manner. However, it is often more difficult to isolate *M. tuberculosis* from a child with pulmonary tuberculosis than from an adult. Therefore, choosing appropriate treatment drugs often requires the results of specimen culture and drug susceptibility tests from the person presumed to be the source of the child's infection. Based on expert opinion, when drug resistance is suspected or no source-case isolate is available, attempts to isolate organisms are critical; approaches including obtaining 3 early morning gastric aspirations (optimally during hospitalization), sputum induction [282], bronchoalveolar lavage [283], or tissue biopsy must be considered. Any information gained from molecular and phenotypic tests conducted on these samples is used to select an individualized regimen for the patient. Because tuberculosis in infants and children <4 years of age is more likely to disseminate and result in subsequent morbidity and mortality, empiric treatment is started as soon as the diagnosis is suspected, and particular care is given to drug dosage selection as an important component of achieving adequate concentrations of bactericidal drugs in body fluids, including the cerebrospinal fluid [284].

Several controlled and many observational trials of 6-month therapy in children with known or presumed drug-susceptible pulmonary tuberculosis have been published [285]. Based on systematic reviews of the literature, both the AAP [77] and the WHO [286, 287], list a 4-drug regimen (INH, RIF, PZA, and EMB) for 2 months followed by a 2-drug (INH and RIF) regimen for 4 months as the preferred regimen for children with suspected or confirmed pulmonary tuberculosis. The AAP Red Book also states that children who are receiving EMB should be monitored monthly for visual acuity and red-green color discrimination if they are old enough to cooperate. The AAP further notes that the use of EMB in young children whose visual acuity cannot be monitored requires consideration of risks and benefits, but it can be used routinely to treat tuberculosis disease in infants and children unless otherwise contraindicated [77]. As an approach to avoiding EMB ocular toxicity, some clinicians use a 3-drug regimen (INH, RIF, and PZA) in the initial 2 months of treatment for children who are HIV uninfected, have no prior tuberculosis treatment history, are living in an area of low prevalence of drug-resistant tuberculosis, and have no exposure to an individual from an area of high prevalence of drug-resistant tuberculosis. However, because the prevalence of and risk for drug-resistant tuberculosis can be difficult to ascertain, the AAP and most experts include EMB as part of the intensive phase regimen for children with tuberculosis. Pyridoxine, 25–50 mg/day, is given to infants, children, and adolescents undergoing INH treatment if they have nutritional deficiencies, symptomatic HIV infection, or are breastfeeding. Pyridoxine is also given to breastfeeding infants of mothers who are receiving INH [42, 77, 288, 289]. The lack of approved pediatric dosage forms for most antituberculosis medications has resulted in the creation and use of improvised formulations. This has entailed crushing tablets or opening capsules to access the drug, followed by weighing or proportioning of the contents that are in turn admixed with food or prepared into a suspension. With the recent development of child-friendly antituberculosis formulations meeting the dosage guidelines set by the WHO, procedures for making such improvised formulations should no longer be needed [290].

In the United States, DOT has become the default programmatic approach to treating children with tuberculosis [17]. Based on expert opinion, parents should not supervise DOT for their children. Even when drugs are administered under DOT, tolerance of the medications must be monitored closely. When feasible, daily dosing is preferred by experts [77, 279, 287]; however, twice- or thrice-weekly dosing has also been endorsed during the continuation phase of treatment for HIV-uninfected children in settings where DOT is well established [77] (see Supplementary Appendix C and Table 3 for dosing of antituberculosis drugs in children).

Monitoring response to treatment in children can be challenging because of the difficulties in demonstrating *M. tuberculosis* in children. Clinical and radiographic worsening may not be accompanied by positive AFB smears or mycobacterial cultures. According to experts, continued child growth and development while on treatment for tuberculosis usually predicts a positive outcome of treatment. A decision to modify the drug regimen should be undertaken with caution. Changes to the regimen are usually based on clinical and radiographic grounds. However, experts note that hilar adenopathy and resultant atelectasis in children on occasion can require 1–2 years to resolve; thus, an improving but persistent abnormality on a chest radiograph in an asymptomatic child is not believed to justify an extension of therapy. If there is concern that poor treatment response may be due to possible drug-resistant tuberculosis, expert opinion is that the child should be fully reinvestigated, verifying contact history and source case drug susceptibility test results, as well as obtaining additional specimens for cultures and drug susceptibility testing.

According to expert opinion, most forms of extrapulmonary tuberculosis in children can be treated with the same regimens as pulmonary disease [77, 286]; however, for children with confirmed or suspected tuberculous meningitis or osteoarticular tuberculosis caused by a drug-susceptible organism, expert opinion is that the duration of the continuation phase should be extended (See "Tuberculous Meningitis"). For tuberculous meningitis, the AAP lists an initial 4-drug regimen of INH, RIF, PZA, and an aminoglycoside or ethionamide for 2 months, followed by 7–10 months of INH and RIF. For patients who may have acquired tuberculosis in geographic areas where resistance to streptomycin is common, kanamycin, amikacin, or capreomycin is used instead of streptomycin [77]. Fluoroquinolones have been studied in adults with tuberculous meningitis [291], and these studies provide some evidence in support of their use; however, there have been no published trials of their use for tuberculous meningitis in children.