References

1. Chengsorn N, Bloss E, Anekvorapong R, Anuwatnonthakate A, Wattanaamornkiat W, Komsakorn S, et al. Tuberculosis services and treatment outcomes in private and public health care facilities in Thailand, 2004–2006. Int J Tuberc Lung Dis. 2009;13:888–94.
2. Uplekar M, Pathania V, Raviglione M. Private practitioners and public health: weak links in tuberculosis control. Lancet. 2001;358:912–6. DOI: 10.1016/S0140-6736(01)06076-7
3. Uplekar M. Involving private health care providers in delivery of TB care: global strategy. Tuberculosis (Edinb). 2003;83:156–64. DOI: 10.1016/S1472-9792(02)00073-2
4. Quy HT, Lan NT, Lönnroth K, Buu TN, Dieu TT, Hai LT. Public-private mix for improved TB control in Ho Chi Minh City, Vietnam: an assessment of its impact on case detection. Int J Tuberc Lung Dis. 2003;7:464–71.
5. Lönnroth K, Thuong LM, Linh PD, Diwan VK. Utilization of private and public health-care providers for tuberculosis symptoms in Ho Chi Minh City, Vietnam. Health Policy Plan. 2001;16:47–54. DOI: 10.1093/heapol/16.1.47
6. Hoa NB, Sy DN, Nhung NV, Tiemersma EW, Borgdorff MW, Cobelens FGJ. A national survey of tuberculosis prevalence in Vietnam. Bull World Health Organ. 2010;88:273–80. DOI: 10.2471/BLT.09.067801
7. Hoa NB, Tiemersma EW, Sy DN, Nhung NV, Gebhard A, Borgdorff MW, et al. Household expenditure and tuberculosis prevalence in Vietnam: prediction by a set of household indicators. Int J Tuberc Lung Dis. 2010;15:32–7.
8. White IR, Royston P, Wood AM. Multiple imputation using chained equations: issues and guidance for practice. Statistics in Medicine. 2010; [Epub ahead of print].
9. Lönnroth K, Lambregts K, Nhien DT, Quy HT, Diwan VK. Private pharmacies and tuberculosis control: a survey of case detection skills and reported anti-tuberculosis drug dispensing in private pharmacies in Ho Chi Minh City, Vietnam. Int J Tuberc Lung Dis. 2000;4:1052–9.
10. Lönnroth K, Thuong LM, Lambregts K, Quy HT, Diwan VK. Private tuberculosis care provision associated with poor treatment outcome: comparative study of a semi-private lung clinic and the NTP in two urban districts in Ho Chi Minh City, Vietnam. Int J Tuberc Lung Dis. 2003;7:165–71.

Address for correspondence: Nguyen B. Hoa, National Tuberculosis Program Vietnam, 463 Hoang Hoa Tham St, Badinh District, Hanoi, Vietnam; email: nguyenbinhhoatb@yahoo.com

Fluoroquinolone-Resistant *Mycobacterium tuberculosis*, Pakistan, 2005–2009

To the Editor: Pakistan is 1 of 22 countries listed by the World Health Organization (WHO) as having a high incidence of tuberculosis (TB). We recently reported an increase in rates of multidrug-resistant (MDR) TB with emergence of extensively drug-resistant TB (*1*). Fluoroquinolone resistance is associated with worse outcome in patients with MDR TB (*2*). Recent evidence suggests emergence and increasing incidence of fluoroquinolone-resistant *Mycobacterium tuberculosis* from several countries, particularly in MDR strains (*3*). We present data from a tertiary care referral center laboratory in Pakistan to assess fluoroquinolone resistance in MDR TB strains during 2005–2009.

The Aga Khan University Hospital and its clinical laboratory have been accredited by the Joint Commission of International Accreditation and designated as a technical partner of the National TB Program. *M. tuberculosis* susceptibility testing is also periodically validated by the WHO Supranational Reference Laboratory network. The microbiology laboratory serves different cities across Pakistan with ≈180 peripheral collection units. Specimens for TB cultures are requested by physicians and received through passive collection and thus are not restricted to programmed surveys. All specimens received at each of the collection units are sent to the central laboratory in Karachi for culture and drug susceptibility testing (DST). Specimens reach the main laboratory within 24 hours after receipt.

During the past 4 years, the laboratory has received 12,000–15,000 specimens annually for *M. tuberculosis* culture; positivity rate has been 15%–20%. Culture and DST are performed at the laboratory in accordance with Clinical Laboratory Standards Institute and WHO recommendations, as described (*4*). During 2005–2008, fluoroquinolone susceptibilities for all MDR and polydrug-resistant isolates were determined by using ciprofloxacin (2 µg/mL). From 2009 onwards, fluoroquinolone susceptibilities were determined by using ofloxacin (2 µg/mL), and second-line DST was performed for all *M. tuberculosis* isolates.

During 2005–2009, a total of 11,263 cultures were reported positive for *M. tuberculosis*. Of these, 34.4% were MDR, and 50.1% were sensitive to all 4 first-line agents (isoniazid, rifampin, pyrazinamide, ethambutol). Because of inconsistencies in testing criteria for fluoroquinolones (fluoroquinolone testing being conducted primarily for MDR cases during 2005–2008), the overall fluoroquinolone-resistance rate could not be determined. However, for MDR strains, fluoroquinolone susceptibilities were consistently determined, and resistance rates increased from 17.41% in 2005 to 42.92% in 2009 (p<0.001, by χ^2 test for trend analysis) (Table).

A progressive increase in fluoroquinolone use and its association with increase in resistance against organisms other than *M. tuberculosis* have been reported from Pakistan (*5*). We report a progressive increase in fluoroquinolone resistance rate in MDR *M. tuberculosis* isolates

Table. Resistance patterns and fluoroquinolone resistance rates of *Mycobacterium tuberculosis* isolates from the Aga Khan University Hospital laboratory, Karachi, Pakistan, 2005–2009*

Year and isolates	Sensitive†	Multidrug resistant	Extensively drug resistant	Other resistance patterns‡	Total
2005					
Total	773	643	5	361	1,782
Fluoroquinolone resistant	NT	112 (17.41)	5 (100)	6 (1.66)	NA
2006					
Total	949	728	11	195	1,883
Fluoroquinolone resistant	NT	128 (17.58)	11 (100)	7 (3.58)	NA
2007					
Total	1,054	782	17	158	2,011
Fluoroquinolone resistant	NT	163 (20.84)	17 (100)	8 (5.06)	NA
2008					
Total	1,305	991	32	256	2,584
Fluoroquinolone resistant	NT	351 (35.41)	32 (100)	17 (6.64)	NA
2009					
Total	1,560	1,181	53	209	3,003
Fluoroquinolone resistant	48 (3.07)	507 (42.92)	53 (100)	23 (11)	631 (21.01)
p value§	NA	<0.001	NA	<0.001	NA
Total	5,641	4,325	118	1,179	11,263

*Values are no. (%) isolates in that category, except p values. NT, not tested; NA, not applicable.
†To isoniazid, rifampin, pyrazinamide, and ethambutol.
‡Other resistance patterns include isoniazid-monoresistant and polydrug-resistant isolates.
§χ^2 trend analysis.

during a 5-year period. This finding is consistent with those of several studies reporting fluoroquinolone resistance from the region. Agrawal et al. have recently reported an exponential increase in fluoroquinolone resistance in India from 3% in 1996 to 35% in 2004 (*6*). A significant increase in fluoroquinolone resistance from 7.7% to 20% in MDR TB was also reported from Taiwan (*7*); the authors correlated this finding with the inappropriate use of fluoroquinolones for managing TB rather than with fluoroquinolone misuse in the community. Another study from the United States and Canada reported 4.1% fluoroquinolone resistance in MDR TB strains (*8*).

In addition to detecting increasing fluoroquinolone resistance in MDR isolates, we have also detected fluoroquinolone resistance in non-MDR, polydrug-resistant *M. tuberculosis* isolates. Moreover, in 2009, a total of 3.1% of isolates susceptible to all first-line agents were fluoroquinolone resistant.

Although our dataset includes samples from throughout Pakistan, sampling limitations prevent us from deriving definite conclusions and generalizing results to the entire population of the country. A referral bias attributable to passive sampling exists because cases referred to our laboratory tend to be more complicated. Moreover, treatment history was not available for patients in our dataset; therefore, increased fluoroquinolone resistance could not be correlated with prior fluoroquinolone use. However, our findings have implications for therapy with fluoroquinolones for TB and other infections.

Fluoroquinolones are freely available as over-the-counter medications to the general population (*9*), which creates potential for misuse of fluoroquinolones by the general population for TB and several other infections, such as enteric fever and genitourinary infections. Furthermore, because national guidelines for treating enteric fever and genitourinary infections do not exist, these drugs are also overprescribed by physicians. We propose control of over-the-counter availability of fluoroquinolones and judicious use of this class of drugs by physicians to prevent further escalation in resistance rates in Pakistan.

Kauser Jabeen, Sadia Shakoor, Shazia Chishti, Afsheen Ayaz, and Rumina Hasan

Author affiliation: Aga Khan University Hospital, Karachi, Pakistan

References

1. Hasan R, Jabeen K, Mehraj V, Zafar F, Malik F, Hassan Q, et al. Trends of *Mycobacterium tuberculosis* (MTB) resistance over a period of 17 years from Pakistan. Int J Infect Dis. 2009;13:e377–82.
2. 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. DOI: 10.1371/journal.pone.0006914
3. World Health Organization. Multidrug and extensively drug-resistant TB (M/XDR-TB). 2010 Global report on surveillance and response. WHO/HTM/TB/2010.3. Geneva: The Organization; 2010. p. 1–58.
4. Hasan R, Jabeen K, Ali A, Rafiq Y, Laiq R, Malik B, et al. Extensively drug-resistant tuberculosis, Pakistan. Emerg Infect Dis. 2010;16:1473–5.
5. Okeke IN, Laxminarayan R, Bhutta ZA, Duse AG, Jenkins P, O'Brien TF, et al. Antimicrobial resistance in developing countries. Part 1: recent trends and current status. Lancet Infect Dis. 2005;5:481–93. DOI: 10.1016/S1473-3099(05)70189-4

6. Agrawal D, Udwadia ZF, Rodriguez C, Mehta A. Increasing incidence of fluoroquinolone-resistant *Mycobacterium tuberculosis* in Mumbai, India. Int J Tuberc Lung Dis. 2009;13:79–83.

7. Huang TS, Kunin CM, Lee SSJ, 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. DOI: 10.1093/jac/dki353

8. Bozeman L, Burman W, Metchock B, Welch L, Weiner M; Tuberculosis Trials Consortium. Fluoroquinolone susceptibility among *Mycobacterium tuberculosis* isolates from the United States and Canada. Clin Infect Dis. 2005;40:386–91. DOI: 10.1086/427292

9. Butt ZA, Gilani AH, Nanan D, Sheikh AL, White F. Quality of pharmacies in Pakistan: A cross-sesctional survey. Int J Qual Health Care. 2005;17:307–13. DOI: 10.1093/intqhc/mzi049

Address for correspondence: Kauser Jabeen, Aga Khan University Hospital, Karachi, Pakistan; email: kausar.jabeen@aku.edu

Hepatitis A Associated with Semidried Tomatoes, France, 2010

To the Editor: In January 2010, two clusters of nontraveler-associated hepatitis A were reported in 3 districts of southwestern France. A single IB strain of hepatitis A virus (HAV) was isolated (FR-2010-LOUR, GenBank accession no. GU646039). We conducted an investigation to describe the outbreak, identify the vehicle of transmission and source of infection, and propose appropriate control measures.

Cases were identified through mandatory notification or through the National Reference Centre for HAV. A total of 59 cases were identified: 49 confirmed cases (resident of France and infected with the outbreak strain) and 10 probable cases (resident of southwestern France and with a locally acquired infection positive for HAV immunoglobulin M against HAV with onset during November 1, 2009–February 28, 2010). Twelve (20%) persons were secondary case-patients (symptom onset 2–6 weeks after contact with a case-patient).

Twenty-eight (47.5%) case-patients were hospitalized, and all recovered. Case-patients were 7–54 years of age (median 31.5 years). The male:female ratio was 1.2:1. Cases were scattered throughout France, with 1 cluster each in Lot and Hautes-Pyrénées districts. Case-patients reported symptom onset during November 20, 2009–February 17, 2010 (Figure), with peaks during December 20, 2009–January 2, 2010, and January 24–30, 2010. The epidemiologic curve suggested a persistent common source of contamination, followed by person-to-person transmission. Of the 47 persons with nonsecondary cases (primary cases and cases that were not able to be classified), 27 (57%) reported having eaten in a sandwich shop. Twenty-four (51%) reported eating semidried tomatoes, 20 of whom reported purchasing semidried tomatoes in 1 of 3 different sandwich shop chains.

We conducted a case–control study of 30 nonsecondary case-patients with symptom onset during November 22, 2010–January 9, 2010; 109 controls (15–60 years of age living in the same district as case-patients and without histories of HAV infection or hepatitis A vaccination) were selected by random digit dialing. Exposures occurring 2–6 weeks before illness onset (case-patients) and before interview (controls) were recorded by telephone by using a standardized questionnaire. Logistic regression was performed (Stata 9.2; StataCorp LP, College Station, TX, USA); p<0.05 was considered statistically significant. Case-patients were more likely than controls to have eaten sandwiches or salads from a sandwich shop (age-adjusted odds ratio 29.1, 95% confidence interval 9.7–87.0) and to have eaten semidried tomatoes (age-adjusted odds ratio 8.5, 95% confidence interval 4.4–30.2).

HAV genotyping was performed as described (*1*). The epidemic strain FR-2010-LOUR was genotype IB. No identical strain was found in the National Reference Centre for HAV sequence database, even though IB strains represented one third of routinely isolated strains. The strain clustered significantly with sequences from patients returning from Turkey.

Trace-back investigations identified a supplier in France that imported frozen semidried tomatoes from Turkey and supplied the 3 sandwich shop chains. In France, the frozen semidried tomatoes were defrosted and processed with oil and herbs before distribution. No heat treatment, disinfection, or washing was conducted after defrosting. The period of distribution of 1 batch matched the estimated period of contamination of nonsecondary cases. This batch was no longer available at the supplier or at the sandwich shops for virologic analysis or for recall.

Our results suggest that this nationwide hepatitis A outbreak was associated with eating 1 batch of semidried tomatoes imported from Turkey and processed in France. Infected food handlers are the most frequently documented source of contamination by HAV of food items, but food also can be contaminated by contact of products or machinery with contaminated water (*2*). Therefore, the tomatoes may have been contaminated during processing by the supplier in France, during production in Turkey, or during growing. Fecal contamination of foods that are not subsequently cooked is a potential source of HAV, and the virus remains