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Systematic Review

First-line drug resistance of *Mycobacterium tuberculosis* strains in Sub-Saharan Africa

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ABSTRACT

Throughout history, natural products have been utilized to treat a variety of diseases; cinchona tree containing quinine to treat malaria, penicillin for the treatment of infectious diseases, and a wide variety of others. Since the discovery of penicillin by Fleming in 1929, a large number of antibacterial agents have been developed and have had a huge impact on human health. However, due to widespread excessive dispensing of antibiotics, certain bacterial pathogens have developed resistant strains via various mutations in their genomic setup. One of such pathogens is *Mycobacterium tuberculosis*, hence the study. This study aims at describing the epidemiology of resistant strains of *Mycobacterium tuberculosis*, its risk factors and potential control strategies in Sub-Saharan Africa. PubMed, BMC and other reliable databases were searched for English research articles published from January 2015 to December 2020 reporting on the molecular epidemiology of *Mycobacterium tuberculosis*. Due to lack of credible data from all Sub-Saharan African countries and first-line drugs, the study was streamlined to the most populous countries in Sub-Saharan Africa, 17 of which were considered in this study, and the two most common first-line drugs (i.e., Rifampicin and Isoniazid). A total of 54 research articles were thoroughly reviewed for the final analysis. Isoniazid had higher monoresistance (8.5%) than Rifampicin (3.6%). Tuberculosis (TB) Monoresistance was highest in Morocco (54%) and lowest in Mali (4.2%), while multidrug resistance highest in Senegal (58.1%), and lowest in Cameroon (1.1%).

Keywords: *Mycobacterium tuberculosis*, Drug-resistant, Sub-Saharan Africa

INTRODUCTION

Tuberculosis (TB) is caused by the bacterium "*Mycobacterium tuberculosis"* which most often affects the lungs. It is spread from person to person through the air (an airborne disease). When people with lung TB cough, sneeze or spit, they propel the TB germs into the air. A person needs to inhale only a few of these germs to become infected. About one-quarter of the world's population has a TB infection, which means many people have been infected with TB bacteria but are not (yet) ill with the disease and cannot transmit it. However, people infected with TB bacteria have a 5-10% lifetime risk of falling ill with TB. Those with compromised immune systems, such as people living with HIV (human immune-deficiency virus), malnutrition, or diabetes or people who use tobacco have a higher risk of falling ill. TB is present in all countries and age groups. It is important to note that child and adolescent TB which is often overlooked by health providers and can be quite difficult to diagnose and treat 11% (1.1 million) of population ill with TB in 2020.

The problem of TB has been complicated by the emergence and spread of multidrug-resistant tuberculosis (MDR- TB). It is a form of TB caused by bacteria that do not respond to isoniazid and rifampicin, the two most effective first-line anti-tuberculosis drugs. MDR- TB is treatable and curable by using second-line drugs, though second-line treatment options are limited and require extensive chemotherapy (up to 2-years of treatment) with medicines that are expensive and toxic.

Worldwide, TB is the 13th leading course of death and the 2nd leading infectious killer after COVID-19 (above HIV/AIDS). In the year 2020 alone, a total of 1.5 million people died from TB (including 214,000 people with HIV), and an estimated 10 million people fell ill with TB worldwide. 5.6 million men, 3.3 million women and 1.1 million children. Also, in year 2020, the 30 high TB burden countries accounted for 86% of new TB cases. Eight of which accounted for 2/3rd of total, with India leading count, followed by China, Indonesia, Philippines, Pakistan, Nigeria, Bangladesh and South Africa.

According to WHO, the largest number of TB cases in 2020 occurred in South-East Asia (43%), then Africa (25%), after which was the Pacific region (18%). A decade ago, the problem of TB in Africa attracted little attention and it didn't even make a chapter in the first edition of disease and mortality in sub-Saharan Africa**.** Part of the reason was that Tb incidence was low and falling in most parts of the continent Cauthen et al. However, there are more cases of TB in Sub-Saharan Africa today and this poses a greater burden. Poverty and political instability which have inhibited, to an extent, effective TB control measures is one of the reasons TB has elevated in this region but the principal reason for the resurgence of TB in Africa is the link between TB and HIV/AIDS. About one-third of the inhabitants of sub-Saharan Africa are latently infected with *Mycobacterium tuberculosis* by Dye et al and they are at higher risk of developing active TB if they are also immunologically weakened by a concurrent HIV infection. HIV-positive people are also more likely to develop TB when newly infected or re-infected with the bacteria.[1,2]

Effective TB prevention and control, diagnosis and treatment, particularly of drug-resistant (DR)-TB, needs a large proportion of national budgets.[4] Moreover, DR-TB also affects economic activity as most TB patients are economically active adults with dependents.[5] Dheda et al revealed that in certain African countries such as South Africa, where DR-TB accounts for less than 3% of all TB cases, over a third of the national TB budget is snapped up by DR-TB alone, which is unmaintainable and threatens to weaken nationwide TB programmes.[4,5] Similarly, a cost analysis study in South Africa by Pooran et al revealed that smear-positive drug sensitive-TB (DS-TB) cost $191.66 per case, whereas smear-negative and retreatment cases cost $252.54 and $455.50, respectively, making the latter two more expensive.[5] The TB menace in Africa is compounded by the burgeoning prevalence of DR-TB, MDR-TB and extensively drug-resistant (XDR-) TB, which are impossible to treat with first-line drugs and result in higher mortalities, increased medication costs and drug-associated toxicities.[4-7,9]

Evidently, early and accurate detection of DR-TB enhances appropriate treatment and informs tailored interventions to break the TB transmission chain.[12] However, dearth of advanced molecular diagnostic tools, well-equipped lab infrastructure and trained personnel in most resource-limited countries in Africa, limit detection of DR-TB to use of non-molecular techniques that are time-consuming and have limited efficiency.[10,11]

Abdelaal et al revealed that DR-TB was high (70%) in previously treated patients than in newly infected patients (30%) whilst Affolabi et al confirmed that patients with a history of TB chemotherapy are more likely to develop MDR-TB strains than newly treated patients.[12,13] These findings buttress the need for efficient, simpler and cheaper TB and DR-TB diagnostics for a comprehensive containment of the TB menace.

The number of antibiotics to which *M. tuberculosis* is resistant to is used to classify the level of resistance (i.e., mono resistance, MDR (multidrug-resistant), and XDR (extensively drug-resistant)). *M. tuberculosis* resistant to only one of the first-line drugs such as isoniazid (INH) and rifampicin (RIF) are referred to as monoresistant, whilst those resistant to at least both INH and RIF are defined as MDR.[14]

Purpose of this review

This review aims at highlighting the prevalence and risk factors of drug-resistant tuberculosis and strategies that can be adopted to control drug resistance of tuberculosis in the most populous countries of Sub-Saharan Africa. We hope that these findings would adequately inform evidence-based public health intervention policies for TB.

METHODS

Study design

A thorough review of published research articles performed to gather and analyse data that answer objectives of study on resistance patterns and risk factors of drug-resistant TB and potential control strategies.

Study area

The 20 most populous countries in Sub-Saharan Africa, as described by Worldometer: Chad, Mozambique, Gabon, Tanzania, Angola, Senegal, Cameroon, Mali, Morocco, Ghana, Sudan, South Africa, Ethiopia, Nigeria, Kenya, Uganda and Zambia (In no particular order).

Search strategy

PubMed, ResearchGate, Science Direct, BMC, African journals online library (AJOL) and free-text web searches using Google Scholar were searched for articles published in English from January 2015 through December 2020 using keywords such as "*Mycobacterium tuberculosis*", "drug-resistant", "Sub-Saharan Africa", "risk factors", "Control Strategies", "MDR-TB" and specific names of each country included in this study.

Inclusion and exclusion criteria

Articles addressing the following were included: (a) Drug-resistant tuberculosis in Sub-Saharan Africa; (b) Risk factors of anti-tubercular drug resistance; (c) Implementable strategies/ policies to control drug-resistant tuberculosis; (d) Studies conducted between 2015 and 2020 and (e) Studies published in English.

The following articles were excluded: (a) Studies published before 2015 (b) Studies that focused only on tuberculosis without any information on drug resistance and (c) Studies without easily interpretable results.

Selection procedure

All the articles gotten were manually reviewed and screened by the two authors, and studies that didn't meet the inclusion criteria listed above were not included.

Statistical analysis

The resistance rates and frequency data for each country included in this study were manually calculated, by each author, using the raw data extracted from the studies, and then re-calculated with Microsoft excel ® 365.

RESULTS

Characteristics of included studies

A total of 317 articles were identified from database searching. Of these, 158 were non-duplicated and underwent further screening, 44 were excluded based on the exclusion criteria, and 61 were excluded because they didn't answer the specific objective of this study. In total, of the 317 articles identified, 263 were excluded and 54 were used in the development of this article. Of the included studies, 31 reported on resistance patterns, 13 on risk factors and 10 on control strategies.

The 54 studies were from the 20 most populous countries in Sub-Saharan Africa; however, adequate data couldn't be gotten for Niger, Madagascar and Burkina Faso.

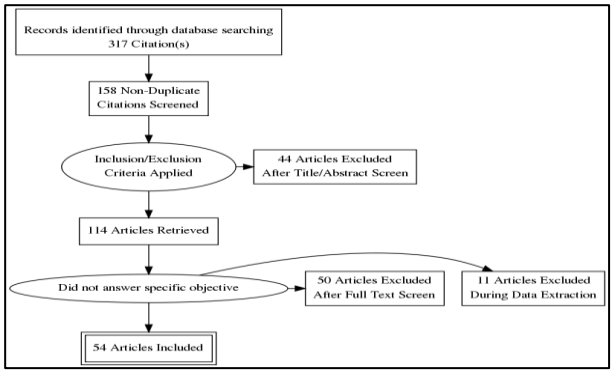

Figure 1: PRISMA diagram of the screening process of the papers reviewed in the study.

PREVALENCE

In the 31 studies on prevalence, a total of 13,574 isolates were gotten from the different sputum specimens (Angola: n=1 study, 308 isolates, Cameroon: n=1 study, 576 isolates, Chad: n=1 study, 311 isolates, Ethiopia: n=3 studies, 818 isolates, Gabon: n=1 study, 124 isolates, Ghana: n=3 studies, 2180 isolates, Kenya: n=3 studies, 652 isolates, Mali: n=1 study, 337 isolates, Morocco: n=2 studies, 773 isolates, Mozambique: n=1 study, 155 isolates, Nigeria: n=4 studies, 239 isolates, Senegal: n=2 studies, 222 isolates, South Africa: n=1 study, 5423 isolates, Sudan: n=3 studies, 401 isolates, Tanzania: n=1 study, 87 isolates, Uganda: n=2 studies, 157 isolates, Zambia: n=1 study, 811 isolates).

Prevalence patterns per country

Angola

Drug susceptibility testing was determined for 308 clinical isolates (192 male and 116 female, 225 new and 83 retreatment patients) by genotype MTBDRplus2.0 in one study in Angola (Segura et al), resulting in a total resistance rate of 34.1% (105/308). The total multidrug (RIF + INH±any other drug) resistance rate was 25%, while the total monoresistance rate was 9.1%. RIF monoresistance was calculated as 0.97% (3/308) while INH monoresistance was calculated as 8.12% (25/308).[11]

Cameroon

One study conducted by Kamgue et al in the central region of Cameroon undertook drug susceptibility testing, using the Lowenstein-Jensen proportion method, of 576 *M. tb* isolates (339 male and 237 female, 517 new and 59 retreatment patients) showed a total resistance rate of 6% (34/576). The total multidrug resistance rate was calculated as 1.1% (6/576), while monoresistance stood at 4.9%. RIF monoresistance stood at 0.2% (1/576) while INH monoresistance was calculated as 4.7% (27/576).

Chad

One study in Chad, Diallo et al testing for drug resistance, using MTBDRplus version 2, of 311 *M.tb* isolates (224 male and 87 female, 236 new and 75 retreatment patients) showed a total drug resistance of 23.5% (73/311). The total multidrug resistance was 4.5%, while the total monoresistance was calculated as 19%. RIF monoresistance stood at 5.5% (17/311) while INH resistance was 13.5% (42/311).[5]

Ethiopia

Drug susceptibility testing was performed on a total of 818 *M. TB* isolates in Ethiopia, according to three studies, using MTBDRplus, Lowenstein-Jensen proportion method and MTBDRplus respectively. The total combined resistance was calculated as 14.8% (121/818),

the total combined multidrug resistance-2.44% (20/818) and total combined monoresistance-12.3% (101/818). Combined RIF monoresistance was 3.3% (27/818) while combined INH monoresistance was 9.05% (74/818).

Gabon

One study by Alame-Emane et al performed drug susceptibility testing, using GeneXpert MTB/RIF assay, on 124 isolates (116 new and 8 retreatment patients) showed a total resistance of 44.4% (55/124). Total multidrug resistance was 14.5% (18/124) while total monoresistance was 29.8% (37/124). RIF monoresistance was calculated as 16.9% (21/124) while INH monoresistance stood at 12.9% (16/124).[9]

Ghana

Three studies performed in Ghana were included in the development of this paper, of which two used MTBDRplus and the third used microplate Alamar blue assay (MABA). A total of 2180 isolates were tested in the studies and a total resistance of 11.5% (251/2180) was recorded. TB multidrug resistance stood at 2.7% (59/2180) while monoresistance stood at 8.8% (192/2180). RIF monoresistance was recorded as 0.9% (20/2180) while INH was recorded as 7.9% (172/2180).

Kenya

Drug susceptibility testing was also performed, according to three studies, on a total of 652 *M. TB* isolates in Kenya; two of the studies used MGIT-960 while one used MTBDRplus. The total combined resistance was 10% (65/652); total combined monoresistance stood at 7.1% (46/652) while total combined multidrug resistance was 2.9% (19/652). RIF monoresistance was recorded as 0.46% (3/652) while INH monoresistance was recorded as 6.6% (43/652).

Mali

One study conducted in Mali by Diarra et al performed Phenotypic DST (MGIT AST/SIRE system) on 337 *M. TB* isolates (236 new and 101 retreatment patients, 258 male and 79 female) recorded a total resistance of 26.4% (89/337). The total multidrug resistance was 22.3% (75/337) while the total monoresistance was calculated as 4.2% (14/337). RIF monoresistance was calculated as 0.6% (2/337) and INH monoresistance was recorded as 3.6% (12/337).[12]

Morocco

Two studies conducted in Morocco for a total of 773 *M. TB* isolates were included in the development of this paper; the first used Lowenstein-Jensen proportional method for drug susceptibility testing while the second used MTBDRplus assay. The total combined resistance gotten from both studies was identified as 68.9% (533/773): a total monoresistance of 54% (418/773) and multidrug resistance of 15% (116/773). RIF monoresistance was calculated as 27.2% (210/773) and INH monoresistance was 26.8% (207/773).

Mozambique

One study conducted in Mozambique by Namburete et al was reviewed for this paper. DST was performed by Genotype MTBDRplus on 155 *M. TB* isolates (77 male, 62 female and 16 unidentified, 41 new, 101 retreatment and 13 unknown patients) and the total resistance gotten was 25.8% (40/155); multidrug resistance was 16.1% (25/155) while monoresistance settled at 9.7% (15/155). RIF monoresistance settled at 1.3% (2/155) while INH was calculated as 8.4% (13/155).

Nigeria

Nigeria was the country with the highest number of studies (4 studies). The total number of isolates tested by the four studies was 239, and the total resistance obtained was 43.6% (103/236). Total multidrug resistance was 24.3% (58/239) and total monoresistance was 18.8% (45/239); RIF monoresistance was 8.8% (21/239) while INH monoresistance was 10% (24/239). Of the four studies, one used the Lowenstein-Jensen proportion method for DST, two used GeneXpert MTB/RIF and the last one used MTBDRplus.

Senegal

Two Senegalese studies, summing to a total of 222 *M. TB* isolates, were reviewed when developing this paper and a total combined resistance of 73.9% (164/222) was recorded. The total combined multidrug resistance was 58.1% (129/222) while monoresistance settled at 15.8% (35/222). RIF monoresistance was calculated as 9.5% (21/222) while INH monoresistance was 6.3% (14/222). Of the 222 isolates, 161 were men and 72 were women. MTBDRplus and GeneXpert MTB/RIF were the tests used.

South Africa

One comprehensive study, by Ismail et al of 5,423 *M. TB* isolates in South Africa, using MGIT 960 for drug susceptibility testing, resulted in a total drug resistance of 10.6% (574/5423). Total monoresistance was 7.8% (423/5423) while total multidrug resistance was 2.8% (151/5423). RIF monoresistance was 1.7% (92/5423) while INH monoresistance was 6.1% (331/5423).[34]

Sudan

Three Sudanese studies (all using the Lowenstein-Jensen proportion method for drug susceptibility testing) summing up to a total of 401 isolates were reviewed in this paper. Total combined resistance was calculated as 41.6% (167/401); total combined multidrug resistance

was 23.2% (93/401) while the total combined monoresistance was 18.5% (74/401). RIF monoresistance settled at 8.5% (34/401) while INH was 10% (40/401).

Tanzania

One comprehensive study of 87 *M. TB* isolates conducted in Tanzania, using whole genome sequencing, was included in this paper. Of the 87 isolates, 40 were male and 47 were female. The total resistance recorded was 44.9% (39/87): multidrug resistance was 27.6% (24/87) while monoresistance was 17.2% (15/87). RIF monoresistance was 5.7% (5/87) and INH monoresistance was 11.5% (10/87).

Uganda

Two studies conducted in Uganda were included in this article. The total number of isolates tested in these studies was 157 (107 new and 50 retreatment patients). One of the studies employed whole genome sequencing for drug susceptibility testing while the other used BACTEC MGIT-960. The total resistance calculated was 62.4% (98/157): multidrug resistance was 21.7% (34/157) while monoresistance was 40.8% (64/157). RIF monoresistance 4.5% (7/157) and INH monoresistance 36.3% (34/157).

Zambia

One comprehensive study of 811 *M. TB* isolates, using the Lowenstein-Jensen proportion method and MGIT liquid culture, conducted in Zambia was reviewed in this paper. Of the 811 isolates, 470 were male, 301 were female and 10 were unidentified based on gender. Total resistance recorded was 38.5% (312/811): multidrug resistance was 31.6% (256/811) while monoresistance was 6.9% (56/811). RIF monoresistance was 1.6% (13/811) while INH monoresistance was 5.3% (43/811).

Table 2: Results of the study.

Country	No. of studies	Total no. of isolates	No. of isolates per study	Test used	Mono resistance (%)	RIF mono (%)	INH mono (%)	MDR (%)	Total resistance (%)
Angola	1	308	308	MTBDRplus2.0	9.1	0.97	8.1	25	34.1
Cameroon	1	576	576	LJ proportion method	4.9	0.2	4.7	1.1	5.9
Chad	1	311	311	MTBDRplus2.0	19	5.5	13.5	4.5	23.5
Ethiopia	3	818	260	MTBDRplus	12.3	3.3	9.05	2.4	14.8
			279	MTBDRplus					
			279	LJ proportion method					
Gabon	1	124	124	GeneXpert	29.8	16.9	12.9	14.5	44.4
Ghana	3	2180	525	MTBDRplus	8.8	0.9	7.9	2.7	11.5
			1490	MTBDRplus					
			165	MABA					
Kenya	3	652	184	MGIT-960	7.1	0.46	6.6	2.9	10
			210	MGIT-960					
			258	MTBDRplus					
Mali	1	337	337	MGIT-960	4.2	0.6	3.6	22.3	26.4
Morocco	2	773	703	LJ proportion method	54	27.2	26.8	15	68.9
			70	MTBDRplus					
Mozambique	1	155	155	MTBDRplus	9.7	1.3	8.4	16.1	25.8
Nigeria	4	239	30	LJ proportion method	18.8	8.8	10	24.3	43.6
			83	MTBDRplus					
			57	GeneXpert					
			69	GeneXpert					
Senegal	2	222	174	MTBDRplus	15.8	9.5	6.3	58.1	73.9
			48	GeneXpert					
South Africa	1	5423	5423	MGIT-960	7.8	1.7	6.1	2.8	10.6
Sudan	3	401	60	LJ proportion	18.5	8.5	10	23.2	41.6
			141	LJ proportion method					
			200	LJ proportion method					

Continued.

Country	No. of studies	Total no. of isolates	No. of isolates per study	Test used	Mono resistance (%)	RIF mono (%)	INH mono (%)	MDR (%)	Total resistance (%)
Tanzania	1	87	87	Whole genome sequencing	17.2	5.7	11.5	27.6	44.9
Uganda	2	157	90	Whole genome sequencing	40.8	4.5	36.3	21.7	62.4
			67	MGIT-960					
Zambia	1	811	811	LJ proportion method	6.9	1.6	5.3	31.6	38.5

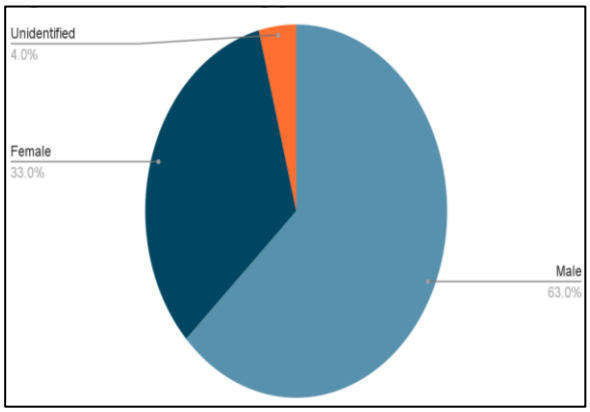

Figure 2: Gender distribution of isolation.

RISK FACTORS

The 13 articles reporting on risk factors met the inclusion criteria and, therefore, were included in the development of this paper. The majority of the included articles cited common factors while a few had slightly different ones. Below is a list of all the risk factors cited in the included articles, in order of commonness among the included studies.

History of previous treatment

10 out of the thirteen studies included concluded that multidrug-resistant tuberculosis has a significantly higher prevalence rate in previously treated patients/relapse patients than in new ones.

Poverty/low socioeconomic status

With poverty comes unfavorable living conditions and poor housing structures. For example, in slums/ overcrowded houses, the frequency and intensity of interpersonal contact are increased and this amplifies the risk of contagion droplet or airborne infection. Also, in a study done in Mubende, Zambia, it was discovered that high transport costs to standard hospitals which result from poor transport infrastructure, and the high cost of tuberculosis treatment could have a negative effect on adherence to treatment which might inherently affect the bacterial susceptibility to current therapeutics and hence promote drug resistance.

Age

Several studies listed age as a risk factor for the spread and acquisition of drug-resistant tuberculosis. People within the age range of 20-34 had the highest rate of prevalence of drug-resistant tuberculosis, possibly due to this age cohort's high mobility and high-risk behavior. This also implies that physically active people are more vulnerable to the disease; it also is alarming because the majority of global workforce falls under this age group.

Inadequate availability of prompt diagnostic and treatment options

Lack of standardized and optimized MTBC cultures and DST procedures, well-equipped and safe labs, and trained personnel operating under quality-assured protocols has proven to be a huge risk factor for the spread and acquisition of drug-resistant tuberculosis. This is particularly true in Sub-Saharan Africa where primary and cheap healthcare is not available in all communities, and as such, access to it is limited.

Close contact with known TB patients

Multiple studies confirmed that those who had previous contact history with TB patients (e.g., people who visited hospitals regularly to see their relatives who had drug-resistant TB or, in some cases, people who were admitted into hospitals/hospital wards with known TB patients and had contact with them) were at a higher risk of contracting drug-resistant TB than those who had had no contact with TB patients.

Cigarette smoking and alcoholism

Studies have shown that heavy smokers (≥20 sticks per day) are more likely to develop MDR-TB because smoking acts as a precipitating factor for developing obstructive and interstitial lung diseases, thereby weakening the person's immune system. Also, 4 of 13 studies stated a correlation between alcoholism and the acquisition of drug-resistant TB.

Natural disasters/wars

Natural disasters like hurricanes, tsunamis, earthquakes and situations like wars and famines lead to an increase in

the number of internally displaced persons which, in turn, could serve as a major risk factor for the spread and prevalence of drug-resistant tuberculosis.

Other risk factors listed by the reviewed articles include HIV coinfection (3 studies), malnutrition (2 studies), unhealthy lifestyle (1 study) and cavitation on chest x-rays (1 study).

CONTROL STRATEGIES

Ten articles reporting on already existing control strategies in Sub-Saharan Africa and/or suggesting new ones to control the spread of drug-resistant tuberculosis were reviewed in the development of this paper. After thoroughly reviewing all 10 papers, the following strategies were identified, which we were able to divide into 2 distinct groups: governmental policies and individual actions.

Governmental policies/ actions

Effective implementation of the DOTS (Directly observed treatment, short-course) strategy. Increasing the number of institutions equipped with drug-resistance tests, for early detection of primary resistance. Tuberculosis control Programs should focus on improving patients' adherence to anti-TB drugs. Health promotion activities about TB should give special attention to 'high risk' groups. Supply of quality drugs and availability of standardized regimens. Administrative control measures to prevent the generation of and/or exposure to droplet nuclei, thereby reducing exposure to the bacteria. These include promptly identifying people with TB symptoms (triage), separating infectious patients, controlling the spread of pathogens (cough etiquette and respiratory hygiene) and minimizing time spent in healthcare facilities. Environmental control measures for high-risk areas, which either remove the bacteria from the air or reduce the concentration of bacteria in the air. Provision of subsidized healthcare facilities to cater for the health needs of vulnerable communities. Designation of infection control officers and committees with the responsibility of developing and monitoring infection control plans regularly to ensure the effectiveness of the interventions implemented.

Individual actions

Personal protective equipment should be used by exposed individuals to protect themselves from inhaling contaminated air e.g., the wearing of respirators. Screening of household contacts. General hospital administrative support and provision of patient psychosocial economic support including food and transport (incentives and enablers). This direct patient socio-economic support is reported to be associated with better treatment outcomes through enhancement of nutritional status, patient adherence, and compliance. Engaging in research to validate and produce normative data which would be useful in the creation and implementation of governmental policies. Individuals could also form groups/organizations that could help in employing some of the strategies that fall under 'government actions/policies.

DISCUSSION

The primary vehicle driving drug resistance in *Mycobacterium tuberculosis* is the acquisition of mutations in genes that code for drug targets or drug-activating enzymes. These are mainly in the form of SNPs, insertions or deletions (indels) and to a lesser extent, large deletions. Drug resistance in TB occurs through two main mechanisms: (i) primary or transmitted drug resistance, which occurs when resistant strains are transmitted to a new host, and (ii) secondary or acquired drug resistance, which occurs through the acquisition of drug resistance mutations to one or more drugs.

Of the 13,574 isolates tested across the 17 countries included in the study, a total of 2,823 isolates showed resistance to either rifampicin or isoniazid or both. Overall rifampicin resistance was 3.7%, isoniazid resistance was 8.5% and multidrug resistance was 8.7% resulting in an overall resistance of 20.8%. Statistics pertaining to the various African regions are summarized thus:

East Africa

Ethiopia, Kenya, Tanzania and Uganda were the East African countries reviewed in this study, of which Uganda and Tanzania had relatively high resistance rates 62.4% and 44.9% respectively) as compared to Ethiopia and Kenya which had 14.8% and 10% resistance rates. Kenya's low resistance rate could be attributed to the Kenya Injectable Free Regimens and the Latent TB Infection Treatment policies which have proven to be effective over the years. Ethiopia, being the first African nation to fully integrate tuberculosis care into its health system, is also benefiting from various effective TB prevention strategies commenced by the Ethiopian government, as seen in their national guidelines for TB, DR-TB and Leprosy in Ethiopia journal, annually released by the Ministry of Health. The dangerously high resistance rates of Uganda and Tanzania only goes to show that whatever TB policies their governments have put in place are not as effective as they should be.

West Africa

Cameroon and Ghana had the lowest resistance rates of 6% and 11.5% respectively while Senegal had a whopping 73.9% and Nigeria had 43.6%. Mali and Chad, though not among the highest or lowest, had relatively high resistance rates of 26.4% and 23.5% respectively. The low resistance rate of Cameroon could only mean that the national tuberculosis strategic plan adopted by the national TB control program has been highly effective

in curbing the spread of drug-resistant strains and should be emulated by the other countries in the West African region that had high resistance rates.

South Africa

It's no surprise that South Africa had the lowest resistance rate among the Southern African countries (10.6%). Besides being the African country with the most readily available research studies on TB and DR-TB, the national strategic plan (NSP) developed by the South African government in 2012, has achieved giant strides since its inception. Southern Africa, in general, had the lowest resistance rates in comparison with the other regions: Zambia-38.5% (highest), Angola (34.1%), and Mozambique (25.8%).

North Africa

Two North African countries included in this study had dangerously high resistance rates of *M. TB*: Morocco with 68.9% and Sudan with 41.6%. Sudan's high resistance rate could be attributed to the frequent crisis and unrest in the region which was cited as a risk factor earlier in this study, while Morocco's rate could only be due to poor healthcare and Inefficient management of infectious diseases.

Gabon, the only Central African country included in this study, had a high resistance rate of 44.4%.

Overall, the resistance rates of the various countries gotten from this study is a huge cause for alarm given that the global TB drug resistance rate stands at about 15%, a value considerably less than the resistance rates obtained for 12 of the 17 countries in this study. In comparison with a previous study by Sekyere et al some countries, such as Morocco, Nigeria, Gabon, Tanzania, Zambia and Uganda, have seen an increase in the occurrence of DR-TB while others (Sudan, Ghana, Cameroon, Ethiopia, Mozambique and South Africa) have seen a reduction in DR-TB occurrence.[14]

Limitations

The unavailability of data in various countries was the biggest limitation experienced in the development of this paper, and a problem that hinders the development of strategies to tackle TB. Many Sub-Saharan African countries, though are high-burden TB regions, have little or no data on TB drug resistance. Also, due to the scarcity of research data on DR-TB for some countries, the data provided in this study might not be a completely accurate representation of DR-TB in those countries.

Also, the lack of uniformity in the tests used for determining drug susceptibility in the various countries included in this study makes it difficult to effectively compare the results of the studies. To address this, standardization of DR-TB test methods and interpretation guidelines should be adopted to allow for better comparability and improved resistance tracking.

CONCLUSION

In summary, the rise and spread of drug-resistant tuberculosis (DR-TB) continues to threaten the effective control and treatment of tuberculosis worldwide, especially in Sub-Saharan Africa which is a high-risk region according to the WHO. However, the availability of routine and research data on *Mycobacterium bacterium* strain susceptibilities is an important step toward designing strategies to tackle the global DR-TB crisis. Although limited information was obtained on inter-country spread, the glaring difference in the resistance rates of various countries in the same region makes inter-country spread a potential risk for which measures to prevent should be put in place. The Cameroon strain of *M. TB*, for example, which is highly transmissible was reported in 80% of the papers reviewed, and if not properly monitored, the WHO would face a major setback in its END TB campaign.

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