Drug-Resistant Tuberculosis in Africa

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ABSTRACT: Africa has the highest incidence rate per capita of tuberculosis, although the rate varies among the African countries from 17.8% in Cameroon to 70% in Botswana, Zambia, and Zimbabwe. Nevertheless, the levels of drug resistance are relatively low, compared to countries like Russia and Estonia. Because treatment of MDR TB is beyond the reach of most African countries, prevention of the development of resistance should be a major priority. Establishment of programs to ensure prompt diagnosis of TB and adequate treatment with supervision should be undertaken by national governments with cooperating partners.

KEYWORDS: initial drug resistance; acquired drug resistance; Africa

Tuberculosis was declared a global emergency by the World Health Organization (WHO) in 1993, in recognition of the large increase in the number of notified cases worldwide. Though this increase was noted in many areas of the world, by far the largest increase occurred in the developing countries of Southeast Asia and sub-Saharan Africa, where 95% of the cases occurred. It has been estimated that in 1997 about 1.86 million people, or 32% of the world's population, were infected with *Mycobacterium tuberculosis*, whereas the number of new cases totaled 7.96 million, with 1.87 million reported deaths. Eighty percent of all the reported incident cases were said to have occurred in 22 countries, and eight of the ten countries with the highest incidence were found in Africa. This increased burden of disease from tuberculosis globally, in an era when effective drug treatment exists, has been ascribed to factors like poor control in areas such as Southeast Asia, eastern Europe and sub-Saharan Africa and co-infection with HIV in some African countries.[1]

Though Southeast Asia and the Western Pacific regions had the highest number of reported cases of TB, Africa had the highest incidence rate per capita with an average of 259/100,000. This region also has the highest rate of HIV infection in TB patients, with an average of 32%,[1] though this figure varies from 17.8% in Cameroon[2] to as high as 70% in Botswana, Zambia,[3] and Zimbabwe. The case fatality rate for tuberculosis in Africa is high, exceeding 50% in some African countries, compared to a global figure of 23%.[4] The high rate of HIV co-infection has contributed to this high case fatality rate.

In order to ensure that TB is brought under control, the WHO has recommended that a target be set of detection of 70% of infectious cases and a treatment success

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TABLE 1. Drug resistance in patients with no history of prior treatment expressed as a percentage of case

Country	Year	Sample	Overall	Resistance to				Polyresistance/	
				1 drug	2 drugs	3 drugs	4 drugs	Any	MDR
Benin	1994–97	333	8.4	6.0	2.1	0.3	0.0	2.4	0.3
Botswana	1994–97	407	3.7	3.4	0.2	0.0	0.0	0.2	0.2
Botswana	1998	638	6.3	5.3	0.8	0.2	0.0 0	0.9	0.5
Cameroon	1995		31.8						
Central African Republic	1999	464	16.4	10.8	3.7	1.7	0.2	5.6	1.1
Ethiopia	1995	167	15.6						
Ghana			54.5						
Guinea	1998	539	14.7	9.8	4.3	0.6	0.0	4.8	0.6
Ivory Coast	1994–97	320	13.4	5.3	6.3	1.6	0.3	8.1	5.3
Kenya	1994–99	445	6.3	5.4	0.9	0.0	0.0	0.9	0.0
Lesotho	1994–97	330	8.8	6.1	2.4	0.3	0.0	2.7	0.9
Mozambique	1999	1028	20.8	12.2	5.8	2.3	0.5	8.7	3.5
Sierra Leone	1994–97	463	28.1	16.6	1.1	1.1	0.2	11.4	1.1
Sierra Leone	1997	117	24.8	17.9	6.0	0.9	0.0	6.8	0.9
South Africa (Hlabisa)	1996		8.9						
South Africa (Mpumalanga)	1997	661	8.0	5.9	1.2	0.5	0.5	2.1	1.5
Swaziland	1994–97	224	11.7						
Uganda	1997	374	19.8	12.8	6.7	0.3	0.0	7.0	0.5
Zimbabwe	1994–96	676	3.3	1.3	1.2	0.1	0.6	1.9	1.9

NOTE: Adapted from the WHO/IUATLD Global Project on Anti-Tuberculosis Drug Resistance Surveillance and other available data.

rate of 85% and that this should be achieved by 2005.[5] One of the biggest barriers for the successful treatment of TB is poor adherence on the part of the patient. Therefore, in 1995 WHO urged the use of DOTS (directly observed treatment, short course) as a priority for effective TB control and as a means of reducing the development of drug resistance. The ability of the DOTS strategy to improve the treatment outcome was demonstrated in a survey conducted by WHO between 1994 and 1998, in which 85% of patients evaluated under DOTS successfully completed treatment

compared to a treatment success of 37% in non-DOTS areas.[3] Drug resistance is, however, a threat to the potential success of TB control efforts.

The development of drug resistance has always been a concern with the use of chemotherapy, and in the case of tuberculosis this became evident soon after the introduction of streptomycin. The use of multidrug therapy as a means of preventing the emergence of drug resistance therefore became standard practice in the treatment of tuberculosis. An increase in the number of drug-resistant isolates was noted in New York City in 1991, primarily due to inadequate treatment. Within a couple of years, however, the number of drug-resistant cases had decreased by 21%, mainly due to improved case management with the use of directly observed treatment.[5]

The levels of drug resistance in a country are generally indicative of the quality of TB control and the use of short-course chemotherapy. Drug resistance may arise as a result of a lack of standardized treatment regimens, poor implementation of the regimens, shortages of drugs, and use of drugs of questionable quality. Other factors include failure to monitor the patients' treatment and nonadherence on the part of the patients. In particular, the level of multidrug resistance provides an indicator of the performance of the national TB program in the country.

The available data on the rates of drug resistance in Africa are not extensive, as many countries have not conducted nationwide surveillance of the level of drug resistance. The available reports generally cover a small area of the country, or the sample size is small and hence can not be considered to be representative of the country as a whole. In collaboration with the International Union Against Tuberculosis and Lung Disease (IUATLD), WHO has conducted a major surveillance of the global rates of drug resistance between 1994 and 1996,[6] and this exercise was repeated between 1997 and 1999.[7] During the surveillance, 16% of the countries were sampled. In the first round 8 countries from the AFRO region (sub-Saharan Africa) were included: these were Benin, Botswana, Ivory Coast, Kenya, Lesotho, Sierra Leone, Swaziland, and Zimbabwe. In the second surveillance, seven African countries were included (Botswana, Central African Republic, Guinea, Mozambique, Sierra Leone, South Africa, and Uganda). Thus, only Botswana and Sierra Leone were assessed in both surveys.

The recommended definition of drug resistance by WHO now applies either to drug resistance among new cases or to drug resistance among previously treated cases.[7] However, because a history of prior treatment for tuberculosis may be difficult to exclude completely, it is more appropriate to classify the resistance as either initial or acquired. The levels of primary drug resistance in Africa vary according to the country assessed. The presence of drug resistance is an indicator of the quality of the treatment delivery process, and resistance occurring in patients with no prior history of treatment reflects poor treatment in the past. The rate of drug resistance in patients with a previous history of treatment for tuberculosis is always much higher than in patients with no history of previous treatment for tuberculosis.

In general, the levels of drug resistance in Africa are low when compared to other parts of the world. This is despite the HIV-associated increase in TB cases and political strife and wars. This is probably a reflection of the presence of relatively well-functioning control programs; 61% of the countries in the WHO's African Region were covered by the DOTS strategy compared to the global average of 42.6%. The more recent introduction of rifampicin may also contribute to this lower incidence of drug resistance.

TABLE 2. Levels of drug resistance to each drug in selected African countries

Country	Sample	Overall	Resistance				Polyresistance/	
			1 drug	2 drugs	3 drugs	4 drugs	Any	MDR
Benin								
Botswana	114	14.91	7.0	2.6	0.9	4.4	7.9	6.1
Botswana	145	22.8	12.4	6.2	4.1	0.0	10.3	9.0
Cameroon								
CAR	33	36.4	12.1	6.1	5.2	3.0	24.2	18.2
Ethiopia								
Ghana								
Guinea	32	50.0	9.4	12.5	15.6	12.5	40.6	28.1
Ivory Coast								
Kenya	46	37.0	30.4	6.5	0.0	0.0	6.5	0.0
Lesotho	53	34.0	20.8	5.7	5.7	1.9	13.2	5.7
Mozambique	122	45.1	22.1	21.3	0.8	0.8	23.0	3.3
Sierra Leone	172	52.9	16.3	24.4	5.2	7.0	36.6	12.8
Sierra Leone	13	61.5	30.8	7.7	23.1	0.0	30.8	23.1
South Africa (Hlabisa)								
South Africa (Mpumalanga)	100	22.0	11.0	11.0	0.0	0.0	11.0	8.0
Swaziland	44	20.5	9.1	4.5	2.3	4.5	11.4	9.1
Uganda	45	51.1	28.9	20.0	2.2	0.0	22.2	4.4
Zimbabwe	36	13.9	5.6	5.6	2.8	0.0	8.3	8.3

NOTE: Adapted from the WHO/IUATLD Global Project on Anti-Tuberculosis Drug Resistance Surveillance and other available data.

In the first survey conducted by WHO and IUATLD, the overall level of resistance among new cases for the African countries was as follows: Zimbabwe, 3.3%; Botswana, 3.7%; Kenya, 6.3%; Benin, 8.4%; Lesotho, 8.8%; Swaziland, 11.7%; Ivory Coast, 13.4%; and Sierra Leone, 28.1%.[7] In this survey, the Dominican Republic had the highest level of resistance to any drug, with a rate of 40.6%. Overall drug resistance to any drug in the second survey, conducted between 1996 and 1999,[7] in the African countries was as follows: Botswana, 6.3%; South Africa's Mpumalanga Province, 8.0%; Guinea, 14.7%; Central African Republic, 16.4%; Uganda, 19.8%; Mozambique, 20.8%; and Sierra Leone, 24.8%. Between the two surveys, the level of resistance in Botswana increased from 3.7% to 6.3%, while for Sierra Leone the rate reduced from 28.1% to 24.8%. The rate of resistance in other countries not included in the WHO survey varies widely from country to country. The available figures are as follows: Malawi, 11.8%; Cameroon, 31.8%[2]; Ghana, 54.5%; Ethiopia, 15.6%[8]; Tanzania, 2.8%[9]; and Senegal, 37%.

TABLE 3. Levels of drug resistance among patients with a history of prior treatment

Country	Year	Sample size	INH		RMP		EMB		SM	
			mono	any	mono	any	mono	any	mono	any
Benin		333	3.3	5.4	0.0	0.3	0.0	0.6	2.7	4.8
Botswana		407	1.2	1.5	0.7	1.0	0.0	0.0	1.5	4.5
Botswana	1999	638	3.6	4.4	0.2	0.6	0.0	0.2	1.6	2.2
Cameroon										
CAR	1998	464	4.1	9.5	0.2	1.3	0.0	2.4	6.5	11.0
Ethiopia										
Ghana										
Guinea	1998	539	4.5	9.3	0.2	0.7	0.0	0.6	5.2	9.5
Ivory Coast		320	3.1	11.3	0.0	5.3	0.0	0.3	2.2	6.9
Kenya		445	5.4	6.3	0.0	0.0	0.0	0.0	0.0	0.9
Lesotho		330	5.2	7.9	0.0	0.9	0.0	0.0	0.9	0.3
Mozambique	1999	1028	7.9	16.5	1.8	5.3	0.0	0.5	2.5	10.5
Sierra Leone		463	2.6	13.0	0.2	1.3	0.6	2.4	13.0	24.0
Sierra Leone	1997	117	3.4	10.3	0.0	0.9	0.0	0.0	14.5	21.4
South Africa (Hlabisa)										
South Africa (Mpumalanga)	1997	661	3.5	5.6	0.2	1.7	0.0	0.5	2.3	3.8
Swaziland		334	3.9	9.0	0.0	0.9	0.3	0.9	2.4	7.2
Uganda	1997	374	6.2	12.5	2.0	5.8	3.0	8.0	5.6	11.2
Zimbabwe		676	6.7	20.0	1.1	3.6	0.2	1.1	11.1	24.1

The levels of resistance to isoniazid in new patients, or primary resistance, varied from 1.2% in Ivory Coast to 12.4% in Cameroon. Resistance to streptomycin ranges from 0% in Kenya to 20.5% in Cameroon. Levels of mono-resistance to rifampicin are low, being less than 1% in most countries where it has been reported (Botswana, Benin, Sierra Leone, Central African Republic, Guinea, and Cameroon) and only Mozambique (1.8%) and Ethiopia (1.8%) had higher rates. Only Sierra Leone (0.6%), Swaziland (0.3%), Cameroon (0.4%), and Uganda (2.4%) have reported any mono-resistance to Ethambutol. The low levels of mono-resistance to rifampicin reflect the recent introduction of rifampicin-containing regimens as well as the tendency to use rifampicin as a combined tablet with isoniazid.

Available data on drug resistance indicates that the rates of resistance are higher to one drug than to two or more drugs. The level of multidrug resistance (MDR) in Africa is relatively low compared to the highest level reported for Ivory Coast (5.3%),[10] Mozambique (3.5%), Zimbabwe (1.9%), South Africa's Mpumalanga Province (1.5%), Sierra Leone (1.1%),[7] and other countries reporting less than 1% of

MDR TB (Botswana, Benin, Lesotho, Swaziland, Guinea, Uganda, and Tanzania). In Kenya no multidrug resistance was reported in the WHO survey conducted between 1994 and 1997, though in the refugee population the level of MDR was 2.9%.[11] It should be noted, however, that the countries included in the WHO surveys are countries that have reasonably well-functioning programs. In countries lacking a well-functioning program, the levels of MDR TB may be much higher. In a survey conducted in Cameroon, where there is no functioning control program, multi-drug resistance was observed in 27.6% of the patients with a previous history of treatment.[12]

The level of drug resistance is substantially higher among patients with a history of prior treatment with antituberculosis drugs than in patients with no previous treatment for tuberculosis. This fact supports the impression that the development of drug resistance is primarily associated with irregular medication and poor control of tuberculosis. In Durban, South Africa, the strongest predictor of drug resistance was a history of prior treatment with antituberculosis therapy (ATT).[13] In Hlabisa, Kwa Zulu-Natal, South Africa, resistance to isoniazid was 6.4% in cases with no prior history of treatment compared to 13.6% in cases with a history of prior treatment.[14] In Uganda, resistance to isoniazid in cases with no history of prior treatment was 6.7% compared to 37.8% in those cases with prior treatment. Rates of MDR TB are similarly higher in cases with prior treatment (4.4%) compared to those with no prior treatment (0.5%).[15]

No significant association has been observed between the level of resistance to TB drugs and HIV serostatus in several studies[2,13,16,17] However, the presence of the increased rates of infection due to co-infection with HIV has placed a strain on the existing control measures for tuberculosis and the ensuing decrease in quality of control can lead to an increase in the overall levels of drug resistance and of MDR TB in particular. The health system has been overburdened by the high levels of HIV infection. In some countries up to 75% of the hospital admissions are due to HIV-related infections: Hospitals are overcrowded, bed-occupancy rates are very high, and isolation of infectious cases may not be possible. Hence, s situation exists in which a patient with active TB may be next to a patient with HIV-related complications, making the possibility of nosocomial infections high. Under these conditions, drug-resistant strains of TB can easily spread within the community.

Although the levels of drug resistance in Africa are relatively low compared to countries such as Russia and Estonia, it is vitally important that every effort be made to maintain a low incidence. Many African countries with high levels of tuberculosis are currently unable to fund tuberculosis control efforts adequately without external support from cooperating partners. Although treatment for tuberculosis is one of the most cost-effective strategies, in some countries the cost is more than the per capita expenditure available for the entire health budget. It therefore follows that treatment of MDR TB will be beyond the reach of most countries.[18] Thus, prevention of the development of resistance should be viewed as a major priority for these countries. Increasing the availability of drugs and putting a mechanism in place to ensure prompt diagnosis of cases and adequate treatment with supervision are important weapons in the battle against increasing multidrug resistance. National governments should therefore work closely with cooperating partners to ensure that tuberculosis remains high on the agenda for the health system through the provision of adequate resources—material, financial, and human—for the fight against tuberculosis.

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