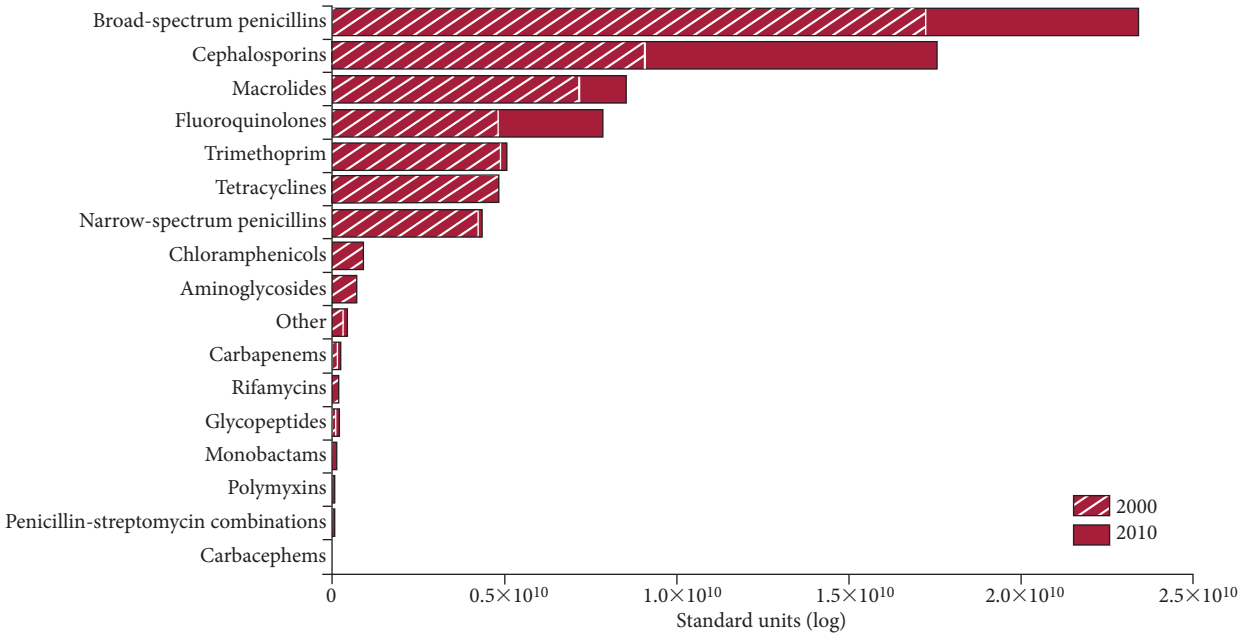

Figure 1.1. Estimates of global antibiotic consumption by class in 2000 and 2010. From Van Boeckel *et al.* (2014), with permission.