Emerging epidemic of drug resistant tuberculosis in vulnerable populations of developing countries.

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Dear Editor!

Mycobacterium tuberculosis remains one of the greatest public health problems in developing countries. However evidence about spread, geographic occurrence and evolutionary genetics of *Mycobacterium tuberculosis* strains is scarce[1]. The foremost dilemma of many World's TB Control Programs is the development of multidrug resistant *tuberculosis* (MDR TB). Although MDR TB cases are continuously being reported both in industrialized and unindustrialized countries, it is more widespread in developing countries with abject values of living[2]. Several socio-economic and biological aspects including poor chemotherapy, poverty, absence of vigilance and smoking are accountable for the TB prevalence. World Health Organization (WHO) has confirmed TB epidemic as a global emergency due to the associated reasons[3]. Several studies and analyses on susceptible groups have demonstrated that tuberculosis is more transferrable when *Mycobacterium tuberculosis* is present in sputum before any active anti-tuberculous treatment[4]. Youngsters are found to be at a larger risk of falling ill with active tuberculosis due to poor immunity while pediatric drug resistant TB undoubtedly specifies the transmission of drug resistant bacilli from grown-ups[5].

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World Health Organization has categorized 22 developing countries as high burden TB countries due to high incidence and prevalence rates of TB in these countries. WHO also categorized 27 countries as high burden MDR-TB countries. Among these 27 countries, 24 are developing countries whereas 3 are developed countries (Table: 1).

Table 1: General Incidence and Prevalence of TB and burden of MDR TB in developing countries (Modified from Global Tuberculosis Report, 2015 [1,10]).

22 High burden TB Countries	Estimated Incidence rate per 100,000	Estimated Prevalence rate per 100,000	27 High MDR-TB countries	Percentage of MDR TB among the notified TB cases (%)
Afghanistan	189	340	Armenia	9.4
Bangladesh	227	404	Azerbaijan	13
Brazil	44	52	Bangladesh	1.4
Cambodia	390	668	Belarus	34
China	68	89	Bulgaria	2.3
DR Congo	325	532	China	5.7
Ethiopia	207	200	DR Congo	2.2
India	167	195	*Estonia	19
Indonesia	399	647	Ethiopia	1.6
Kenya	246	266	Georgia	12
Mozambique	551	554	India	2.2
Myanmar	369	457	Indonesia	1.9
Nigeria	322	330	Kazakhstan	26
Pakistan	270	341	Kyrgyzstan	26
Philippines	288	417	*Latvia	8.2
Russian Federation	84	109	*Lithuania	14
South Africa	834	696	Myanmar	5.0
Thailand	171	236	Nigeria	2.9
Uganda	161	159	Pakistan	3.7
UR Tanzania	327	528	Philippines	2.0
Viet Nam	140	198	Republic of Moldova	24
Zimbabwe	278	292	Russian Federation	19
			South Africa	1.8
			Tajikistan	8.1
			Ukraine	22
			Uzbekistan	23
			Viet Nam	4.0

* Developed Countries.

Community based evidence about drug resilient TB in a developing country - Pakistan is missing. Laboratory data shows an increase in frequency of MDR from 14% in 1999 to 28% in 2004 and 47% in 2006[6]. According to WHO estimates in Pakistan, the incidence of MDR TB in new cases is 3.2% while 35% in re-treatment cases. Of all the MDR-TB cases, 51%, 23%, 15% and 3.5% occur in Punjab, Sindh, North West Frontier Province (NWFP), and Baluchistan, with the rest being distributed inside the tribal areas and in Azad Kashmir[7]. It is clear that drug resistance is seemingly linked with treatment failure, relapse, complications, and deaths which presents danger to nationwide TB control programs[8]. Global organizations, including the World Health Organization (WHO), intensely highlight the need for diagnosis of TB in missing cases particularly of the exposed groups and likewise, evidence on anti-TB drug resistance including XDR from countries (such as Pakistan) that lack mechanisms for piloting drug resistance surveys[1,9].

Mostly the diagnosis of TB in developing countries relies on conventional methods such as microscopy and culturing. But these conventional methods have certain disadvantages. Microscopy is less sensitive and culture is time consuming[11]. MGIT liquid culture is less time consuming as compared to solid LJ culture (takes 6-8 weeks) but still it takes more than 2-4 weeks to detect any viable bacilli[12]. Moreover, conventional methods cannot detect drug resistance. In order to stop the transmission of MDR-TB and to get better outcome, we need rapid and effective alternatives for early diagnosis of drug resistant TB (DR-TB) in very little time after sputum collection[13]. Such assays require highly trained professionals which can target specific genes. The most commonly used assay is Xpert® MTB/RIF (Cepheid, USA), which can detect not only the presence of MTB but also resistance to rifampicin in just 2 hours[14]. Line probe assays (LPAs), have been developed to replace current conventional tests. LPA can detect resistance to first and second line anti-tuberculosis drugs in less than 1 day[15]. The advance in PCR, sequencing, and oligonucleotide assay have increased the sensitivity, specificity, and speed of these tests[16]. Among these improvements, International agreement has been reached to use RFLP study of IS6110 (repetitive DNA which is specific to MTB) for subtyping *M. tuberculosis* isolates to enable evaluation of patterns among different strains

worldwide. RFLP patterns help in epidemiological studies and provide information about origin of outbreaks and cross-contamination[17]. In addition to RFLP typing of IS6110, spoligotyping (spacer oligonucleotide typing) is also used to distinguish strains depending on DNA polymorphism of the *M. tuberculosis* direct repeat (DR) chromosomal region[18].

There is no data existing from developing countries on the incidence of TB/MDR-TB in domestic interactions of MDR-TB patients[1]. Domestic contacts of MDR-TB suggest more recurrent threat of developing active TB and MDR-TB but such studies are rare[19]. Homelessness is a miserable condition, incorporating several liabilities that strikingly intensify the risk of being diseased, having latent TB infection (LTBI) and developing active disease. Homeless people generally have 10 to 85 times greater occurrence of LTBI and active TB and they may become a source of TB epidemics[20]. These realities highlight the significance of a steadfast and multidisciplinary methodology to these patients. Nonetheless, there is a dearth of epidemiological studies aiming on TB treatment aftermaths in vagrant people; few studies have addressed the influence of vagrancy on treatment consequences, and the existing facts came from high-income countries[20]. But the homelessness is more common in low-income countries. Mostly people live in inadequate housing or overcrowded houses where multigenerational families are confined into small places[20].

To get better outcomes of TB control programmes for vulnerable individuals is a challenging chore which necessitates the multidimensional interventions, comprising governmental and communal engagements. Here are numerous obstacles, from funding to hominoid care and adherence to TB treatment is firmly subjected to malady perception and stigmatization[21]. Furthermore, TB treatment is linked with high direct/indirect expenditures, so communal funding is necessary to attain compliance. Emphasis on DOT approach together with incentives at each visit and bonuses after completion will contribute towards positive outcome. The blend of DOT with community support not only helps in healthier consequences but also empowerment of vagrant patients.

Conflict of interest

There is no conflict of interest involved.

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