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Editorial

MULTI DRUG RESISTANT TUBERCULOSIS: WHAT WILL HAPPEN IN DEVELOPING COUNTRIES ?

by
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Since 1990 several outbreaks of multi-drug resistant (MDR) tuberculosis (TB) defined as tuberculosis resistant to rifampicin and isoniazid, have been reported in the United States [1-5] and in Europe [6-8]. The first of the outbreaks in the US occurred in hospitals and prisons but recently there have also been reports from outbreaks in the community [9]). Eighty percent of the patients involved were HIV infected, some of which developed active and infectious TB within a few weeks after exposure. The case fatality rate was about 80% with a median interval between diagnosis and death of 4 to 16 weeks. There has been documented transmission of MDR TB to health care workers, about one third of hospital personnel exposed to patients with MDR TB showing skin test conversion [10]. So far, at least 20 health care workers in the US have developed active MDR TB, of whom 7 have died. Of the ones who died, 5 were known to be HIV infected [10]. The degradation of health services for the inner city poor is believed to have created the conditions that favour the occurrence of these outbreaks. Drug resistant TB is known to develop as a result of low compliance. Delayed diagnosis of drug resistant TB resulting in prolonged infectiousness [2,10] and inadequate infection control measures with timely isolation of patients are responsible for the outbreaks in prisons, shelters for the homeless and hospitals.

The same conditions which favoured the outbreaks in the developed world are also present in most developing countries, especially in Africa. The World Health Organisation (WHO) estimates that, at present, there are 9 million persons with HIV infection in Africa [11]. About 60% of the HIV infected adults are also infected with tubercle bacilli and are at risk for developing active TB. For dually infected persons the risk of developing active TB has been estimated at 5-10% per year [12]. Compliance with antituberculous treatment is generally poor. In several African countries high levels of primary isoniazid resistance in the range of 15 to 20% have already been observed [13-15]. On the other hand in Zambia the prevalence of primary isoniazid resistance was less than 5% [16]. In some African countries already more than 1% of the Mycobacterium strains are resistant to rifampicin [14,15,17]. In Asia the prevalence of drug resistant TB might be even higher [14]. In low resource health care settings there may be important delays in the diagnosis of TB, isolation of patients is less than optimal and – at least in parts of Africa – the HIV seroprevalence of patients admitted to

hospitals can be as high as 50% [18]. Under these circumstances major outbreaks of MDR TB are to be expected in low income countries.

Even if MDR TB were to occur only in HIV infected persons this would already create a dramatic situation. There would be a rapid spread of MDR TB among hospitalised patients but also among health care workers, of whom 10 to 20% may be HIV seropositive, and HIV infected family members. However it is unlikely that the transmission of MDR TB will be restricted to HIV infected persons. So far there is no evidence to suggest that MDR Mycobacterium strains are less infectious and less pathogenic than susceptible strains [8]. In the 1960's isoniazid resistant bacilli were believed to be less infectious and less pathogenic than isoniazid susceptible bacilli [19]. This belief was based on findings of a reduced virulence of isoniazid resistant bacilli in the guinea pig [20]. This finding however was never confirmed in a mouse model [21]. Moreover, several epidemiological studies have shown that isoniazid resistant bacilli are not only infectious but also capable of causing severe disease even in non-immuno compromised individuals [22-23]. In a large case control study, Snider *et al* observed a similar risk of infection among persons exposed to drug resistant bacilli compared with persons exposed to drug susceptible bacilli 124]. HIV infected individuals with pulmonary TB are probably not less infectious than HIV seronegative TB patients and there is no evidence that after exposure to TB non-HIV infected individuals are less likely to become infected with TB than HIV infected individuals [25,26].

In conclusion, at present we have no arguments to believe that MDR TB will not be able to cause disease in HIV seronegative individuals. It is expected however that outbreaks among HIV seronegative individuals will be smaller and will develop later because only 10% of the infected individuals will develop active TB, 5% within 5 years after exposure, another 5% during the rest of their live [27]. As the incidence of active TB in developing countries is much higher than in the developed world it is to be expected that once MDR TB is introduced in this part of the world also a higher incidence of MDR TB is to be expected.

It is clear that once MDR TB establishes itself in developing countries, it will spread among HIV seropositive as well as HIV seronegative individuals and will mean a catastrophe for TB control programs. How can we prevent this ? Drug resistant TB does not develop in patients who are compliant with the treatment. Therefore improving compliance should be the top priority of TB control programs in developing as well as developed countries. In New York city it was shown that the use of directly observed therapy (DOT) led to a decrease in the incidence of new TB cases as well as MDR TB [25].

The WHO is now promoting short course anti-tuberculous treatment regimens including rifampicin [11]. Such regimens are very effective, but if patients are not compliant because of the weak health infrastructure, rifampicin resistant TB will rapidly develop. Another potential danger is the introduction in developing countries of TB chemoprophylaxis for HIV infected individuals [29], especially if such regimens include rifampicin, as in clinical trials in Haiti and Uganda [30]. Before starting prophylaxis one should exclude the existence of active TB infection. This may be very difficult in low resource countries. If an HIV infected individual with active TB receives TB chemoprophylaxis, resistance to antituberculosis drugs may rapidly develop.

In order to improve patient compliance, existing TB control programs should be strengthened using the existing tools for TB control. This implies the decentralization and integration of TB programs in the general health services [31,32]. Operational research is needed to explore new ways to improve compliance with available anti-tuberculous drugs [33]. In areas of the developing world where the HIV seroprevalence is still low, it is important to improve TB control programs before the HIV and TB burden increases considerably. With improved TB control programs the prevalence of drug resistant TB will also decrease [34].

Surveillance of MDR TB should be organised throughout the world. At present we have very little reliable information about the prevalence of drug resistant TB in developing countries. Reasons for this include the absence of reliable laboratory facilities in these countries, the lack of systematic sample surveys and the lack of sufficient clinical information including reliable treatment histories of the patients that provided the samples. So far studies conducted in Zaire [16], Rwanda [35], Zambia [16,36], Ivory Coast [15], Kenya [37] have not shown an association between MDR TB and HIV, nor an increased incidence of MDR TB. Most of these studies however were performed in cities/countries where TB control is relatively well organised or included TB patients enrolled in cohort studies where the compliance with treatment was high. Mycobacterium strains should also be obtained from newly diagnosed TB cases outside research settings and from areas with weak to non-existing control programs. It is the intention of the WHO and the International Union against Tuberculosis and Lung Disease (IUATLD) to assist developing countries with such surveillance efforts [38].

In order to avoid an increasing problem of an incurable disease (MDR TB), scientists, public health officials, governments and funding agencies will have to respond more rapidly and more adequately than they have done in the past with AIDS. To prevent the MDR TB problem, improvement of TB programs and thus the strengthening of the general health services should be more than ever a priority.

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