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Surveillance of resistance to antituberculosis drugs in developing countries

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SUMMARY. **Resistance to antituberculosis drugs is caused by poor management of tuberculosis control. It gives rise to treatment failure, relapse, further transmission of resistant tuberculosis, and multidrug-resistant tuberculosis. Widespread occurrence of multidrug-resistant tuberculosis would constitute a major threat to tuberculosis control in resource-poor countries. Although the impact of HIV on drug resistance is not yet fully understood, it is likely to exacerbate problems caused by drug resistance. In particular, HIV-related adverse effects of thiacetazone, together with the risks of transmission of HIV by parenteral administration of streptomycin, reduce the armamentarium available to tuberculosis control programmes in high HIV prevalence countries, and could encourage the development of resistance to the remaining drugs. While the prime need is to ensure, by good management and supervision, that resistance does not occur in the first place, surveillance of drug resistance is essential to determine the current scale and nature of the drug resistance problem, as well as to define the correct solutions.**

RÉSUMÉ. **La résistance aux drogues antituberculeuses est provoquée par une prise en charge inadéquate de la lutte contre la tuberculose, dont résultent des échecs du traitement, des rechutes, une transmission accrue d'une tuberculose résistante et une tuberculose résistant à plusieurs drogues. La survenue étendue d'une tuberculose résistant à plusieurs drogues serait une menace majeure pour la lutte antituberculeuse dans les pays dépourvus de ressources. Bien que l'impact du VIH sur la résistance aux antibiotiques ne soit pas encore complètement connu, il est susceptible d'exacerber les problèmes créés par cette résistance. En particulier, les effets nuisibles du thiacétazone associé au VIH, plus les risques de transmission du VIH par l'administration parentérale de streptomycine, réduisent les armes dont on dispose pour les programmes de lutte anti-tuberculeuse dans les pays de haute prévalence de VIH, et pourraient encourager le développement de la résistance aux autres drogues. Tandis que la première nécessité est de s'assurer tout d'abord, par une prise en charge et une surveillance adéquates, qu'une résistance ne se produit pas, la surveillance de la résistance est importante afin de déterminer le niveau courant et la nature du probléme de la résistance aux drogues, et également de définir les solutions adéquates.**

RESUMEN. **La resistencia a los medicamentos antituberculosos es causada por un manejo deficiente del control de la tuberculosis. Esto produce un aumento de los fracasos del tratamiento, de las recaídas, de la transmisión ulterior de bacilos de la tuberculosis resistentes y del número de tuberculosis multirresistentes. La amplitud de la aparición de tuberculosis multirresistentes debería ser considerada como una amenaza importante para el control de la tuberculosis en los países de escasos recursos. Aunque aún no está totalmente esclarecido el impacto del VIH sobre la resistencia a los medicamentos, es probable que exacerbe los problemas causados por la resistencia a los medicamentos. En particular, los efectos adversos de la tioacetazona ligados a la infección con VIH, junto con los riesgos de transmisión de la infección VIH por la administración parenteral de estreptomicina, reducen las armas disponibles para el control de la tuberculosis en los países con alta prevalencia de infección VIH y puede influir en el desarrollo de resistencia a los medicamentos restantes. Aunque la necesidad primordial es que la resistencia no aparezca, por un buen manejo y supervisión del tratamiento, la vigilancia de la resistencia a los medicamentos es esencial para determinar la dimensión actual y la naturaleza del problema de la resistencia y para definir las soluciones apropiadas.**

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ANTITUBERCULOSIS DRUG RESISTANCE: CAUSES

What is generally understood by drug resistance is that a patient infected with resistant strains of *Mycobacterium tuberculosis* will fail to respond to treatment with the drug concerned. There are more precise and complex laboratory definitions,[1,2] but they are less suitable for the purposes of this paper. Resistance to antituberculosis drugs is the inevitable result of poor management of tuberculosis control.[3] Poor management takes many forms: most commonly, poor supervision of the patient's drug-taking, as well as the prescription of regimens with an insufficient number of drugs to which the patient's organisms are likely to be susceptible, inadequate dose or duration of therapy, and poor drug supplies, such that drugs are taken irregularly. In the past, patients have taken much of the blame for poor compliance,[4] but it is now recognised that tuberculosis services and their staff are not entirely innocent.[5,6] Drug resistance is thought by some to be a measure of medical malpractice. Either way, such deficiencies lead to patients acquiring resistance. If they then transmit the resistant organisms to their contacts, and if those contacts later develop tuberculosis also, then these latter cases are said to have primary resistance.

THE IMPACT OF ANTITUBERCULOSIS DRUG RESISTANCE

Whatever tuberculosis programmes might do to cause drug resistance it is clear that drug resistance can do considerable harm to tuberculosis treatment. Failure of treatment, which is commonly defined as the persistence of positive cultures for *M. tuberculosis* at the end of the treatment period, is more likely to occur if the initial organisms were resistant. Moreover, the more potent the drug, and the more drugs to which an organism is resistant, the greater the chances of treatment failure. Probably the best of the very few studies in this area was conducted by the British Medical Research Council (BMRC) trials in Africa, Hong Kong and Singapore.[7] Of 11 patients with isolates resistant to rifampicin, 9 of whom also had organisms resistant to another drug or drugs, 5 (45%) patients failed on treatment and a further 3 (27%) had a subsequent relapse. On the other hand, resistance to just isoniazid and/or streptomycin led to chemotherapy failure in only 12% of 264 patients.

MULTIDRUG-RESISTANCE

In recent years attention has focused on multidrug-resistant (MDR) strains of *M. tuberculosis*. MDR strains are usually defined as those that are resistant to at least rifampicin and isoniazid, and often to other drugs as well. While occasional MDR strains have been isolated from time to time over the past few decades, it is outbreaks of MDR tuberculosis in the United States which have brought it into the limelight.[8–15] These outbreaks have been characterised by an association with the human immunodeficiency virus (HIV) and by an alarmingly high mortality, often over 80%, despite the availability of a full range of reserve drugs. Widespread occurrence of MDR, especially primary MDR, would constitute a major threat to tuberculosis control, particularly to resource-poor countries, since effective treatment would become impossibly expensive.[16]

However, there are grounds for some optimism. Rates of resistance do not rise inexorably. In Styblo's classic study in Kolin, in the former Czechoslovakia,[17] for example, the introduction of stronger control measures, especially supervision of all patients in hospital, ensured that almost all patients completed their therapy. The prevalence and incidence of resistance declined. Nevertheless, the single most important measure against resistance is to ensure that it does not happen. This is achieved by making certain that all patients complete a full course of adequate treatment.

THE ROLE OF HIV

The impact of HIV on drug resistance is not yet fully understood. The MDR outbreaks in the US suggest that HIV might be associated with antituberculosis drug resistance. HIV-associated tuberculosis in some societies, such as parts of the US[11] and Zaire,[18] is associated with poorer adherence to therapy than in the case of patients with tuberculosis alone, and this could lead to the acquisition of resistance. HIV-infected tuberculosis patients are up to 20 times more likely than HIV-negative patients to have household contacts who are themselves HIV infected[19] and these contacts are particularly susceptible to contracting tuberculosis,[20,21] which would likely be resistant if the source case also had resistant disease. On the other hand, the few studies, in the US,[12,22] Haiti[23] and Africa,[24,25] that have so far measured resistance levels in more representative groups of patients have not found an excess of resistance in the HIV-positive groups.

One can intuitively see that the impact of resistance will depend on the number and efficacy of the drugs available to treat tuberculosis. There are, in current use in the developing world, 6 main drugs for the treatment of tuberculosis: isoniazid (H), rifampicin (R), pyrazinamide (Z), ethambutol (E), streptomycin (S) and thiacetazone (T). The first 3 are the most essential. Streptomycin is given parenterally, and therefore constitutes a risk for HIV and hepatitis B virus transmission in those areas where sterilization of injection equipment cannot be guaranteed. The World Health Organisation (WHO) does not therefore recommend it for use in areas with a high prevalence of HIV infection.[26] However, the risk has never been quantified for tuberculosis control programmes with sufficient supplies and equipment. Furthermore, though, the cost of streptomycin has also increased considerably over the past few years. In addition, HIV infection has been shown greatly to increase the risk of severe, and potentially fatal, cutaneous hypersensitivity reactions in patients treated with thiacetazone.[26–29] It is therefore advised not to use this drug either in individual patients known or suspected to be infected with HIV. The armamentarium available for treating tuberculosis is thus somewhat reduced in high HIV prevalence areas.

Further, there is a possibility that withdrawal of thiacetazone might actually create resistance to more powerful drugs. If the commonly used regimen of 2SHRZ/6TH (an initial phase of 2 months of daily SHRZ, followed by 6 months of a continuation phase of T and H) is altered to 2EHRZ/6EH in some areas, then a proportion (unknown) of those patients with isoniazid resistance will, in effect, receive monotherapy in the continuation phase. Ethambutol resistance is therefore probable in a percentage (unknown) of patients so treated. Since the retreatment regimen recommended by the International Union Against Tuberculosis and Lung Disease (IUATLD)[30] and WHO consists of 2SHRZE/HRZE/5HRE, the continuation phase will again, in effect, be monotherapy, this time with rifampicin. Rifampicin resistance in a proportion (again, unknown) is the likely result. This is the domino theory of resistance. Surveillance will at least help to determine the present unknowns in this scenario.

It is already clear that new, effective, low-cost antituberculosis drugs are urgently needed in the fight against tuberculosis in both developing and industrialized worlds.

SURVEILLANCE FOR ANTITUBERCULOSIS DRUG RESISTANCE

Until recently, few countries in the world, rich or poor, considered it necessary to carry out systematic surveillance for antituberculosis drug resistance. The USA, for example, ceased surveillance in 1986, although it was resumed in 1993. It was generally maintained in some other countries in the industrialized world that the recommended treatment regimens were designed to succeed even in the presence of resistance to one or two of the commonly used drugs; the minority of patients who failed to respond to treatment could be investigated for resistance as the need arose; surveillance was expensive, resources were limited, and, in any case, tuberculosis was disappearing fast. The occurrence of MDR, and the rising incidence of tuberculosis in many Western countries[31–33] due to HIV, immigration and the failure to maintain adequate health services in deprived inner cities, has led to a reexamination of this position.

Likewise, in the developing world, in spite of a general failure to control tuberculosis, surveillance for drug resistance was not an issue until recently. Nevertheless, a number of countries, such as Kenya,[34] Tanzania[35] and Korea,[3] conducted nationwide surveys at 5 or 10 year intervals to assess the extent of their tuberculosis problems. Ongoing surveillance was conducted in Algeria.[36] Representative information on drug resistance was included in each of these surveys. In East Africa, it was clearly not a major problem, with resistance to one or more drugs varying from 7–10% between 1964 and 1984. In Korea, primary resistance to one or more drugs rose to 31% of isolates tested in 1960, but fell to 15% in 1990 with the introduction of improved tuberculosis control. Acquired resistance was as high as 75% in 1980, falling to 47% in 1990. Apart from these 4 studies, which also had their share of methodological problems, the majority of published work has suffered from at least one of 3 major deficiences, making interpretation difficult, if not impossible: selection bias (in favour of patients referred to major hospitals and thus more likely to have resistant disease); failure to distinguish clearly between those patients who had had previous treatment from those who had not; and the use of non-standard or unclear laboratory methods. Our current level of ignorance of the scale and nature of drug resistance in the developing world is therefore profound, although we know that HIV is plentiful, and that MDR exists there (M. Kinyanjui and W. Githui, personal communication).

For those industrialized countries with large tuberculosis burdens among immigrant populations, such as the Netherlands, Switzerland[33] and Canada, information on resistance levels in the countries of origin of their immigrants is essential for proper formulation of domestic treatment policy. The risk of drug resistance in immigrants can be 10 times that of native born patients.[37]

AIMS OF SURVEILLANCE

The potential benefits of suitable surveillance for drug resistance are many. At an international level, surveillance could determine the geographical extent and severity of resistance in given countries or regions, and thus determine the need for major, international changes in treatment policy. Such information would also determine the extent of the need for international research into new chemotherapeutic agents, or new combinations of drugs. At a national level, a surveillance system would provide a useful indicator of tuberculosis control programme performance and assessment of the need for changing current treatment policy, identify districts or health centres in need of support, and determine the risk factors for resistance.

But there are potential disadvantages. By diverting scarce resources to resistance surveillance, the essential tuberculosis control targets of curing 85% of all new smear-positive cases diagnosed and finding 70% of all cases could be jeopardised. However, it is in precisely those countries with poor programme performance that resistance could be predicted. National resources should then, perhaps, focus on achieving the targets, and donor agencies on resistance surveillance.

RECOMMENDATIONS

The Tuberculosis Programme at WHO has developed a strategy which will determine the nature and extent of antituberculosis drug resistance in regions of the developing world. Countries with viable tuberculosis control programmes will be encouraged and assisted to develop their own surveillance systems using guidelines for surveillance drawn up by the Programme, which avoid the defects, mentioned above, of many previous resistance surveys. With the collaboration of the IUATLD, it is intended to establish a network of supra-national reference laboratories to provide the quality control and standardization of susceptibility testing that will be essential for international comparison. At the same time, much needed support will be given to national reference laboratories in developing countries to develop their own capacity for work on drug resistance.

CONCLUSIONS

Antituberculosis drug resistance, and especially multidrug-resistance, constitutes a major threat to tuberculosis control programmes. This danger is amplified by the presence of HIV. Our current state of knowledge about the extent and severity of resistance, especially in the developing world, is woefully inadequate. Surveillance for drug resistance is therefore essential. WHO is taking the initiative, together with the IUATLD, to set up such a system.

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