which more commonly occurs at higher dosage (Tsukamara *et al.*, 1985; Heifets and Lindolm-Levy 1987; Palmero *et al.*, 2004). In a meta-analysis of the treatment of 9153 MDR-TB patients, those in whom ofloxacin was used in combination regimens had 2.5 times the treatment success compared to those with no fluoroquinolones (95% CI: 1.6–3.9), although treatment success rates were not as high as in those patients who received later-generation quinolones (Ahuja *et al.*, 2012). Notably, fluoroquinolone resistance has been reported as an independent predictor of MDR-TB treatment failure and death (Yew *et al.*, 2003; Chan *et al.*, 2004). As with other tuberculosis drugs, regimens containing ofloxacin therapy for MDR-TB must always include several other drugs which are active against the isolate, otherwise resistance is likely to rapidly emerge (Tsukamura *et al.*, 1985; Hong Kong Chest Service/British Medical Research Council, 1992).

Background usage of quinolones in the community for reasons other than treatment of TB has been associated with the development of fluoroquinolone-resistant TB. In patients with culture-confirmed TB in Tennessee, more than 10 days fluoroquinolone exposure given for any reason prior to the diagnosis of TB was strongly associated with a high risk of fluoroquinolone-resistant TB, compared with no exposure to fluorquinolones (20.8%, OR: 17.0, 95% CI: 5.1–56.8, $p < 0.001$) (Devasia *et al.*, 2009). Between 2000 and 2010, 306/3546 (8.6%) of patients hospitalized for TB in a large Beijing hospital had ofloxacin-resistant isolates. The independent risk factors associated with ofloxacin resistance were being single (adjusted odds ratio [aOR]: 1.65), being a migrant living in Beijing (aOR: 2.15), being a migrant from another area (aOR: 5.07), prior TB treatment (aOR: 2.84), exposure to fluoroquinolones (aOR: 2.73), having chronic obstructive pulmonary disease (COPD) (aOR: 3.53), having COPD with known exposure to fluoroquinolones (aOR: 2.47), and having MDR-TB (aOR: 1.67) (Liu *et al.*, 2011). In a study of 2788 TB patients in Korea, rates of ofloxacin resistance were low in TB treatment-naïve patients and were much higher in TB treatment-experienced patients (1.1% vs. 8.5%, $p < 0.05$). The median duration of fluoroquinolone exposure was 7 days. There was no difference in fluoroquinolone exposure in the 3 months prior to TB diagnosis between ofloxacin-resistant TB cases and ofloxacin-susceptible TB cases (1/39, 2.6% vs. 93/2749, 3.4%, $p = 1.000$) (Park *et al.*, 2007). In the study by Devasia *et al.* (2009), fluoroquinolone usage data was obtained by searching the pharmacy database associated with federal Medicaid benefits, whereas the fluoroquinolone usage data in the studies by Liu *et al.* (2011) and Park *et al.* (2007) were obtained by search of hospital medical records only and hence is likely to under-report the usage data. This could account for some of the differences in results between these three studies.

Ofloxacin has been used in the preventive therapy of pediatric contacts of ofloxacin-susceptible MDR-TB. 186 South African children were given chemoprophylaxis with ofloxacin 15–20 mg/kg daily, ethambutol and isoniazid for 6 months. The combination was well tolerated apart from four children having grade 3 hallucinations and insomnia. Seven TB cases developed within 12 months' follow-up, and no cases were culture-confirmed so no drug susceptibilities were available. Five of these children had had poor adherence to the preventive therapy (Seddon *et al.*, 2013).

7g. Hansen's disease (leprosy)

Ofloxacin has demonstrated impressive activity against *M. leprae* in laboratory studies and in clinical trials, in which it was found to have better activity than either ciprofloxacin or pefloxacin (Ji and Grosset, 1991; Gelber, 1994; Ji *et al.*, 1994). Its major role and first-line WHO recommendation is in the treatment of paucibacillary leprosy with a single skin lesion. The current WHO guidelines recommend rifampicin 600 mg, ofloxacin, and minocycline 100 mg (ROM) as a single dose (WHO Expert Committee on Leprosy, 1998). In the largest study of this topic, treatment-naïve Indian patients with paucibacillary disease and a single skin lesion had slightly lower cure rates on single-dose ROM compared to 6 months' dapsone 100 mg daily and rifampicin 600 mg monthly. Cure rates with single-dose ROM were 327/697 (46.9%) compared to 374/684 (54.7%) with multidrug therapy, relative risk 0.86, 95% CI: 0.77–0.95 (Single Lesion Multicentre Trial Group, 1997).

The same single-dose combination of ROM has been studied in paucibacillary disease with 2–5 skin lesions. The largest study was of 1526 patients in a randomized, double-blind trial in five Indian centers treated with either single-dose ROM or standard WHO paucibacillary treatment with 6 months dapsone 100 mg daily and rifampicin 600 mg monthly. Cure rates were the same (72% vs. 72.1%, $p = 0.95$) but the relapse rate after 36 months of follow-up was much higher in the single-dose arm with 38 relapses, 28 of which were in the first 18 months. Relapse rates per 100 patient-years were 1.13 in the ROM group and 0.35 in the 6-months rifampicin–dapsone group ($p = 0.001$). The authors recommended single-dose ROM only when careful follow-up for relapse was available (Manickam *et al.*, 2012).

Ofloxacin plays a much smaller role in the treatment of multibacillary leprosy, where standard therapy is dapsone, rifampicin, and clofazamine for 12–24 months (WHO Expert Committee on Leprosy, 1998). Based on ofloxacin's excellent activity against *M. leprae* in animal models, WHO in 1991 organized a four-arm trial comparing standard therapy for 12–24 months versus 1 month of daily rifampicin and ofloxacin only versus standard therapy for 12 months plus 1 month of daily rifampicin and ofloxacin. However, follow-up was short, which was a major criticism in multibacillary disease where relapse typically begins more than 6 years after multiple drug therapy (Fajardo *et al.*, 2009). In a sub-study of 230 Filippino patients treated on the four-arm WHO trial followed for 9–12 years, the relapse rates for the 1-month rifampicin–ofloxacin combination regimen alone were unacceptably high at 11% at 9 years and 25% at 12 years. This was much higher than in the other three arms, which had relapse rates of 0–3% ($p < 0.05$). Relapses occurred late, commencing at 5 years after initiation of therapy (Fajardo *et al.*, 2009).