Management of TB in Refugee Populations

January 2012

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Globalization and migration have emphasized the importance of global public health. Diseases uncommon in one area of the world may quickly emerge in another, imported by global travelers[1]. Countries that receive these global travelers may be unprepared to address the needs of these foreigners and the diseases they bring. Therefore, identification and treatment of emerging infections at their site of origin would not only limit the spread of disease but also save resources of the host countries[2]. In low-incidence countries, screening of migrants at entry has little overall impact and is not a very cost-effective tuberculosis (TB) control strategy. More effective alternatives include contact tracing delivered through primary care and increased investment in global tuberculosis control[3]. TB and especially multidrug-resistant TB in migrant populations are important public health problems and must be adequately addressed in the refugee camps prior to the arrival of these immigrants in the United States.

Among the many challenges faced by the refugee populations, displacement, scarcity of shelter, overcrowding, language and cultural barriers, nutritional deficiencies and lack of health education contribute to delayed TB diagnosis and its spread in the community. In fact, Dr Kunchok Dorjee argues that migration itself is a large driver of tuberculosis due to increased risk of HIV, challenges of directly observed therapy (DOT) implementation, poor treatment adherence and subsequent emergence of drug resistant strains[4].

World Health Organization (WHO) estimates that there were 8.8 million new cases of tuberculosis in 2005. The same year, 1.6 million deaths world-wide were attributed to tuberculosis. Over 90% of TB patients and TB deaths occur in developing countries[5]. The Office of the United Nations High Commissioner for Refugees (UNHCR) estimates that in 2006 there were over 32 million refugees and displaced persons, with over 85% of them originating from countries with high TB burdens. For example, The International Organization for Migration (IOM) estimates that more than 3% of the population in Thailand consists of migrants, most coming from Myanmar. While both countries have a high burden of TB, Myanmar is believed to have both a large epidemic of HIV-associated TB and Multidrug-resistant tuberculosis (MDR-TB), which poses a problem for refugees, the native population, and the countries that will eventually resettle these refugees[6].

Currently, 56% of TB cases in the United States occur in foreign-born persons, with refugee populations being particularly vulnerable to both TB and drug-resistant TB[7]. Annually, 50,000 - 70,000 refugees get re-settled in the United States, and all undergo pre-immigration screening for TB. However, despite that, refugees have exhibited high TB incidence rates shortly after arrival in the United States. Maloney et al postulate that one contributor to high post-arrival TB rates is the low sensitivity of the current pre-immigration TB screening algorithm, which has been estimated to identify <35% of all TB cases[8]. For example, in 2004, an MDR-TB outbreak was documented in a newly-arrived group of Hmong refugees. Subsequently, MDR-TB was also documented in other refugees in the camp where the Hmong were living prior to departure. In this case, the MDR-TB outbreak occurred in a population where TB rates were already elevated but unfortunately went unrecognized due to poor resources for screening. Since half of the MDR-TB cases were sputum smear-negative, many of the cases were missed until the refugees were screened again in the US, where superior laboratory facilities were available. The outbreak led to major changes of practices for the Hmong refugees, including enhancement of pre-immigration TB screening with the addition of imaging, TB cultures and sensitivity testing regardless of sputum smear results[9]. Unfortunately, the addition of a TB culture laboratory is not an option for every refugee camp, although the US Department of State, the CDC and other organizations have begun implementing this improved screening algorithm in most risky countries.

Multidrug-resistant tuberculosis is becoming a growing threat with an estimated 440,000 new cases and 150,000 deaths worldwide in 2009[10]. MDR-TB is defined as bacteria resistant to the most effective anti-TB medications (isoniazid and rifampicin). The disease may be acquired as a primary infection or it may develop in the course of the patient's treatment. This form of tuberculosis does not respond to the standard six month medical management with first-line anti-TB drugs and therefore requires a prolonged course of expensive, yet less potent and more toxic, medications.

In 1994, WHO developed a 5-point strategy known as Directly Observed Treatment Short course (DOTS) to combat the rising incidence of TB worldwide. The main goals of DOTS are to detect 70% of smear-positive TB cases and to successfully treat 85% of new smear positive TB cases. While successful in some places, DOTS has been difficult to implement among refugees and displaced populations as well as in areas of conflict[11]. WHO and its partners also created the Green Light Committee (GLC) in 2000 to help combat the costs associated with MDR-TB treatment in resource-limited settings. The GLC is a multi-institutional

partnership that helps provide second-line drugs to patients who might not otherwise get this treatment. Pilot projects by the GLC in Estonia, Latvia, Peru, the Philippines and the Russian Federation have shown that management of MDR-TB is feasible and cost-effective. However, all of these projects were implemented under a functional TB program and guidelines developed by WHO. Therefore, refugee populations would largely be ineligible to benefit from this program, as directly-observed therapy is difficult to administer to a population that is on the move.

WHO argues that before a TB program can be implemented for a refugee population, several criteria must be met. For example, TB must be shown to be an important problem in that population, other basic needs of the population must be met (e.g. food and shelter), and availability of basic health services to the refugees must be available so that appropriate screening and referral can be arranged for TB suspects.

Once the refugee community has met the above guidelines, TB control should become one of the core services provided in the community. The management of TB in a refugee population tends to focus on identification of smear-positive pulmonary TB by microscopy with subsequent treatment of those cases, as smear-positive patients are at greatest risk of spreading the infection in the community. The most telling symptom in recognition of TB in persons over fifteen years of age is cough longer than two weeks; however, weight loss, fever, hemoptysis, night sweats and other symptoms are also important indications of the disease. According to International Standards for Tuberculosis Care, each person must have three sputum samples examined by microscopy, with early samples being most likely to be positive for acid-fast bacilli (AFB)[12]. If all three sputum samples return negative but the patient is still suspected of having TB based on persistent symptoms, broad-spectrum antibiotics are recommended for a week to treat bacterial infection, however one must be careful not to administer quinolones or other antibiotics that may compromise TB treatment in the future. If no improvement is seen after antibiotic therapy, three more sputum samples should be collected for microscopy. However, if the second set of sputum samples is AFB-negative, clinicians must rely on chest x-rays and medical judgment to decide if the patient must be started on tuberculosis therapy[13].

Smear-positive TB cases, which represent 65% of the total number of pulmonary TB cases in adults, must trigger screening of all appropriate household contacts. On the other hand, the diagnosis of smear-negative TB tends to be very imprecise in refugee populations, since TB cultures are usually unavailable and the diagnosis largely relies on symptoms and imaging when it is available. In addition, extrapulmonary TB must be considered, especially in patients with chronic lymphadenopathy. The diagnosis of extrapulmonary TB is even more difficult as it usually requires a culture-positive specimen or histological evidence, which may be beyond the scope of available laboratory services.

Appropriate treatment is determined based on extent of disease, anatomical site, and history of prior TB treatment. Once the patient is appropriately classified into a treatment category according to history of exposure to TB drugs, therapy can be initiated. The treatment course is divided into two phases: initial and continuation. The initial or intensive phase consists of 3-5 drugs given daily and under direct observation for 2-3 months. The subsequent continuation phase involves administration of 2-3 drugs three times per week for 4-6 months under direct observation of a health worker or a trained community member. The drugs are chosen from standardized combinations of rifampicin, INH, pyrazinamide, ethambutol, and streptomycin. The specific drug combinations used in the treatment phases are dependent on the category of public health risk posed by the patient. For example, category I includes newly identified smear-positive pulmonary TB patients and new cases of severe extrapulmonary TB and is therefore the highest priority for treatment. The progression to continuation phases of treatment is contingent on a negative sputum microscopy following two months of intensive phase treatment. If the sputum remains positive, intensive phase is prolonged for an additional month at which point the patient is started on continuation phase regardless of smear results. However, if sputum results remain positive at five months of treatment, the patient is categorized as treatment failure, at which point the probability of MDR-TB is high and re-treatment is initiated with a different regimen.

As evidenced by these standard regimens, TB treatment commits the patient to many months of therapy, which may be difficult in displaced and migrant populations. However, shorter regimens of therapy are beginning to gain approval from the global TB community. The TB Trials Consortium (TBTC) has recently completed a 10-year, 8,000-patient study of short treatment for latent TB infection. The trial showed that a 3-month regimen of rifapentine plus isoniazid was as effective as a traditional 9-month regimen but had a higher treatment-completion rate[14]. Researchers are also conducting studies that may allow for shorter regimens for active TB treatment in the future, thus ensuring higher compliance and completion rates.

Adherence to treatment plays a major role in ensuring the cure of TB and many measures are taken to ensure full compliance. Direct observation by a clinician or a trained community member ensures correct and timely drug administration. Continuing education of

patients, community members and staff about the importance of adherence to treatment and about the side-effects is also paramount to compliance. Home visits and individual assessments of non-compliers as soon as treatment interruption occurs may also prevent treatment failures. For example, on the Thai-Burmese border, clinicians suggest that treatment outcomes depend on the program's capacity to respond to individual patients' needs and constraints. These refugee camps, located in the Tak Province of Thailand, house thousands of Burmese refugees, both registered and illegal migrants, as well as Thai Karen villagers. The authors of a review concerning this population noticed a reduction of TB cases in the area over the last twenty years. One of the successes was increasing the proportion of male patients in the treatment program. Historically, males are more likely to work outside the camps and thus potentially hinder treatment adherence. Therefore, adapting the treatment guidelines in a way that was acceptable to the male patients significantly increased desired outcomes. Unfortunately, worse outcomes were noted in migrants and Karen villagers due to fewer sources of assistance from aid agencies[15].

When assistance from aid agencies is limited, local resources could be employed to make for a successful treatment program. Churachandpur district, India, is one of the areas not fully covered by the Indian Revised National Tuberculosis Control Program. With a population of 180,000 and a combination of civil conflict, population displacement, limited TB treatment and control services, with high incidence of HIV, TB was a large burden. However, the area demonstrated that good control and treatment of TB are possible as long as WHO guidelines are modified and adapted for local use. For example, hiring a part-time local community outreach worker from each ethnic group in the area increased adherence by helping to access all affected communities. The outreach workers were chosen based on recommendations from the elders of the affected communities. These outreach workers also lived in the same areas as their patients, with travel distances less than 6 km round-trip to patient's homes. The authors of the article argue that selection of the outreach workers by their local communities and ethnic leaders lent a degree of ownership and empowerment to the patients. The authors further conclude that taking into account ethnic sensitivities helped maximize compliance and ensure safety of personnel[16].

Some studies even show that refugee camps may actually have better treatment outcomes than settled groups in the area. In 2005, a comparison study in Khartoum, Sudan showed that displaced groups had better treatment outcomes. The study was conducted at the time when Sudan had already endured twenty years of civil war and several periods of severe drought, resulting in four million people fleeing their homes. In the refugee camps around Khartoum, prevalence of TB was higher than the settled population, with 120 sputum smear positives per 100,000 and 90 per 100,000 respectively. The camps also had more retreatment cases, longer delays from diagnosis to treatment, and several camps had been moved, thus disrupting the stability desired for TB treatment. Despite all of these factors, the camp TB treatment outcomes actually compared favorably to the settled population. Several factors may have contributed to this success. First, the camps served a smaller population, which shortened the patients' travel distance to the clinic. The camps were also better able to emphasize the importance of adherence and otherwise provide better education. The medical assistants were hired from the refugee populations and resided in the camps along with the patients, which may have reduced cultural barriers to delivery of care and education. Finally, the camp clinic had a separate waiting area designated for the TB patients, which may have emphasized the seriousness of TB when compared to other medical problems[17].

The above observations are not unique to Sudan. A review article from 1998 looked at a wide range of results of TB management in refugee camps worldwide and found that it often compared favorably to local programs[18]. Studies also show that programs applying DOTS are generally more likely to succeed[19, 20]. And while DOTS is generally more difficult in displaced and migrant populations, refugee camps may actually create enough stability for TB management programs to achieve good results.

TB treatment in refugee camps faces many challenges. Overcrowding, higher rates of HIV and poor nutrition of refugees and displaced peoples encourage both development and spread of TB, while access to good TB management programs may be reduced. Health care is often provided by international relief agencies, which lack staff capable of navigating the local cultural barriers and may only be able to provide intervention for a limited period of time. Implementing TB programs in unstable settings may also contribute to increasing rates of resistance, thus doing more harm than good to the population. In addition, one of the greatest challenges to TB management in refugee camps is still expected to be the availability and quality of laboratory testing and screening. For example, in its latest TB newsletter, the CDC reported that it anticipated that the latest revisions of TB technical instructions would increase the number of referrals for medical follow-up. This was expected due to the introduction of screening for latent TB among children in high-risk countries. However, 46% of referrals with a reported positive tuberculin skin test turned out to be negative when the patients were re-screened in the United States[21]. The

quality of overseas screening must be improved so that treatment can be administered swiftly and without unnecessary taxation of already limited public health resources in the area. However, when international guidelines are adopted to fit the treatment population, to minimize cultural barriers, maximize education, improve screening, and increase access to the right medications, the burden of TB in the refugee communities can decrease dramatically and WHO's 2012 World TB slogan, *Stop TB in my lifetime*, may become a reality.

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