Barriers to reaching the targets for tuberculosis control: multidrug-resistant tuberculosis

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Abstract The development and expansion of WHO's DOTS strategy was successful, with 83% of the world's population living in countries or parts of countries covered by this strategy by the end of 2004.

Treatment success in the 2003 DOTS cohort of 1.7 million patients was 82% on average, close to the 85% target. Treatment success was below average in the African Region (72%), which can be partly attributed to occurrence of HIV co-infection, and in the European Region (75%), partly due to drug resistance. Drug resistance, specifically multidrug resistance and extensive drug resistance, is a serious threat to public health in all countries, especially in the Russian Federation, where the highest rates of multidrug resistance are presently accompanied by a rapid increase in HIV infection.

Based on the experience of the first projects approved by the Green Light Committee, the treatment success of patients with multidrug-resistant tuberculosis (MDR-TB) is lower than that of drug-susceptible cases, but nevertheless reaches 70%.

The collaborative effort of different organizations, professionals and communities is needed to address the development and spread of multidrug resistance and extensive drug resistance, which combined with the epidemic of HIV infection is one of the barriers to dealing effectively with TB. This effort should be directed towards facilitating the diagnosis and treatment of TB patients, in particular by improving access to drug susceptibility testing and strengthening treatment delivery by rigorous adherence to DOTS as outlined by the Stop TB Partnership.

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Une traduction en français de ce résumé figure à la fin de l'article. Al final del artículo se facilita una traducción al español. الترجمة العربية لهذه الخلاصة في نهاية النص الكامل لهذه المقالة.

Introduction

"The existence, in the lungs, of those peculiar productions to which the name of Tubercles has been restricted by modern anatomists, is the cause, and constitutes the true anatomical character, of Consumption" (Bishop, 1918).[1]

In 2004 it was estimated that 4.3% of all new and previously treated tuberculosis (TB) cases worldwide were multidrug-resistant (MDR-TB).[2]

The United States Centers for Disease Control and Prevention (CDC) and WHO published, in 2006, the results of a worldwide survey[3] examining resistance to second-line anti-TB drugs, showing that 2% of *Mycobacterium tuberculosis* isolates were extensively resistant (XDR-TB), that is strains resistant to at least rifampicin and isoniazid, a fluoroquinolone and one or more of the following injectable drugs: kanamycin, amikacin, capreomycin. In the Republic of Korea and Latvia, the proportion of XDR-TB cases among MDR-TB cases was as high as 15% and 19%, respectively, over the period 2000–2004. Patients with XDR-TB were 64% more likely to die or have treatment failure than patients with MDR-TB.[3] In the United States of America, the cure rate of XDR-TB patients was 31%, which is only slightly greater than the estimated proportion of spontaneously healed tuberculosis.[4] Highly drug-resistant TB in a setting in rural South Africa with a high prevalence of HIV infection was reported in 2006, with 98% mortality within 30 days of seeking care.[5,6]

From a short-term perspective it is difficult to estimate the global trend in drug resistance, but in the period since 1943 there is hardly any doubt that resistance has increased. For patients with drug-resistant TB this means that they might be in a similar situation as in the pre-chemotherapy era, when individuals with TB were "consumed" by the disease.

Background

The first anti-TB drug, streptomycin, was isolated in 1943 and its therapeutic introduction saved many lives. However, early trials in United Kingdom and the USA showed that resistance to streptomycin developed during monotherapy and that patients' symptoms deteriorated.[7,8] The concept of combined chemotherapy was based on this observation. By 1950, the success of combined drug chemotherapy for TB was established.[9] In the following decades more drugs were introduced for the TB treatment, and unfortunately further resistance developed.[10]

In 1960, the British Medical Research Council developed fully-supervised chemotherapy to ensure patient adherence to the prescribed treatment regimen, which was proved to prevent development of multidrug resistance.[11] It was not, however, until the 1980s that the International Union Against Tuberculosis and Lung Disease (IUATLD) gradually implemented this fully-supervised chemotherapy under programmatic conditions in the United Republic of Tanzania and other African countries.[12]

In the 1990s, WHO developed the DOTS strategy as a package of five elements aimed at achieving at least 70%

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detection and 85% cure rate. This strategy, which is now a fundamental pillar of the new Stop TB strategy announced in 2006,[13] has been widely accepted. Out of a total of 211 countries and territories, 200 report annually to WHO on their progress achieved in TB control. By the end of 2004, 83% of the world's population lived in countries or parts of countries covered by DOTS.

Treatment success in 2003 by a cohort of 1.7 million patients was 82% on average, very close to the global target of 85% set for 2005. However, treatment success was below average in the African Region (72%), which can be partly attributed to HIV co-infection, and in the European Region (75%), partly due to drug resistance.[14]

Almost 40 years after introduction of directly observed combination chemotherapy for TB, and with the accumulated knowledge of the mechanisms leading to development of drug resistance, the latter still remains one of the main barriers to TB control. The management of patients with drug-resistant TB is more complicated because of the longer treatment time, lesser effectiveness of second-line anti-TB drugs and more side-effects. Furthermore, the high price of second-line drugs means that management of MDR-TB is a significant financial burden on programmes.[15,16]

What do we know about the prevalence of drug resistance?

Since 1994, data on anti-TB drug resistance have been collected globally by various WHO/IUATLD Global Projects on Anti-Tuberculosis Resistance Surveillance and published in 1997, 2001 and 2004; the last report includes data from 77 countries or settings. Already in 1994, anti-TB drug resistance was reported in virtually every country surveyed.

In 2004, resistance data were available on 55 779 never previously treated cases, representing 20% of the reported global new smear-positive TB cases.[17,18] Of the ten countries or areas with the highest prevalence of MDR-TB (Fig. 1), all of which had a prevalence of > 6.5% of drug resistance among never-previously-treated cases, six were in Eastern Europe[17,18] with prevalences of MDR-TB as follows: 14.2% (Kazakhstan); 13.7% (Tomsk oblast, Russian Federation); 13.2% (Karakalpakstan, Uzbekistan); 12.2% (Estonia); 9.4% (Lithuania); and (9.3%) Latvia. Drug-resistance data were available for the city of Dashoguz in Turkmenistan (3.8%) and Orel oblast in the Russian Federation (2.6%).[17,18]

Although the probability of drug resistance is 3 to 4 times higher in re-treated than in never previously treated patients, data on resistance in the former group is scarce. Only 8405 previously treated cases, representing 2.3% (the denominator does not include relapses) of reported previously treated cases, were surveyed. The reported highest values of MDR-TB among previously treated cases were in Oman (58.3%) and Kazakhstan (56.4%),[17,18] followed by Lithuania (53.3%), Estonia (45.3%), Tomsk oblast in the Russian Federation (43.6%), Orel oblast in the Russian Federation (42.4%), Karakalpakstan in Uzbekistan (40.2%), Egypt (38.2%) and Henan in China (36.6%).[17,18]

WHO estimates that 62% of the global total of 424 000 cases of MDR-TB are in China, India and the Russian Federation. XDR-TB has been identified in over 40 countries on six continents.[3] Additional surveys, which complement the existing data, are under way in China, India and the countries of the former Soviet Union.[2]

Global response to the MDR-TB challenge

In 1999, WHO established the Working Group on DOTS-Plus for MDR-TB to explore the feasibility, effectiveness and cost-effectiveness of treating MDR-TB under programmatic conditions in low- and middle-income countries. In 2001 it was integrated into the Stop TB Partnership in 2001 and is now named the Stop TB Working Group on MDR-TB (see: http://www.stoptb.org/).

The Green Light Committee (GLC), housed and managed by WHO, was launched as a subgroup of the Working Group in 2000. The aim of the GLC is to increase access to low-price, quality-assured second-line drugs worldwide, while ensuring their proper use to prevent increased drug resistance.[15]

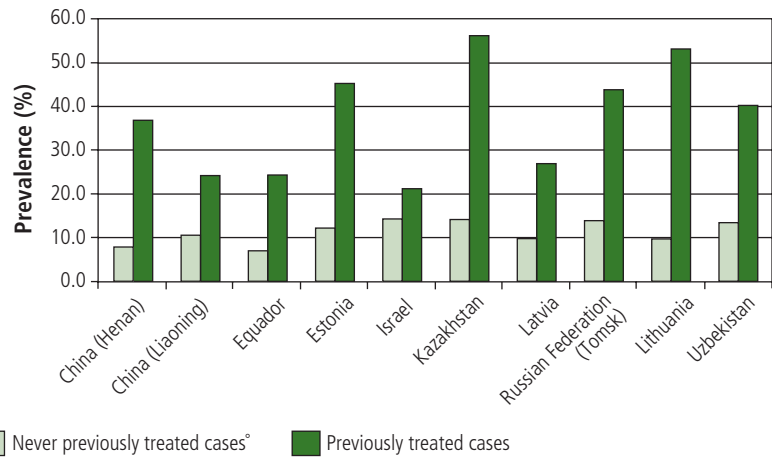
Through negotiations with pharmaceutical companies, the GLC was able to reduce the cost of second-line drugs, making them affordable for middle- and low-income countries. The prices have been reduced by up to 99% compared with prices in the open market.[16] The first countries to benefit from the GLC mechanism were Estonia, Latvia, Peru, the Philippines, and the Russian Federation (Tomsk oblast). By December 2006 there were 53 GLC-approved projects in 42 countries worldwide.

The GLC has assisted WHO in developing a policy and technical guidelines for management of drug-resistant TB[19] and is assisting countries in developing technically and scientifically consistent proposals for projects on management of MDR-TB to access quality-assured second-line drugs. Many countries are receiving external financial assistance for their projects, especially through the Global Fund to Fight AIDS, Tuberculosis and Malaria.[14]

Culture and drug susceptibility tests for all cases of TB are considered the gold standard for diagnosis, treatment and surveillance of drug resistance. However, such tests are not feasible routinely in most settings, where WHO instead recommends periodic surveys to monitor trends.[18]

The Global Plan to Stop TB 2006–2012 includes the provision of culture

Fig. 1. **Prevalence of multidrug-resistant tuberculosis (MDR-TB) in the ten countries or areas where it is most prevalent**



and drug susceptibility testing by 2015 to all re-treatment cases in at-risk populations, such as category I failures and contacts of patients with MDR-TB.[14,18]

The treatment success for drug-resistant TB, in particular MDR-TB and XDR-TB, is lower than that of drug-sensitive TB.[3] The encouraging treatment success rates for MDR-TB patients from GLC-approved projects in Estonia, Latvia, the Philippines (Manila) and the Russian Federation (Tomsk oblast) have been as high as 70%; higher among never previously treated patients (77%) and lower (69%) among previously treated patients.[20]

Conclusion

More than 40 years after the introduction of supervised combination chemotherapy for treatment of TB, many countries, particularly developing countries, have not adopted the principles of international standards of care with DOTS,[21] thus contributing to the development and spread of drug-resistant TB. These standards should be adopted by following the 2005 Stop TB strategy.

Drug resistance, particularly MDR-TB and XDR-TB, is a serious challenge that is jeopardizing TB control worldwide. Careful data collection and analyses from the GLC-approved project sites has provided more information about successes and challenges in managing drug-resistant cases. The most worrisome situation is in the former Soviet Union, where the highest rates of MDR-TB and XDR-TB are combined with the fastest-growing epidemic of HIV infection in the world.

The joint efforts of different organizations, professionals and communities is needed to address the development and spread of MDR-TB and XDR-TB, which combined with HIV epidemic is one of the barriers in dealing effectively with TB. This effort should be directed at facilitating diagnosis and treatment of TB patients, in particular by improving access to drug susceptibility testing and strengthening treatment delivery by rigorous adherence to DOTS as outlined by the Stop TB Partnership. ■

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Résumé

Obstacles à la réalisation des objectifs de la lutte antituberculeuse : tuberculoses multirésistantes

Le développement et l'élargissement de la stratégie DOTS de l'OMS se sont opérés avec succès, le taux de couverture des divers pays du monde ou des parties de pays couverts par cette stratégie atteignant 83 % à la fin de l'année 2004.

En 2003, on a relevé, parmi une cohorte de 1,7 millions de malades, un taux de succès du traitement de 82 % en moyenne, proche de l'objectif de 85 %. Ce taux était inférieur à la moyenne dans la Région africaine de l'OMS (72 %), résultat partiellement attribuable à la fréquence de la co-infection TB/VIH, et dans la Région européenne de l'OMS (75 %), du fait notamment de la pharmacorésistance aux antituberculeux. Cette pharmacorésistance, et plus particulièrement la multirésistance et la pharmacorésistance étendue, représentent une menace grave pour la santé publique dans tous les pays, notamment la Fédération de Russie, où des taux élevés de multirésistance s'observent en même de temps qu'une rapide propagation de l'infection à VIH.

D'après l'expérience acquise avec les premiers projets approuvés par le Comité Feu vert, le taux de succès du traitement est moindre chez les personnes atteintes de tuberculose multirésistante (TB-MR) que chez les cas sensibles aux antituberculeux, mais atteint néanmoins 70 %.

Un effort de collaboration entre les diverses organisations, professions et communautés s'impose pour faire face au développement et à la propagation de la multirésistance et de la pharmacorésistance étendue qui, en association avec l'épidémie d'infection à VIH, font partie des obstacles à une prise en charge efficace de la TB. Cet effort doit avoir pour objectif de faciliter le diagnostic et le traitement des malades tuberculeux, à travers notamment un élargissement de l'accès aux tests de pharmacosensibilité et une amélioration de la délivrance du traitement, reposant sur une observance plus stricte du DOTS, comme le préconise le Partenariat Halte à la tuberculose.

Resumen

La tuberculosis multirresistente, un obstáculo para alcanzar las metas de la lucha antituberculosa

El desarrollo y expansión de la estrategia DOTS de la OMS fue un gran éxito, pues al final de 2004 la cobertura de la misma era del 83% de la población de los países o zonas considerados.

El éxito terapéutico en la cohorte de 1,7 millones de pacientes tratados con DOTS en 2003 fue del 82% por término medio, cerca de la meta del 85%. El éxito terapéutico se situó por debajo de la media en la Región de África (72%), lo que puede atribuirse parcialmente a la aparición de la coinfección por VIH, así como en la Región de Europa (75%), en parte debido a la farmacorresistencia. Este problema, específicamente la multirresistencia y la farmacorresistencia extensa, es una grave amenaza para la salud pública en todos los países, sobre todo en la Federación de Rusia, donde a las tasas más elevadas de multirresistencia se une un rápido aumento de la infección por VIH.

A juzgar por la experiencia de los primeros proyectos aprobados por el Comité Luz Verde, el éxito terapéutico entre los pacientes con tuberculosis multirresistente (TB-MR) es inferior al de los casos sensibles a los medicamentos, pero no obstante alcanza el 70%.

Es preciso un esfuerzo de colaboración entre diferentes organizaciones, profesionales y comunidades para abordar el desarrollo y propagación de la multirresistencia y la farmacorresistencia extensa, que sumadas a la epidemia de infección por VIH constituyen uno de los obstáculos al tratamiento eficaz de la tuberculosis. Este esfuerzo debe orientarse a facilitar el diagnóstico y el tratamiento de los pacientes con tuberculosis, en particular mejorando el acceso a las pruebas de farmacosensibilidad y fortaleciendo el suministro de tratamiento mediante un cumplimiento riguroso del DOTS conforme a lo indicado por la Alianza Alto a la Tuberculosis.

ملخص

العوائق أمام بلوغ أهداف مكافحة السل: السل المقاوم لأدوية متعدِّدة

حقَّق تطوير وتوسيع استـراتيجية منظمة الصحة العالمية للمعالجة القصيرة الأمد تحت الإشراف المباشر نجاحاً ملحوظاً تمثل بتغطية 83% من سكان العالم الذين يعيشون في البلدان أو في أجزاء من البلدان المغطَّاة بهذه الاستـراتيجية عام 2004.

وقد حقَّقت هذه المعالجة عام 2003 نجاحاً لدى 1.7 مليون مريض بلغ في معدلـه الوسطي 82%، وهو ما يقرب من 85% من الهدف المتوخَّى تحقيقه. إلا أن نجاح المعالجة كان أقل من المعدل الوسطي في الإقليم الأفريقي (72%) ويعود ذلك جزئياً إلى العدوى المصاحبة بالإيدز، وإلى المقاومة للمعالجة ولاسيَّما المقاومة لأدوية متعدِّدة، والمقاومة الشديدة للأدوية. وهذه المقاومة من التحدِّيات الخطيرة التي تواجهها الصحة العمومية في جميع البلدان، ولاسيَّما في الاتحاد الروسي، حيث تـتـرافق أعلى معدلات المقاومة لأدوية متعدِّدة في الوقت الحاضر مع ازدياد سريع في العدوى بالإيدز.

وبناءً على الخبرات المكتسبة من المشاريع الأولى التي حازت على موافقة لجنة الضوء الأخضر، فإن معدلات نجاح المعالجة لدى مرضى السل المقاوم لأدوية متعدِّدة كانت أخفض مما لدى الحالات المستجيبة للأدوية، ولكنها مع ذلك وصلت إلى 70%. وتمس الحاجة إلى الجهود التعاونية التي تضم منظمات وأطباء ومجتمعات لمجابهة نشوء وانتشار المقاومة لأدوية متعدِّدة والمقاومة الشديدة للأدوية، وهما يتحالفان مع العدوى بجائحة الإيدز ليشكّلوا معاً أحد العوائق أمام المعالجة الفعَّالة للسل. وينبغي توجيه الجهود لتسهيل التشخيص والمعالجة لمرضى السل، ولاسيَّما لتحسين الحصول على اختبارات الاستجابة للمعالجة وتعزيز المعالجة بزيادة الالتـزام باستـراتيجية المعالجة القصيرة الأمد للسل تحت الإشراف المباشر، كما تنص عليه الشراكة من أجل دحر السل.

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