first-line drugs plus streptomycin be used in all instances of relapse and treatment default. Patients with treatment failure and those relapsing or defaulting with a high likelihood of MDR-TB should receive a regimen that includes second-line agents and is based on their history of anti-TB treatment and the drug resistance patterns in the population (Table 202-3). Once drug susceptibility test results are available, the regimen can be adjusted accordingly.

DRUG-RESISTANT TB

Strains of *M. tuberculosis* resistant to individual drugs arise by spontaneous point mutations in the mycobacterial genome that occur at low but predictable rates (10^{-7}–10^{-10} for the key drugs). Resistance to rifampin is associated with mutations in the *rpo*B gene in 95% of cases; that to isoniazid with mutations mainly in the *kat*G (50–95% of cases) and *inh*A (up to 45%) genes; that to pyrazinamide in the *pnc*A gene (up to 98%); that to ethambutol in the *emb*B gene (50–65%); that to the fluoroquinolones in the *gyr*A–*gyr*B genes (75–95%); and that to the aminoglycosides mainly in the *rrs* gene (up to 80%). Because there is no cross-resistance among the commonly used drugs, the probability that a strain will be resistant to two drugs is the product of the probabilities of resistance to each drug and thus is low. The development of drug-resistant TB is almost invariably the result of monotherapy—i.e., the failure of the health care provider to prescribe at least two drugs to which tubercle bacilli are susceptible or of the patient to take properly prescribed therapy. In addition, the use of drugs of substandard quality may cause the emergence of drug resistance. Drug-resistant TB may be either primary or acquired. Primary drug resistance is that which develops in a patient infected from the start by a drug-resistant strain. Acquired resistance is that which develops during treatment with an inappropriate regimen. In North America, Western Europe, most of Latin America, and the Persian Gulf States, rates of primary resistance are generally low and isoniazid resistance is most common. In the United States, although rates of primary isoniazid resistance have been stable at ~7–8%, the rate of primary MDR-TB has declined from 2.5% in 1993 to 1% since 2000. As described above, MDR-TB is an increasingly serious problem in some regions, especially in the states of the former Soviet Union and some countries of Asia **(Fig. 202-11)**. Even more serious is the recently described occurrence of XDR-TB due to MDR strains that are also resistant to any fluoroquinolones and to any of three second-line injectable agents (amikacin, kanamycin, and capreomycin). Creation of drug-resistant TB can be prevented by adherence to the principles of sound treatment: inclusion of at least two quality-assured, bactericidal drugs to which the organism is susceptible; use of fixed-drug-combination products; supervision of treatment with patient support; and verification that patients complete the prescribed course. Transmission of drug-resistant strains can be prevented by implementation of respiratory infection-control measures (see below).

Although the 6-month regimen described in Table 202-3 is generally effective for patients with initial isoniazid-resistant disease, it is prudent to include at least ethambutol and possibly pyrazinamide for the full 6 months and to consider extending the treatment course to 9 months. In such cases, isoniazid probably does not contribute to a successful outcome and could be omitted. In case of documented resistance to both isoniazid and ethambutol, a 9- to 12-month regimen of rifampin, pyrazinamide, and a fluoroquinolone can be used. Any patients whose isolates exhibit resistance to rifampin should be managed as if they had MDR-TB (see below), with the addition of isoniazid if susceptibility to this agent is confirmed via rapid testing or is presumed. MDR-TB, in which bacilli are resistant to (at least) isoniazid and rifampin, is more difficult to manage than is disease caused by drug-susceptible organisms because these two bactericidal drugs are the most potent agents available and because associated resistance to other first-line drugs as well (e.g., ethambutol) is not uncommon. For treatment of MDR-TB, the WHO recommends that in most patients five drugs be used in the initial phase of at least 8 months: a later-generation fluoroquinolone, an injectable agent (the aminoglycosides amikacin or kanamycin or the polypeptide capreomycin), ethionamide (or prothionamide), either cycloserine or PAS, and pyrazinamide. Ethambutol can be added (Table 202-3). Although the optimal duration of treatment is not known, a course of at least 20 months is recommended for previously untreated patients, including the initial phase with an injectable agent, which is usually discontinued at 4 months after culture conversion.

In late 2012, the FDA granted accelerated approval of bedaquiline, a diarylquinoline antibiotic. This new drug, when given for the first 24 weeks (400 mg daily for 2 weeks followed by 200 mg thrice weekly for 22 weeks), has been shown to increase the efficacy of the WHO standard regimen for MDR-TB with faster sputum conversion.

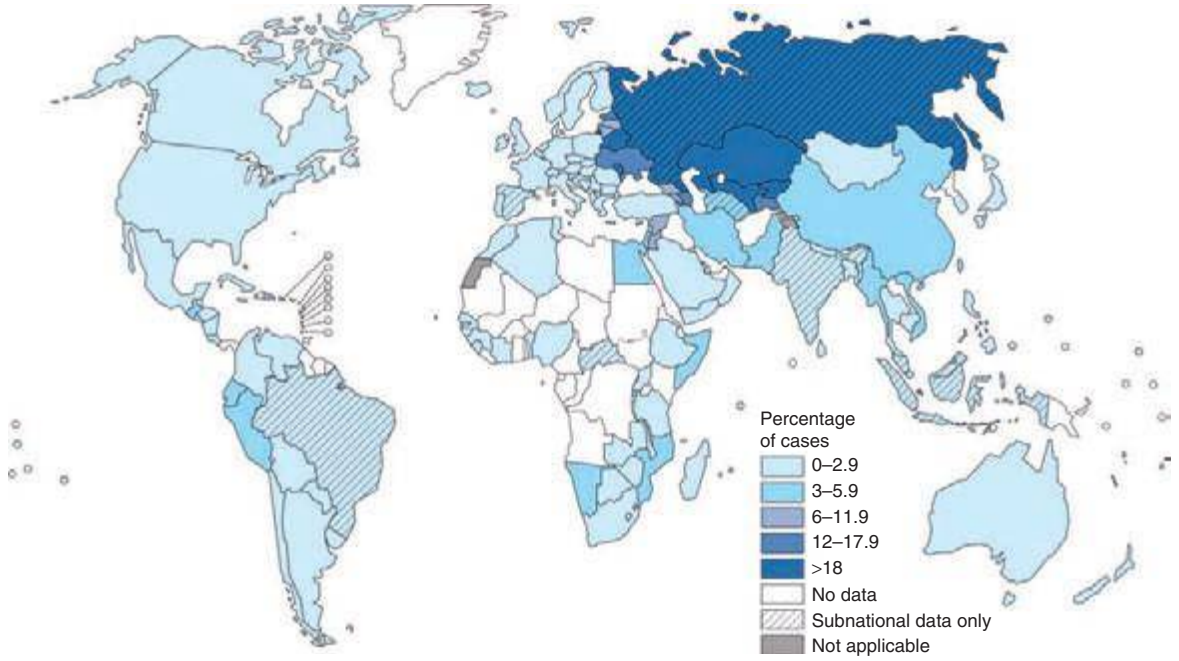

FIGURE 202-11 **Percentage of new tuberculosis cases with multidrug resistance** in all countries surveyed by the World Health Organization (WHO) Global Drug Resistance Surveillance Project during 1994–2013. *(See disclaimer in Fig. 202-2. Courtesy of the Global TB Programme, WHO; with permission.)*