March 2015

Fluoroquinolone-resistant tuberculosis: implications in settings with weak healthcare systems

Kauser Jabeen
Aga Khan University, kauser.jabeen@aku.edu

Sadia Shakoor
Aga Khan University, sadia.shakoor@aku.edu

Rumina Hasan
Aga Khan University, rumina.hasan@aku.edu

International Journal of Infectious Diseases 32 (2015) 118–123

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Fluoroquinolone-resistant tuberculosis: implications in settings with weak healthcare systems

Kauser Jabeen, Sadia Shakoor, Rumina Hasan *

Department of Pathology and Microbiology, Aga Khan University, Stadium Road, PO Box 3500, Karachi 74800, Pakistan

ARTICLE INFO

Article history:
Received 14 November 2014
Received in revised form 5 January 2015
Accepted 6 January 2015

Corresponding Editor: Eskild Petersen, Aarhus, Denmark

Keywords:
Tuberculosis
Drug-resistant tuberculosis
Fluoroquinolone resistance
Health systems

SUMMARY

Fluoroquinolones (FQ) play an essential role in the treatment and control of multidrug-resistant tuberculosis (MDR-TB). They are also being evaluated as part of newer regimens under development for drug-sensitive TB. As newer FQ-based regimens are explored, knowledge of FQ resistance data from high TB burden countries becomes essential. We examine available FQ resistance data from high TB burden countries and demonstrate the need for comprehensive surveys to evaluate FQ resistance in these countries. The factors driving FQ resistance in such conditions and the cost of such resistance to weak healthcare systems are discussed. The need for a comprehensive policy for addressing the issue of FQ resistance is highlighted.

1. Introduction

The latest Global Tuberculosis Report estimates that 3.5% of new and 20.5% of previously treated tuberculosis (TB) cases diagnosed in 2013 were multidrug-resistant (MDR).[1] There has been considerable recent progress in the treatment of TB, and the TB drug pipeline now holds the promise of a number of new TB drugs, as well as novel regimens,[2] including for the treatment of MDR-TB. Despite such progress, the success rate for MDR-TB treatment globally is reported to be only 48%, with weak healthcare systems recognized as contributing to low cure rates.[1] Weaknesses in healthcare systems are recognized to be drivers of antimicrobial resistance in low- and low–middle-income countries (LIC and LMIC).[3]

Fluoroquinolones (FQ) are broad-spectrum antibiotics that were shown to be useful in the treatment of TB in 1984,[4] and have since become essential components of TB regimens, particularly for drug-resistant disease (Table 1).

The emergence of FQ-resistant *Mycobacterium tuberculosis* (MTB) is thus a cause for significant concern. FQ act by inhibiting DNA gyrase, an enzyme required for bacterial DNA synthesis. MTB resistance to FQ is associated primarily with mutations in DNA gyrase, a tetramer composed of two A and two B subunits, encoded by *gyr*A and *gyr*B, respectively.[13] Mutations in the *gyr*A gene are associated with high-level FQ resistance, while mutations in *gyr*B are associated with low-level resistance. A second mechanism conferring FQ resistance in MTB is through efflux pumps that act by removing the drug from bacterial cells.[5,14]

This review explores the relationship between FQ resistance in TB and healthcare system constraints, and considers options for addressing this concern.

2. FQ resistance in high TB burden countries

The 2014 Global Tuberculosis Report indicates a FQ resistance rate of 17% in MDR-TB strains tested.[1] Amongst the 22 high TB burden countries, however, data on FQ-resistant MTB are limited, with reports in some cases based on a small sample size (Table 2). While much of the available FQ resistance data is for MDR-TB, FQ resistance in non MDR-TB is reported from China, India, and Pakistan (Table 2). The prevalence of FQ resistance in MTB has led to discussions related to the use of FQ agents for infections other than TB (in particular community-acquired pneumonia (CAP)) in driving such resistance.[40]

3. Prior FQ exposure as a risk factor for FQ-resistant TB

FQ exposure is a recognized risk factor for the development of FQ resistance in many nosocomial as well as community-acquired pathogens.[41–44] Higher FQ-resistant MTB in patients with a history of respiratory infections has been attributed to widespread FQ

* Corresponding author. Tel.: +922134861640-41.
E-mail address: rumina.hasan@aku.edu (R. Hasan).

http://dx.doi.org/10.1016/j.ijid.2015.01.006

Table 1
Fluoroquinolone agents used in the treatment of tuberculosis

Agent	Activity against MTB (MIC ranges, μg/ml)[5]	Use in TB treatment regimens[a]	Programmatic recommendations (WHO)[6,7]
Second-generation			
Ofloxacin	1.0–2.0	Has been used as first- and second-line agent[8,9]	Recommended for inclusion in MDR-TB regimens Not currently recommended as first-line agent
Ciprofloxacin	0.5–4.0	In vitro activity, but may lack in vivo efficacy. Trials as first-line agent for drug-sensitive TB resulted in higher relapse rates[10,11]	Not recommended
Levofloxacin	1.0	More efficacious than ofloxacin for second-line treatment, but ofloxacin resistance may lead to treatment failure[8,12]	Recommended for inclusion in MDR-TB regimens Not currently recommended as first-line agent
Third-generation			
Gatifloxacin	0.2–0.25	Has been used in standard first- and second-line regimens. New data on shortened regimens available[8]	Not included in WHO guidelines. Lower preference due to side effects
Fourth-generation			
Moxifloxacin	0.12–0.5	Has been used in standard first- and second-line regimens. New data on shortened regimens available[8]	Recommended for inclusion in MDR-TB regimens Not currently recommended as first-line agent

MTB, *Mycobacterium tuberculosis*; MIC, minimum inhibitory concentration; TB, tuberculosis; WHO, World Health Organization; MDR, multidrug-resistant.
[a] First- and second-line, where mentioned, refer to standard regimens. First-line treatment for drug-sensitive TB: 2 months of HRZE + 4 months of HR (where H = isoniazid, R = rifampicin, Z = pyrazinamide, and E = ethambutol); 4 months of HRE is used in settings with high isoniazid resistance. Second-line treatment regimens are used for MDR-TB; it is recommended that these include at least a fluoroquinolone in addition to pyrazinamide, an injectable anti-TB drug, ethionamide (or prothionamide), and either cycloserine or para-aminosalicylic acid.[7]

usage in these individuals.[18] The impact of FQ on the development of resistance in MTB has mostly been discussed in the context of CAP.[45–48] A recent meta-analysis evaluating the association of prior FQ usage and the development of resistance in MTB reports a three-fold higher risk of FQ-resistant MTB in patients prescribed FQ before TB diagnosis.[40] Prolonged FQ exposure (defined as more than 10 days of treatment), or multiple FQ prescriptions have been highlighted as significant risk factors for the development of FQ resistance in MTB.[45,49,50] Evidence such as this has led to strong recommendations for avoiding FQ in national CAP guidelines.[51] Despite these recommendations, the majority of national CAP treatment guidelines in TB-endemic countries continue to include FQ as first-line treatment due to the fact that high global resistance rates amongst respiratory pathogens to alternative agents, including macrolides, limit options.[48]

A recent review of global FQ resistance rates reports a much higher odds ratio for FQ resistance in MDR-TB as compared to non-MDR-TB.[52] Such resistance is associated with the use of a second-line therapy including FQ in the management of MDR-TB[31,52,53] and is attributed to inadequate treatment protocols.[54,55] Hence strict supervision of second-line therapy is recommended.[56] These recommendations are supported by a recent study from Taiwan, where for both primary FQ resistance and acquired FQ resistance, rates decreased significantly following the implementation of a successful directly observed therapy DOT-Plus programme.[57]

4. Impact of FQ resistance on MTB treatment

Considerable data are available reporting delayed sputum culture conversion and treatment failure in TB patients with FQ resistance.[51,58–60] Resistance to ofloxacin has been linked with delayed culture conversion in a recent study from Pakistan.[61] An earlier systematic review of 36 trials reporting end-of-treatment or follow-up outcomes for MDR-TB patients had reported FQ resistance as being associated with poor outcomes (including any of death, default, transfer out, or treatment failure).[62] While the results of this review may have been biased due to trial and outcome heterogeneity, the findings are nevertheless a cause for concern given the significant role of FQ in MDR-TB treatment. These findings are consistent with another more recent study that analysed individual patient data from 31 published cohorts of patients with MDR-TB and extensively drug-resistant TB (XDR-TB).[63] Using data on drug sensitivity, treatment, and outcome (cure/treatment completion, failure/relapse/death), this study reports in vitro susceptibility to second-line drugs including FQ as being consistently and significantly associated with higher odds of treatment success.[63] More worrisome is the emergence of XDR-TB strains in patients on second-line treatment. A study performed in nine countries reported an XDR acquisition rate of 17% in patients with baseline FQ resistance.[53]

Attempts to shorten the duration of first-line TB therapy have led to the inclusion of FQ in shorter, 4-month regimens.[64] Recent phase 3 trials of three such regimens, two containing moxifloxacin and the third gatifloxacin, do not show non-inferiority of the shorter regimens, indicating that shortening treatment to 4 months was not effective.[65–67] Moreover, these regimens have raised concern about the efficacy in areas with high FQ resistance, wherein treatment failure and the emergence of MDR-TB strains is likely.

In contrast, excellent outcomes for a 9-month gatifloxacin-based regimen have increased optimism for improved and shorter MDR-TB management.[68–71] However, given that FQ resistance was the strongest risk factor for a bacteriologically unfavourable outcome, the protocol needs to be evaluated in high FQ-resistant TB settings.[71] Whether a higher dose of newer FQ may still be successful in such settings requires investigation.

5. Cross-resistance to newer FQ and other second-line TB drugs

The use of newer FQ for the management of ofloxacin-resistant MDR- and XDR-TB is recommended.[72] Nevertheless, a significant proportion of ofloxacin-resistant strains are also resistant to the newer FQ.[36,73,74] Newer FQ should thus not be used indiscriminately for drug-resistant TB in high FQ resistance settings without prior susceptibility testing.[59,75] Additionally FQ resistance has

Table 2
Fluoroquinolone resistance in *Mycobacterium tuberculosis* in high TB burden countries (2004–2014)

Country	Location	Study period	Population (*n*)		Resistance as % of strains tested (number resistant[a])[b]					
					CIP	OFX	LVX	MXF	GAT	FQ[b]
Bangladesh	Dhaka[15]	2013	PT cases (84)			8.3			5.9	
Brazil	Rio[16]	2001	MDR (8)		0	0	0		0	
China	Deqing County[17]	2004–2005	Non-MDR (146)		**5.5**	**1.4**	**2**			
			MDR (18)		17	11	5.6			
	Guanyun County[17]	2004–2005	Non-MDR (152)		**7.2**	**3.2**	**3.2**			
			MDR (35)		5.7	5.7	2.9			
	National DR-TB survey[18]	2007	All cases	N (3037)		2.7				
				PT (829)		8.7				
			MDR	N (175)		24.9				
				PT (226)		27.5				
	Shandong Province[19]	2007–2009	MDR	N (47)						66
				PT (18)						83
	Lianyungang City[20]	2011–2012	Smear-positive	N (816)		5.1				
				PT (196)		18.4				
Ethiopia	Amhara Region[21]	2009	Smear-positive	N (241)		0				
				PT (46)		0				
India	Nationwide[22]	2001–2004	MDR	PT (1498)		11.3				
	Delhi[23]	2008–2009	Non-MDR (47)			**14.9**				
			MDR (55)			38.2				
	Delhi[24]	2007–2010	Non-MDR (231)			**20.7**				
			MDR (130)			36.2				
	Tibetan refugee settlements[25]	2010–2011	MDR	N (28)		28.6				
				PT(23)		21.7				
Indonesia	Mimika District[26]	2003–2004	MDR (12)		0					
Pakistan	Karachi[27]	1996–2006	MDR (577)							7
	Nationwide	2005–2006	MDR (1371)							17.5
	laboratory-based[28]	2007	MDR (782)							20.8
		2008	MDR (991)							35.4
		2009	Non-MDR (1560)							**3**
			MDR (1181)							43
	Karachi, community-based[29]	2006–2009	Non-MDR	N (131)						**4.6**
				PT (21)						**4.8**
			MDR	N (21)						4.8
				PT (24)						16
Philippines	Manila[30,31]	2003–2008	MDR (2485)				7			
		2005–2008	MDR (397)							7.1
Russian Federation	Vladimir[32]	2006	MDR	N (22)		0				
				PT (160)		18				
	Orel[32]	2006	MDR	N (18)		1				
				PT (57)		23				
	Archangel[33]	2005	MDR (77)			2.3				
	Orel, Vladimir[31]	2005–2008	MDR (115)							18.3
S. Africa	4 provinces[31]	2005–2008	MDR (293)							12.6
	Cape Town[34]	2007–2009	MDR	Children (26)		7.7				
	Cape Town[35]	2009–2011	MDR	Children (23)		22				
Thailand	Nationwide[36]	2003–2011	MDR	N		10.2 (38)	5 (17)	3.8 (13)	0.9 (3)	
				PT		15.4 (62)	8.3 (29)	6.4 (23)	2 (7)	
				Total		15 (191)	8.6 (97)	6.7 (77)	2.2 (25)	
	4 provinces[31]	2005–2008	MDR (51)							9.8
	Nationwide[37]	2001–2009	MDR			10.3 (70)	7.2 (34)	4.9 (24)	1.3 (6)	
Uganda	Kampala[38]	2003–2006	MDR (51)			5.9				
UR Tanzania[39]		2009–2010	All cases	N (291)	0.7			0.35		

TB, tuberculosis; CIP, ciprofloxacin; OFX, ofloxacin; LVX, levofloxacin; MXF, moxifloxacin; GAT, gatifloxacin; FQ, fluoroquinolone (ciprofloxacin/levofloxacin/ofloxacin); PT, previously treated patients; MDR, multidrug-resistant; DR, drug-resistant; N, new patients. Published data from the following high-burden countries could not be identified and thus were not included: Afghanistan, Cambodia, DR Congo, Kenya, Mozambique, Myanmar, Nigeria, Vietnam, and Zimbabwe.

[a] Number resistant is shown where the study sample was not uniform for each FQ tested.

[b] FQ resistance among non-MDR-TB is shown in bold font.

been reported to have a much higher co-resistance to other first-line and second-line agents used in the treatment of TB.[76]

6. Healthcare system constraints driving FQ resistance

While a number of factors may contribute to FQ resistance in the community, resistance in MTB is driven to a significant extent by poor FQ pharmacokinetic/pharmacodynamic (PK/PD) exposure in patients with active disease.[77] Such faulty dosing stems as much from insufficient implementation of regulations related to the use of FQ in TB or CAP, as from inadequate regulations for controlling drug quality and antimicrobial usage in the community.

Inappropriate TB treatment by inadequately trained professionals, physicians, pharmacists, and allied health workers, particularly in the private sector, is common in weak healthcare systems.[78] Many TB patients receive either unwarranted FQ therapy or treatment with alternative FQ with poor activity. In high TB burden countries, up to 30% of patients receive ciprofloxacin,[79] an agent not recommended for use in TB due to narrow mutant prevention windows.[50]

Both counterfeit as well as substandard FQ preparations are rife in many developing countries.[80] The use of counterfeit antibiotics has been reported from Nigeria, India, Bangladesh, Burma, Cameroon, Vietnam, Cote d'Ivoire, and several other countries.[81]

Factors contributing to the easy availability of substandard preparations include inadequate approval and regulatory policies and improper manufacturing practices and quality assurance in manufacturing.[82] In India alone, >60 000 brands of various drugs are marketed, but are not registered,[83] therefore not subject to any policies that may exist.

In such systems, antibiotics are often used as a substitute for poor policy control and regulations and to fill practice gaps in preventing infections, e.g., vaccine coverage, hygiene practices, and health education of communities.[84] Such usage is promoted by physician behaviour and malpractice. Prescriptions for monetary benefits or for incentives offered by manufacturers or vendors of counterfeit FQ preparations abound in high TB burden countries.[83] Hospitals may also rely on pharmaceuticals for the generation of income for employees.[78] Prescription malpractice also includes offering more expensive brands to well-off patients and cheaper brands to the poor or uninsured, resulting in sustained sales of counterfeit drugs of varying quality.[78]

The over-the-counter (OTC) sale of drugs is in fact an important predictor of FQ-resistant MTB.[85] TB patients, mostly belonging to the lower socioeconomic strata of society and unable to afford costly private physician consultations,[86] self-medicate with better-known (and pharmacy-driven) antibiotics including those for CAP.[87]

In the generation of FQ-resistant MTB, the contribution of FQ in the non-healthcare-associated environment is also significant. This includes the presence of small amounts of FQ in the food chain as a result of unregulated use in farm animals, as growth supplements in medicated feeds,[88] in aquaculture,[89] in domestic water contaminated with farm effluents,[90] and in adulterated food products.[91] Moreover in high TB burden countries where farming is often the principal occupation, a number of patients have direct contact with sick animals on therapeutic veterinary FQ. Despite the US Food and Drug Administration ban on the veterinary use of enrofloxacin,[92] it is still used in countries with weak healthcare systems.[93] Oxolinic acid and flumequine are other quinolones in common use by farms, veterinarians, and in aquaculture that have documented cross-resistance with FQ for human use.[92]

An equally important contributor to the increased consumption of FQ (hence resistance) in weak healthcare systems is the lack of availability of reliable antibiotic susceptibility data,[84] both for MTB and for other bacterial infections. Inadequate surveillance strategies, poor quality laboratory data, and limited awareness of resistance epidemiology among healthcare workers lead to the overuse of FQ in CAP, assuming beta-lactam or tetracycline resistance. The generation of such data is essential for creating awareness and better therapeutic regimens.

7. The cost of increasing FQ resistance in weak healthcare systems

We have described the many inadequacies of weak healthcare systems leading to FQ resistance in TB. Here, we outline the burgeoning inadequacies in weak healthcare systems that in turn result from FQ resistance in MTB. The operational goals of healthcare systems are health, responsiveness, and financial risk protection for the community.[94] Increasing FQ resistance in MTB affects each of these goals directly or indirectly.

7.1. Financial impact

The treatment of several diseases requires out-of-pocket expenditure for patients and TB is no different. Despite the efforts of the World Health Organization and the Stop TB Partnership toward DOTS and DOTS-Plus coverage in high TB burden countries, weak healthcare systems are unable to ensure 100% treatment coverage; the contribution of the private sector in such care is thus considerable. As highlighted above, FQ resistance may result in either poly or XDR-TB. The cost of XDR-TB treatment, prolonged regimens, unaffordable medications, and surgery are still borne by patients to a considerable extent. Adding to this cost are the emotional and social costs of depression due to prolonged illness, poverty, and social isolation.

7.2. Impact on health

Any antibiotic resistance directly affects population health through adding to the microbial resistance gene pool and making eradication/control difficult. Health equity is also affected by a mismatch of resources against the greatest need. FQ are increasingly prescribed for other infections for which other effective treatments exist,[95] in contrast to TB, for which a limited number of anti-TB drugs are known.

7.3. Impact on responsiveness

Public health responsiveness to manage community expectations is affected directly as a consequence of resistance. Communities now know TB to be a treatable disease, however expectations are not met when XDR-TB or MDR-TB with FQ-only resistance (pre-XDR) fail treatment. Moreover, there are increasingly fewer resources to meet other expectations such as contact tracing and prevention in such cases.

All such constraints on the healthcare system lead to sustained transmission and an increasing incidence of FQ-resistant TB.

- Implementation of FQ DST prior to initiating FQ-based first- or second-line TB drug regimens
- Increase surveillance for FQ-resistant MTB in high TB burden settings including amongst non-MDR-TB strains
- Increase training of physicians particularly in the private sector to correctly diagnose and treat active TB disease
- In high burden settings, ensure responsible use of FQ in non-TB infections particularly CAP
- Closer integration of TB programmes within the healthcare system to allow screening of patients with repeated and chronic respiratory infections for MTB
- Healthcare system strengthening to improve diagnostics including DST overall, including for bacteria other than MTB, and thus implementation of directed and appropriate care
- Policies to apprehend OTC FQ sales
- A comprehensive approach to registering pharmaceuticals, monitoring of manufacturing quality and distribution practices, and post-marketing audits of available formulations
- Monitoring of FQ consumption in the country including for veterinary usage
- Implementation of the One Health Concept

Figure 1. Suggestions for containment of fluoroquinolone resistance in *Mycobacterium tuberculosis* (FQ, fluoroquinolone; DST, drug-sensitivity testing; TB, tuberculosis; MTB, *Mycobacterium tuberculosis*; MDR, multidrug-resistant; CAP, community-acquired pneumonia; OTC, over-the-counter).

8. Approach to the problem of FQ-resistant MTB

Keeping in view the manifold and system-wide causes of the increase in FQ resistance, the response to contain resistance must also be system-wide. The development and approval of policies to overcome the aforementioned constraints are the first steps required. These are summarized in Figure 1.

Addressing workforce shortages and training inadequacies are the next steps in strengthening systems. Initiatives must involve all components of the healthcare system, agriculture, aquaculture, and animal health following the model of the One Health Initiative, which proposes that the integration of human with veterinary and environmental health interventions enhances disease control efforts.[96]

However, in weak healthcare systems, the challenge is the implementation of policies. To facilitate implementation, policymakers must also ensure cultural acceptability, economic feasibility, and endorsement by the healthcare community. The allocation of resources, redistribution of finances, and recruitment of public, private, and international funders, as well as stakeholder engagement, are essential to improve policy responsiveness. If these steps can be taken by policymakers at a national level, healthcare systems can be improved to incorporate stewardship of FQ usage.

Conflict of interest: None to declare.

References

1. World Health Organization. Global Tuberculosis Report 2014. WHO/HTM/TB/2014.08. Geneva: WHO; 2014 Available at:http://www.who.int/tb/publications/global_report/en/ (accessed: November 10, 2014).
2. Zumla AI, Gillespie SH, Hoelscher M, Philips PP, Cole ST, Abubakar I, et al. New antituberculosis drugs, regimens, and adjunct therapies: needs, advances, and future prospects. *Lancet Infect Dis* 2014;**14**:327–40.
3. Laxminarayan R, Duse A, Wattal C, Zaidi AK, Wertheim HF, Sumpradit N, et al. Antibiotic resistance—the need for global solutions. *Lancet Infect Dis* 2013;**13**:1057–98.
4. Gay JD, DeYoung DR, Roberts GD. In vitro activities of norfloxacin and ciprofloxacin against *Mycobacterium tuberculosis*, *M. avium* complex, *M. chelonei*, *M. fortuitum*, and *M. kansasii*. *Antimicrob Agents Chemother* 1984;**26**:94–6.
5. Ginsburg AS, Grosset JH, Bishai WR. Fluoroquinolones, tuberculosis, and resistance. *Lancet Infect Dis* 2003;**3**:432–42.
6. World Health Organization. Treatment of tuberculosis guidelines. In: WHO/HTM/TB/2009.420.4th edition., Geneva: WHO; 2010 Available at:http://www.who.int/tb/publications/2010/9789241547833/en/ (accessed: December 28, 2014).
7. World Health Organization. Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis. In: WHO/HTM/TB/2014. 11. Geneva: WHO; 2014 Available at:http://www.who.int/tb/publications/pmdt_companionhandbook/en/ (accessed: December 28, 2014).
8. Ziganshina LE, Titarenko AF, Davies GR. Fluoroquinolones for treating tuberculosis (presumed drug-sensitive). *Cochrane Database Syst Rev* 2013;**6**:CD004795.
9. Yew WW, Kwan SY, Ma WK, Khin MA, Chau PY. In-vitro activity of ofloxacin against *Mycobacterium tuberculosis* and its clinical efficacy in multiply resistant pulmonary tuberculosis. *J Antimicrob Chemother* 1990;**26**:227–36.
10. Shandil RK, Jayaram R, Kaur P, Gaonkar S, Suresh BL, Mahesh BN, et al. Moxifloxacin, ofloxacin, sparfloxacin, and ciprofloxacin against *Mycobacterium tuberculosis*: evaluation of in vitro and pharmacodynamic indices that best predict in vivo efficacy. *Antimicrob Agents Chemother* 2007;**51**:576–82.
11. Yew WW, Chan CK, Leung CC, Chau CH, Tam CM, Wong PC, et al. Comparative roles of levofloxacin and ofloxacin in the treatment of multidrug-resistant tuberculosis: preliminary results of a retrospective study from Hong Kong. *Chest* 2003;**124**:1476–81.
12. Ziganshina LE, Squire SB. Fluoroquinolones for treating tuberculosis. *Cochrane Database Syst Rev* 2008;(1). CD004795; 1–59.
13. Hawkey PM. Mechanisms of quinolone action and microbial response. *J Antimicrob Chemother* 2003;**51**(Suppl 1):29–35.
14. Malik S, Willby M, Sikes D, Tsodikov OV, Posey JE. New insights into fluoroquinolone resistance in *Mycobacterium tuberculosis*: functional genetic analysis of *gyrA* and *gyrB* mutations. *PLoS One* 2012;**7**(6):e39754.
15. Noor R, Akhter S, Rahman F, Munshi SK, Kamal SM, Feroz F. Frequency of extensively drug-resistant tuberculosis (XDR-TB) among re-treatment cases in NIDCH, Dhaka, Bangladesh. *J Infect Chemother* 2013;**19**:243–8.
16. Lourenco MC, Junior IN, De Souza MV. In vitro activity of ciprofloxacin, ofloxacin, levofloxacin, sparfloxacin and gatifloxacin against multidrug-resistant *Mycobacterium tuberculosis* in Rio de Janeiro Brazil. *Med Mal Infect* 2007;**37**:295–6.
17. Hu Y, Mathema B, Wang W, Kreiswirth B, Jiang W, Xu B. Population-based investigation of fluoroquinolones resistant tuberculosis in rural eastern China. *Tuberculosis (Edinb)* 2011;**91**:238–43.
18. Zhao Y, Xu S, Wang L, Chin DP, Wang S, Jiang G, et al. National survey of drug-resistant tuberculosis in China. *N Engl J Med* 2012;**366**:2161–70.
19. Li X, Wang H, Jing H, Wang Y, Yu C, Wang J, et al. Population-based surveillance of extensively drug-resistant tuberculosis in Shandong Province, China. *Int J Tuberc Lung Dis* 2012;**16**:612–4.
20. Liu Q, Zhu L, Shao Y, Song H, Li G, Zhou Y, et al. Rates and risk factors for drug resistance tuberculosis in northeastern China. *BMC Public Health* 2013;**13**:1171.
21. Tessema B, Beer J, Emmrich F, Sack U, Rodloff AC. First- and second-line anti-tuberculosis drug resistance in northwest Ethiopia. *Int J Tuberc Lung Dis* 2012;**16**:805–11.
22. Paramasivan CN, Rehman F, Wares F, Sundar Mohan N, Sundar S, Devi S, et al. First- and second-line drug resistance patterns among previously treated tuberculosis patients in India. *Int J Tuberc Lung Dis* 2010;**14**:243–6.
23. Verma JS, Nair D, Rawat D, Manzoor N. Assessment of trends of ofloxacin resistance in *Mycobacterium tuberculosis*. *Indian J Med Microbiol* 2011;**29**:280–2.
24. Jain A, Dixit P, Prasad R. Pre-XDR and XDR in MDR and ofloxacin and kanamycin resistance in non-MDR *Mycobacterium tuberculosis* isolates. *Tuberculosis (Edinb)* 2012;**92**:404–6.
25. Salvo F, Dorjee K, Dierberg K, Cronin W, Sadutshang TD, Migliori GB, et al. Survey of tuberculosis drug resistance among Tibetan refugees in India. *Int J Tuberc Lung Dis* 2014;**18**:655–62.
26. Kelly PM, Ardian M, Waramori G, Anstey NM, Syahrial H, Tjitra E, et al. A community-based TB drug susceptibility study in Mimika District, Papua Province, Indonesia. *Int J Tuberc Lung Dis* 2006;**10**:167–71.
27. Rao NA, Irfan M, Soomro MM, Mehfooz Z. Drug resistance pattern in multidrug resistance pulmonary tuberculosis patients. *J Coll Physicians Surg Pak* 2010;**20**:262–5.
28. Jabeen K, Shakoor S, Chishti S, Ayaz A, Hasan R. Fluoroquinolone-resistant *Mycobacterium tuberculosis*, Pakistan, 2005-2009. *Emerg Infect Dis* 2011;**17**:564–6.
29. Rafiq Y, Jabeen K, Hasan R, Jafri S, Laiq R, Malik F, et al. Fluoroquinolone resistance among *Mycobacterium tuberculosis* strains from Karachi, Pakistan: data from community-based field clinics. *Antimicrob Agents Chemother* 2011;**55**:929–30.
30. Gler MT, Guilatco RS, Guray CV, Tupasi TE. Screening outcomes from patients with suspected multidrug-resistant tuberculosis: lessons learned in the Philippines. *Int J Tuberc Lung Dis* 2012;**16**:1326–30.
31. Dalton T, Cegielski P, Akksilp S, Asencios L, Campos Caoili J, Cho SN, et al. Prevalence of and risk factors for resistance to second-line drugs in people with multidrug-resistant tuberculosis in eight countries: a prospective cohort study. *Lancet* 2012;**380**:1406–17.
32. Punga VV, Jakubowiak WM, Danilova ID, Somova TR, Volchenkov GV, Kazionnyy BY, et al. Prevalence of extensively drug-resistant tuberculosis in Vladimir and Orel regions, Russia. *Int J Tuberc Lung Dis* 2009;**13**:1309–12.
33. Toungoussova OS, Mariandyshev AO, Bjune G, Caugant DA, Sandven P. Resistance of multidrug-resistant strains of *Mycobacterium tuberculosis* from the Archangel oblast, Russia, to second-line anti-tuberculosis drugs. *Eur J Clin Microbiol Infect Dis* 2005;**24**:202–6.
34. Seddon JA, Hesseling AC, Marais BJ, Jordaan A, Victor T, Schaaf HS. The evolving epidemic of drug-resistant tuberculosis among children in Cape Town, South Africa. *Int J Tuberc Lung Dis* 2012;**16**:928–33.
35. Schaaf HS, Hesseling AC, Rautenbach C, Seddon JA. Trends in childhood drug-resistant tuberculosis in South Africa: a window into the wider epidemic? *Int J Tuberc Lung Dis* 2014;**18**:770–3.
36. Chaiprasert A, Srimuang S, Tingtoy N, Makhao N, Sirirudeeporn P, Tomnongdee N, et al. Second-line drug susceptibilities of multidrug-resistant tuberculosis strains isolated in Thailand: an update. *Int J Tuberc Lung Dis* 2014;**18**:961–3.
37. Prammananan T, Chaiprasert A. Leechawengwongs M. 8-years experience of fluoroquinolone susceptibility testing of multidrug-resistant *Mycobacterium tuberculosis* isolates from Siriraj Hospital, Thailand. *Int J Antimicrob Agents* 2011;**37**:84–5.
38. Temple B, Ayakaka I, Ogwang S, Nabanjja H, Kayes S, Nakubulwa S, et al. Rate and amplification of drug resistance among previously-treated patients with tuberculosis in Kampala, Uganda. *Clin Infect Dis* 2008;**47**:1126–34.
39. van den Boogaard J, Semvua HH, van Ingen J, Mwaigwisya S, van der Laan T, van Soolingen D, et al. Low rate of fluoroquinolone resistance in *Mycobacterium tuberculosis* isolates from northern Tanzania. *J Antimicrob Chemother* 2011;**66**:1810–4.
40. Migliori GB, Langendam MW, D'Ambrosio L, Centis R, Blasi F, Huitric E, et al. Protecting the tuberculosis drug pipeline: stating the case for the rational use of fluoroquinolones. *Eur Respir J* 2012;**40**:814–22.
41. van der Starre WE, van Nieuwkoop C, Paltansing S, van't Wout JW, Groeneveld GH, Becker MJ, et al. Risk factors for fluoroquinolone-resistant *Escherichia coli* in adults with community-onset febrile urinary tract infection. *J Antimicrob Chemother* 2011;**66**:650–6.
42. Gallini A, Degris E, Desplas M, Bourrel R, Archambaud M, Montastruc JL, et al. Influence of fluoroquinolone consumption in inpatients and outpatients on ciprofloxacin-resistant *Escherichia coli* in a university hospital. *J Antimicrob Chemother* 2010;**65**:2650–7.
43. Adam HJ, Hoban DJ, Gin AS, Zhanel GG. Association between fluoroquinolone usage and a dramatic rise in ciprofloxacin-resistant *Streptococcus pneumoniae* in Canada, 1997-2006. *Int J Antimicrob Agents* 2009;**34**:82–5.

44. Hsu DI, Okamoto MP, Murthy R, Wong-Beringer A. Fluoroquinolone-resistant *Pseudomonas aeruginosa*: risk factors for acquisition and impact on outcomes. *J Antimicrob Chemother* 2005;**55**:535–41.
45. Long R, Chong H, Hoeppner V, Shanmuganathan H, Kowalewska-Grochowska K, Shandro C, et al. Empirical treatment of community-acquired pneumonia and the development of fluoroquinolone-resistant tuberculosis. *Clin Infect Dis* 2009;**48**:1354–60.
46. Shen GH, Tsao TC, Kao SJ, Lee JJ, Chen YH, Hsieh WC, et al. Does empirical treatment of community-acquired pneumonia with fluoroquinolones delay tuberculosis treatment and result in fluoroquinolone resistance in *Mycobacterium tuberculosis*? Controversies and solutions. *Int J Antimicrob Agents* 2012;**39**:201–5.
47. Goyet S, Vlieghe E, Lim K, van Griensven J, Borand L, Thong P, et al. Fluoroquinolone resistance and *Mycobacterium tuberculosis*: CAP guidelines play an important role. *Int J Tuberc Lung Dis* 2014;**18**:628–30.
48. Grossman RF, Hsueh PR, Gillespie SH, Blasi F. Community-acquired pneumonia and tuberculosis: differential diagnosis and the use of fluoroquinolones. *Int J Infect Dis* 2014;**18**:14–21.
49. Devasia RA, Blackman A, Gebretsadik T, Griffin M, Shintani A, May C, et al. Fluoroquinolone resistance in *Mycobacterium tuberculosis*: the effect of duration and timing of fluoroquinolone exposure. *Am J Respir Crit Care Med* 2009;**180**:365–70.
50. van der Heijden YF, Maruri F, Blackman A, Mitchel E, Bian A, Shintani AK, et al. Fluoroquinolone susceptibility in *Mycobacterium tuberculosis* after pre-diagnosis exposure to older- versus newer-generation fluoroquinolones. *Int J Antimicrob Agents* 2013;**42**:232–7.
51. Yew WW, Chan CK, Chau CH, Tam CM, Leung CC, Wong PC, et al. Outcomes of patients with multidrug-resistant pulmonary tuberculosis treated with ofloxacin/levofloxacin-containing regimens. *Chest* 2000;**117**:744–51.
52. Ho J, Jelfs P, Sintchenko V. Fluoroquinolone resistance in non-multidrug-resistant tuberculosis—a surveillance study in New South Wales, Australia, and a review of global resistance rates. *Int J Infect Dis* 2014;**26**:149–53.
53. Cegielski JP, Dalton T, Yagui M, Wattanaamornkiet W, Volchenkov GV, Via LE, et al. Extensive drug resistance acquired during treatment of multidrug-resistant tuberculosis. *Clin Infect Dis* 2014;**59**:1049–63.
54. Huang TS, Kunin CM, Shin-Jung Lee S, Chen YS, Tu HZ, Liu YC. Trends in fluoroquinolone resistance of *Mycobacterium tuberculosis* complex in a Taiwanese medical centre: 1995-2003. *J Antimicrob Chemother* 2005;**56**:1058–62.
55. Park IN, Hong SB, Oh YM, Lim CM, Lee SD, Lew WJ, et al. Impact of short-term exposure to fluoroquinolones on ofloxacin resistance in HIV-negative patients with tuberculosis. *Int J Tuberc Lung Dis* 2007;**11**:319–24.
56. Daley CL, Horsburgh Jr CR. Editorial commentary: Treatment for multidrug-resistant tuberculosis: it's worse than we thought! *Clin Infect Dis* 2014;**59**:1064–5.
57. Chien JY, Lai CC, Tan CK, Yu CJ, Hsueh PR. Direct observation therapy-plus can prevent acquired resistance to fluoroquinolones among patients with multidrug-resistant tuberculosis in Taiwan. *Clin Infect Dis* 2013;**56**:1054–5.
58. Falzon D, Gandhi N, Migliori GB, Sotgiu G, Cox HS, Holtz TH, et al. Resistance to fluoroquinolones and second-line injectable drugs: impact on multidrug-resistant TB outcomes. *Eur Respir J* 2013;**42**:156–68.
59. Migliori GB, Lange C, Girardi E, Centis R, Besozzi G, Kliiman K, et al. Fluoroquinolones: are they essential to treat multidrug-resistant tuberculosis? *Eur Respir J* 2008;**31**:904–5.
60. Kurbatova EV, Gammino VM, Bayona J, Becerra MC, Danilovitz M, Falzon D, et al. Predictors of sputum culture conversion among patients treated for multidrug-resistant tuberculosis. *Int J Tuberc Lung Dis* 2012;**16**:1335–43.
61. Basit A, Ahmad N, Khan AH, Javaid A, Syed Sulaiman SA, Afridi AK, et al. Predictors of two months culture conversion in multidrug-resistant tuberculosis: findings from a retrospective cohort study. *PLoS One* 2014;**9**:e93206.
62. Johnston JC, Shahidi NC, Sadatsafavi M, Fitzgerald JM. Treatment outcomes of multidrug-resistant tuberculosis: a systematic review and meta-analysis. *PLoS One* 2009;**4**:e6914.
63. Bastos ML, Hussain H, Weyer K, Garcia-Garcia L, Leimane V, Leung CC, et al. Treatment outcomes of patients with multidrug-resistant and extensively drug-resistant tuberculosis according to drug susceptibility testing to first- and second-line drugs: an individual patient data meta-analysis. *Clin Infect Dis* 2014;**59**:1364–74.
64. Takiff H, Guerrero E. Current prospects for the fluoroquinolones as first-line tuberculosis therapy. *Antimicrob Agents Chemother* 2011;**55**:5421–9.
65. Jindani A, Harrison TS, Nunn AJ, Phillips PP, Churchyard GJ, Charalambous S, et al. High-dose rifapentine with moxifloxacin for pulmonary tuberculosis. *N Engl J Med* 2014;**371**:1599–608.
66. Merle CS, Fielding K, Sow OB, Gninafon M, Lo MB, Mthiyane T, et al. A four-month gatifloxacin-containing regimen for treating tuberculosis. *N Engl J Med* 2014;**371**:1588–98.
67. Gillespie SH, Crook AM, McHugh TD, Mendel CM, Meredith SK, Murray SR, et al. Four-month moxifloxacin-based regimens for drug-sensitive tuberculosis. *N Engl J Med* 2014;**371**:1577–87.
68. Lalloo UG. Short-course Bangladesh regimen for multidrug-resistant tuberculosis: a step in the right direction? *Int J Tuberc Lung Dis* 2014;**18**:1137–8.
69. Van Deun A, Maug AK, Salim MA, Das PK, Sarker MR, Daru P, et al. Short, highly effective, and inexpensive standardized treatment of multidrug-resistant tuberculosis. *Am J Respir Crit Care Med* 2010;**182**:684–92.
70. Piubello A, Harouna SH, Souleymane MB, Boukary I, Morou S, Daouda M, et al. High cure rate with standardised short-course multidrug-resistant tuberculosis treatment in Niger: no relapses. *Int J Tuberc Lung Dis* 2014;**18**:1188–94.
71. Aung KJ, Van Deun A, Declercq E, Sarker MR, Das PK, Hossain MA, et al. Successful '9-month Bangladesh regimen' for multidrug-resistant tuberculosis among over 500 consecutive patients. *Int J Tuberc Lung Dis* 2014;**18**:1180–7.
72. World Health Organization. Guidelines for the programmatic management of drug-resistant tuberculosis. In: WHO/HTM/TB/2011.6. Geneva: WHO; 2011 Available at:http://whqlibdoc.who.int/publications/2011/9789241501583_eng.pdf (accessed: November 10, 2014).
73. Jiang RH, Xu HB, Li L. Comparative roles of moxifloxacin and levofloxacin in the treatment of pulmonary multidrug-resistant tuberculosis: a retrospective study. *Int J Antimicrob Agents* 2013;**42**:36–41.
74. Koh WJ, Lee SH, Kang YA, Lee CH, Choi JC, Lee JH, et al. Comparison of levofloxacin versus moxifloxacin for multidrug-resistant tuberculosis. *Am J Respir Crit Care Med* 2013;**188**:858–64.
75. Jo KW, Lee SD, Kim WS, Kim DS, Shim TS. Treatment outcomes and moxifloxacin susceptibility in ofloxacin-resistant multidrug-resistant tuberculosis. *Int J Tuberc Lung Dis* 2014;**18**:39–43.
76. Ajbani K, Nikam C, Shetty A, Soman R, Rodrigues C. Multidrug-resistant tuberculosis with fluoroquinolone resistance: sinister association with other drugs and ominous implications for treatment. *Clin Infect Dis* 2014;**59**:138–9.
77. Pasipanodya JG, Gumbo T. A new evolutionary and pharmacokinetic–pharmacodynamic scenario for rapid emergence of resistance to single and multiple anti-tuberculosis drugs. *Curr Opin Pharmacol* 2011;**11**:457–63.
78. Laxminarayan R, Heymann DL. Challenges of drug resistance in the developing world. *BMJ* 2012;**344**:e1567.
79. Wells WA, Ge CF, Patel N, Oh T, Gardiner E, Kimerling ME. Size and usage patterns of private TB drug markets in the high burden countries. *PLoS One* 2011;**6**:e18964.
80. Glass BD. Counterfeit drugs and medical devices in developing countries. *Res Rep Trop Med* 2014;**5**:11–22.
81. Okeke IN, Lamikanra A, Edelman R. Socioeconomic and behavioral factors leading to acquired bacterial resistance to antibiotics in developing countries. *Emerg Infect Dis* 1999;**5**:18–27.
82. Shakoor O, Taylor RB, Behrens RH. Assessment of the incidence of substandard drugs in developing countries. *Trop Med Int Health* 1997;**2**:839–45.
83. Bhargava A, Kalantri SP. The crisis in access to essential medicines in India: key issues which call for action. *Indian J Med Ethics* 2013;**10**:86–95.
84. Leung E, Weil DE, Raviglione M, Nakatani H. The WHO policy package to combat antimicrobial resistance. *Bull World Health Organ* 2011;**89**:390–2.
85. Shin SS, Keshavjee S, Gelmanova IY, Atwood S, Franke MF, Mishustin SP, et al. Development of extensively drug-resistant tuberculosis during multidrug-resistant tuberculosis treatment. *Am J Respir Crit Care Med* 2010;**182**:426–32.
86. Spence DP, Hotchkiss J, Williams CS, Davies PD. Tuberculosis and poverty. *BMJ* 1993;**307**:759–61.
87. Abdulah R. Antibiotic abuse in developing countries. *Pharmaceut Reg Affairs* 2012;**1**. 1000e106.
88. Love DC, Davis MF, Bassett A, Gunther A, Nachman KE. Dose imprecision and resistance: free-choice medicated feeds in industrial food animal production in the United States. *Environ Health Perspect* 2010;**119**:279–83.
89. Cabello FC. Heavy use of prophylactic antibiotics in aquaculture: a growing problem for human and animal health and for the environment. *Environ Microbiol* 2006;**8**:1137–44.
90. Wei R, Ge F, Huang S, Chen M, Wang R. Occurrence of veterinary antibiotics in animal wastewater and surface water around farms in Jiangsu Province. *China Chemosphere* 2011;**82**:1408–14.
91. Companyo R, Granados M, Guiteras J, Prat MD. Antibiotics in food: legislation and validation of analytical methodologies. *Anal Bioanal Chem* 2009;**395**:877–91.
92. Marshall BM, Levy SB. Food animals and antimicrobials: impacts on human health. *Clin Microbiol Rev* 2011;**24**:718–33.
93. Pulla P. Doctors' leaders in India call for ban on prophylactic antibiotics in poultry. *BMJ* 2014;**349**:g5052.
94. Murray CJ, Frenk J. A framework for assessing the performance of health systems. *Bull World Health Organ* 2000;**78**:717–31.
95. Van Boeckel TP, Gandra S, Ashok A, Caudron Q, Grenfell BT, Levin SA, et al. Global antibiotic consumption 2000 to 2010: an analysis of national pharmaceutical sales data. *Lancet Infect Dis* 2014;**14**:742–50.
96. Rabinowitz PM, Kock R, Kachani M, Kunkel R, Thomas J, Gilbert J, et al. Toward proof of concept of a one health approach to disease prediction and control. *Emerg Infect Dis* 2013;**19**(12):e130265.