Commentary

Commentary on Tuberculosis and HIV/AIDS in Pakistan: Success in disease control and prevention demands serious quality improvement research and programmatic efforts

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A challenge for Pakistani practitioners is securing access to manuscripts published in journals to which they do not have ready access. The future of print journals may not be a bright one, given trends towards on-line/open-access electronic publishing. Nonetheless, most peer-reviewed scientific communications in the past 5 years havestill occurred within the print journal media. As with two prior supplements in 2006 (HIV) and 2009 (tuberculosis [TB]), we are providing this editorial to orient you to the rich data and vital information presented within this supplement to the Journal of the Pakistan Medical Association (Vermund et al, 2006; Vermund et al, 2009). Thesereprinted papers in the field of HIV/AIDS and TB in Pakistan are from a wide swath of local and international journals, updated the two previously published compendia.[1,2] Their full reference are:

1. Vermund SH, Shah SA, Altaf A, Kristensen S, Khanani R, Mujeeb AS (eds.). Special Issue of JPMA on HIV/AIDS Research Publications in Pakistan. J Pak Med Assn 2006;56(suppl 1): S-1-77.

2. Vermund SH, Altaf A, Samo RN, Khanani R, Baloch N Qadeer A, Shah SA (eds.). Tuberculosis in Pakistan: A decade of progress, a future of challenge. J Pak Med Assn 2009; 59(4-Suppl 1): S1-S8.

The HIV/AIDS papers

Since our 2006 HIV/AIDS reprint compendium was published,[1] the HIV epidemic has continued to explode in Pakistan among injection drug users (IDUs) and trends are markedly upward, too, for transgender hijra sex workers. Surveys from 2011 have shown peaks of 42.2% seroprevalence for IDUs in Karachi and 12.3% HIV seroprevalence in hijra sex workers in Karachi and 15% in Larkana.[3] HIV is now an endemic disease in Pakistan and can only get much worse without serious public health and community intervention. We cite each paper in this compendium below and hope these summaries give the readers of this editorial a sense of the challenges facing HIV control and prevention efforts in Pakistan. The brief summaries are no substitute for the substantial and important details in the papers themselves.

A 2003 survey of IDUs in Karachi, Sindh Province, was done prior to the Canada-Pakistan HIV/AIDS Surveillance Project, just before the huge incidence surge began in Karachi in 2004-2005 that continues to this writing in 2012 (Altaf et al 2007).[4] Only registered IDUs within a needle exchange/harm reduction program (n=161) were included, suggesting that other IDUs not included in the study might well have had even higher risk. Both a questionnaire and blood samples were used, the latter to test for HIV (ELISA with confirmatory testing of positives), hepatitis B and

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hepatitis C (both ELISA), and syphilis (RPR with confirmation by TPHA). Mean age of IDUs was 36 years with drug use having been initiated at a mean age of 16 years. An average of 2.3 injections per day was reported and group sharing of needles/syringes was reported by 80% of subjects. Paying for sex was common (58.3%) but using a condom was not (36% ever use). Over a quarter (28%) of IDUs had sold their blood. Given that this survey preceded the well-documented upsurge of HIV in IDUs in Pakistan (with the exception of the earlier Larkana upsurge), only 0.6% (1 of 161) of IDUs was positive, though prevalence of hepatitis B was 7.5%, hepatitis C was 94.3%, and syphilis was 13.1%. Hepatitis C positivity was associated with earlier sexual debut and lower condom use, while hepatitis B was associated with younger age of IDUs. Syphilis-infected IDUs reported having paid for sex and never using a condom significantly more often than syphilis-uninfected IDUs.4 Hence, the warning signs were crystal clear given the Larkana trends among IDUs and the evidence of needle-sharing and hepatitis C in this Karachi population.

The surge in HIV spread among IDUs was first noted in the city of Larkana in Sindh Province. A 2002 survey found 17 of 183 IDUs (9.3%) to be HIV-infected during surveillance screening in 2002, far higher than any prior Pakistani seroprevalence survey in any vulnerable subgroup (Rehman et al, 2007). In a tiny nestedstudy of 7 cases and 14 controls, cases were more likely than controls to have shared needles in groups, reused a syringe from another IDU, had sex with sex workers, had >3 casual sex partners, and initiated sex at <18 years of age, though all these associations could have been due to chance. Subjects were of exceedingly high social risk in that they were unlikely to have had any formal education, some were married, and many lived on the street.[5]

Also from the Canada-Pakistan HIV/AIDS Surveillance Project, Saleem et al (2008) report results of a diverse 2005 survey used a variety of recruitment strategies (snowball, time-location cluster, and cluster sampling) for high risk persons in Rawalpindi in Punjab. The groups studied included 200 IDUs, 101 male sex workers, 101 hijras, and 203 female sex workers (FSW). Among the FSWs, two-thirds were illiterate, 71% were married, over a third reported a prior STI, and only 17% reported consistent condom use (not specified whether with clients and/or regular partners). Male sex workers and hijras reported <4% consistent condom use. Among IDUs, one in four had shared a needle during their last injection and their HIV knowledge of STIs/HIV was the lowest of the four groups.[6]

A 2007 study using mixed qualitative and quantitative methods was conducted among at-risk disenfranchised persons in Rawalpindi, Punjab Province (Mayhew et al, 2009). First, interviews were conducted with 38 IDUs and sex workers (female, male, or hijra), followed by a survey of 813 IDU and sex workers. Persons in these HIV-STD vulnerable groups interacted both socially and sexually. Reports of human rights violations were exceedingly common. Violence from personal relations and sex worker clients were reported in verbal, physical, and sexual spheres. The police were reported to have had full latitude to harass, exploit, and abuse persons from all these vulnerable groups. Health service providers were largely insensitive to the service needs of these populations.[7]

Pakistan is a highly diverse nation and HIV prevention planning must acknowledge these diversities. In a sophisticated survey of the size and distribution of FSW populations and the distribution of client-FSW encounters in seven cities, a two-stage process mapped locations where FSWs met their clients, estimated the size of the FSW population at each location and described the type of sex work (Blanchard et al, 2008). Of 34,480 FSWs who were mapped, 40% were street-based, 57.5% home-based, and 2% brothel-based; this demonstrated how much more hidden they are compared to such countries as India or Thailand, for example, where brothels are more prevalent. Of the subset of 2869 of FSWs who participated in a nested survey, a diversity of commercial approaches was revealed. For example, home-based FSWs ranged from only 32% to fully 75% of the total, depending upon the city. The study indicated that local strategies for outreach and intervention will need to consider the specific circumstances in the given area for effective program planning in a nation as diverse as Pakistan.[8]

A recurring theme of research among sex workers in Pakistan is how theoretically high the risk is, yet how low HIV seroprevalence remains (Hawkes, 2009). Sex workers (men, women, or hijras) in Rawalpindi (Punjab) and Abbottabad (Khyber PakhtunkhwaProvince, formerly known as the North-West Frontier Province) were surveyed and assessed for STIs (gonorrhea, Chlamydia, syphilis, trichomoniasis, HIV, herpes simplex virus type 2, and syphilis). Three cultural groups of male sex workers were noted: Bantha men who have a male gender identity; Khotki men who dress as men but have feminized qualities; and Khusra who are transgender biological males who dress mostly as women (like

hijras). While HIV prevalencewas low (<0.5%) in 917 male and hijra sex workers and was nil in 533 FSW, high STI infection rates were noted, especially among khusra sex workers. For example, more than half of khusra sex workers had HSV-2 infection and in Rawalpindi, more than half had syphilis. The multivariable analyses from this study are complex and well worth reading. For example, forced sex at the time of first coitus was a risk factor for STIs, while use of a condom during last sex was associated with lower STI. Violence against all sex worker groups was reported as common.[9]

A second study in 2005of hijra sex workers (Khan et al, 2008) was highly compatible with the aforementioned work of Hawkes et al, 2009. Hijras are males with a female gender identity whose cultural roots are deep in south Asian countries of the Indian subcontinent. Hijras live in marginalized communities often headed by a guru, or teacher. Transgender males who identify themselves as female are sometimes calledzenanas. Non-commercial sexualrelations or regular commercial sex with a chawa (male non-Hijra) can link the chain of risk to non-casual partners, as many chawa are married, also frequent FSW or other male sex workers. The study used questionnaires and STI genital/blood samples from 206 hijras from Karachi and 203 from Lahore. Hijras were young, had an early sexual debut, often used alcohol and drugs, and had many sexual liaisons alongside the commercial ones, with men including other hijras and with women. Selling of sex was reported by 84% of hijras and condom use was uncommon. In fact, 42% of hijrasreported "never needing" a condom! Experiencing physical abuse, forced sex, and human rights violations were commonly reported. Syphilis seropositivity was detected in 50% and 18% had gonorrhea (laboratory techniques not detailed).[10]

HIV spread is likely through sex work in Pakistan, just as elsewhere in the world. It is rare, however, that clients of sex workers are recruited successfully for interviews, as clients tend to be furtive and reluctant to be engaged by investigators. Nonetheless, there was one such improbable survey that successfully studied 203 clients of hijra (transgender) sex workers in Karachi (Siddiqui, 2012). Reported condom use during the last sexual act with ahijra sex worker was reported by only 42% of men. Casual (i.e., not regular) or better educated clients were more likely to use condoms. Fully 40% of hijra sex worker clients were married, nearly one in five had ever used drugs or alcohol, and half reported also engaging with FSW in the last month. The theoretical bridges from higher to lower risk populations in Pakistan are evident.[11]

HIV remains highly concentrated in Pakistan. HIV prevalence is exceedingly low in the general population of women in Pakistan; of the 14% of 5263 women in Punjab who had a risk factor (unspecified by the authors) on a screening questionnaire, only 2 of 779 (<0.3%) were HIV seropositive (Mahmud and Abbas, 2009).[12] It is plausible that comparatively strict social norms for sexual behavior and near-universal male circumcision in this Muslim country may blunt the efficiency of general heterosexual spread of HIV.

Tuberculosis

Since our 2009 TB reprint compendium was published,[2] Pakistan has maintained its dubious distinction as the eighth highest TB rate in the world with an estimated 2010 incidence rate of 231/100,000 population (WHO 2011). Government data suggest that the Directly Observed Treatment Short-course (DOTS) Program had extended coverage from 9% of all government tuberculosis clinics to 100% between 2000 and 2005 (National TB Control Program)

Tuberculosis has not been fueled by HIV nearly as much as it has in Africa (Memon, 2007). A 2003-2004 study of medical patients in the Civil Hospital and Sindh AIDS Control Program clients in the Services Hospital, both in Karachi. Volunteer patients were tested for both HIV (ELISA) and TB (positive sputum acid fast bacilli (AFB) smear-positiveand/or caseous granulomatous lesion on histopathology). Dual HIV/TB infection was diagnosed in 38 of 196 (19.4%) of patients. Among 126 patients with HIV, 38 (30.2%) had probable TB. HIV was exclusively in men, most of whom had contracted it while working in the Gulf States, subsequently having been deported back to Pakistan after screening positive. Among 70 patients with TB, none had HIV.13Given that the study preceded the rise of HIV among IDUs, it is plausible that there is a stronger HIV-TB link today than when this study was conducted in 2003-2004. Illicit sexual relationships were reported commonly, but few details were provided by the authors.

In late 2006-early 2007, Saqib et al (2011) studied the delays in TB diagnosis and treatment among 252 sputum smear-positive adults (half men and half women) in Rawalpindi, Punjab Province, with about 80% being 15-35 years of age. Total delay was defined as the time from onset of symptoms to the start of treatment. A median delay of 56 days (8 weeks) was estimated; delayed cases were more likely to be young, with cough and fever. Missed opportunities for

diagnosis were very common, as more than half of patients had a history of contact with previously diagnosed TB patients and 63% had visited health care providers within three weeks of symptom onset but only 35% reporting any TB work-up. The authors highlighted the need for practitioner education and engagement of the private practice sector.[14]

Only a few studies of multi-drug resistant TB (MDR-TB) have been reported from Pakistan. Saeed et al (2009) assessed the efficacy of treatment from a retrospective chart review of 176 re-treated MDR-TB adult patients from 1993-2002 who had managed at the Military Hospital in Rawalpindi, Punjab Province. Most patients were administered four standard first line anti-TB drugs (rifampicin, isoniazid, pyrazinamide, and ethambutol) along with any of two second line drugs (usually ofloxacin or clarithromycin, but ciprofloxacin/levofloxacin and/or amikacin were also used)with modified treatment as per drug susceptibility testing (e.g., all these MDR-TB patients had rifampicin and isoniazid stopped once sensitivities were established). Patients were quite ill judging from the fact that 53% of these relatively young (mean age=32.3±8.7 years) men were judged to have moderately advanced disease and almost 30% had "extensive"disease. The mean duration of TB diagnosis before therapy was41.1±14.3 months and 70% of the menhadreceived >2 prior regimens. Bacteriological cure was documented in 90% and favorable radiological responses were seen in 78% of cases. Effective application of best practices resulted in remarkable success of MDR-TB therapy in Pakistan.[15]

Rao et al (2009) reported far less success with MDR-TB in a major Sindh TB hospital in Karachi. Outcomes of MDR-TB cases seen from 1996-2006, with follow-up to June 2007, were characterized. Standard practice was to admit MDR-TB cases for 3-6 months until sputum specimens became negative on 4to 6 drugs. Post-discharge, patients were followed monthly at the hospital outpatient department for an additional 18 months. Of the 579 adults (60% men), the mean age was 32.4+12.6 years of age. Treatment cured only 227 (39%) persons, with a documented in-patient mortality of 4.6%. Fully 14% left treatment during the admission period while an additional 41% were lost to follow-up during treatment. Treatment failure was observed in three patients. Hence, cure rates were high (?88%) in persons staying in therapy, but high treatment refusal and loss to follow-up rates undermined the program, with 60% of patients leaving the MDR-TB treatment program or dying.[16]

Trends in extensively resistant tuberculosis (XDR-TB) have been reported by Hasan et al. (2010) from specimens sent for spoligotyping to the Aga Khan University tuberculosis reference laboratory from all over Pakistan. The study of 9523 specimens sent from 2006-2009 demonstrated a rise in the proportion of XDR-TB specimens from 1.5% in 2006 to 4.5% in 2009 even as the proportion of MDR-TB was stable at 38-39% in each year. Spoligotyping was done and the genotypes confirmed earlier work identifying a preponderance of CAS1 strains, though XDR-TB strains were genetically diverse, likely derivative of inadequate TB treatment. Beijing family strains represented 9% of XDR-TB isolates but only 3% of the MDR-TB isolates, suggesting the importance of Beijing XDR-TB strains. The authors highlighted the local and international significance of the rising XDR-TB rates in Pakistan, suggesting that the global community should be concerned as well as the Pakistani authorities.[17]

Household determinants of Mycobacterium tuberculosis infection (tuberculin skin test [TST] positivity) were studied in 1999 among 359 familial contacts of 77 index pulmonary TB patients (AFB sputum smear-positive) in Umerkot, a remote district of Sindh Province (Akhtar and Rathi, 2009). For BCG unvaccinated household contacts of index cases, infection was defined as a Mantoux test TST with a skin induration >10 mm at 72 hours post-TST; for BCG vaccinated household contacts, the screening threshold was >15 mm. Multilevel logistic regression analyses were performed with characteristics of household contacts at the first level and that of households at the second level were performed to control for the effects of individual-level factors. TB infection prevalence by TST positivity among household contacts of index patients was 49.9% (179/359). Household-level predictors of TST positivity among contacts were female sex of the index TB patient (adjusted odds ratio [ORadj] = 2.2; 95% CI: 1.3-3.9%) and higher density of AFB on the sputum smear (ORadj = 3.2; 95% CI: 1.9-5.5%). Characteristics of the index case that were also significantly associated with TST positivity in various analyses among contacts included a longer duration of infection, a history of hemoptysis, a higher educational achievement, and sleeping in the same room as the contact. The older the contact, the more likely they had TST positivity, and no association was noted between TST positivity and the presence of a BCG scar. The authors suggested that "both individual-level and household-level characteristics need to be taken into account while prioritizing contacts for investigations to improve TB control and prevention in resource-

constrained countries such as Pakistan."[18]

The public and private sectors do not always mesh comfortably in Pakistan, as is also common elsewhere. Investigators sought to improve TB case detection through a Public Private Mix model that engaged private practitioners in district Thatta District, Sindh Province. First, they conducted a survey (Ahmed, Ahmed, et al, 2009) of knowledge, attitudes, and practices of 22 private physicians regarding tuberculosis management in January 2007 at Thatta, a rural district of Sindh Province. An average of five suspected TB cases were seen each month perphysician. Only 14% of these doctors advised sputum microscopy for TB diagnosis and more than 2 of 5 did not prescribe TB treatment regimens compatible with the national DOTS guidelines. Fully 85% of physicians failed to follow treatment using sputum microscopy, relying instead on clinical and radiographic improvements. About 60% patients did not adhere to the TB regimen and physicians did not follow-up patients who were lost to follow-up.[19] After the survey, National TB Control Program staff trained 23 consenting physicians (from among ?200 in the district of whom about 50 saw TB patients and were invited for the training) on the Directly Observed Treatment Short course (DOTS) approach.[20] TB cases diagnosed by private practitioners through sputum microscopy were registered with the district TB control program, with medicines provided by the National TB Control Program. The initiative was correlated temporally with a modest rise in sputum smear-positive cases discovered in the 2007 intervention period, from 188 to 211, with the percentage of estimated new infectious tuberculosis cases detected rising from 69% to 77%. It was not certain that this initiative was responsible for these changes, however.Public-private partnerships have not yet been brought to scale in Pakistan. Set-backs such as the massive 2010 and 2011 floods in Sindh and Punjab did not generate as much concern for TB programs as that expressed for polio program disruptions.[21]

In a retrospective case series conducted from late 2005 to early 2007 cases at a large private tertiary care hospital in Karachi, Sindh Province, Chandiret al (2010) identified 194 patients withextrapulmonary TB. Mean age of patients was 34 ± 16 years, and 75% of patients were female. Three of five cases were seen in the lymph nodes or spine and the cure rate was only 41% (no difference by sex). The authors state that most Pakistani physicians treat patients for extrapulmonary TB for prolonged 12-24 month time periods, relying only on their clinical symptoms for feedback on treatment efficacy.[22]

Hepatic complications of anti-TB therapy were studied by Tariq et al (2009) for 500 patients cared for in a major medical center in Khyber PakhtunkhwaProvincebetween May 2006 to April 2007. About 55% were men and nearly one-third were over age 50 years. Hepatotoxicity was seen in 21 (4.2%) patients who had clinically evident hepatitis; 20 recovered and one (0.2%) died of fulminant hepatic failure. A trend was noted for older patients to have more hepatitis, but this was not assessed in detail. Hence, the treatment benefit far outweighs the drug toxicity risks, though vigilance as to hepatotoxicity of anti-TB drugs is needed.[23]

It is surprising in Pakistani surveillance statistics to see more TB cases in young women than among young men, though older men outnumber older women with TB. Codlin et al (2011) used surveillance and hospital data to document that notified TB case rates were 20-30% higher in young women compared to men in Pakistan, a dramatic contrast to global data in which the male:female (M:F) ratio of new smear-positive TB cases is about 2:1. In comparing TB case notification statistics by sex and age in 2008 from Pakistan and India, the authors note that the overall M:F ratio is 1.05 in Pakistan and 2.28 in India.[24] The need to investigate whether this represents poor surveillance among men or a genuine difference in transmission and infection dynamics is apparent.

We hope that this special issue of JPMA will serve as a helpful guide as to key HIV and TB issues in Pakistan, providing a compendium of recent work in these two topics. Success in disease control and prevention will demand a more serious effort on the part of the government and private sectors alike to improve quality and coverage of programs. Quality improvement, clinical/microbiological, behavioral, and outcomes research have important roles to play.

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