Patterns of resistance to first-line anti-tuberculosis drugs among patients in Abuja, Nigeria: 2009-2012

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ABSTRACT

Introduction: Nigeria is among the top ten countries with a high burden of Tuberculosis (TB) worldwide. Drug-resistant TB is a global health burden, but disproportionately higher among TB patients in resource-constrained countries like Nigeria. We described the pattern of resistance to first-line anti-TB drugs among patients tested at the National Tuberculosis and Leprosy Control Program (NTBLCP) reference laboratory in Abuja, Nigeria. **Methods:** We extracted 520 TB culture-positive records from the laboratory unit of Zankli Medical Services, Abuja, Nigeria from 2009 to 2012. The variables we analyzed included the patient's sociodemographic characteristics (age, sex, location, occupation), HIV status and Drug Resistance Testing (DST) results. . We estimated the proportion of the different forms of drug resistance to TB first-line drugs. **Results:** The median age of the patients was 32 (interquartile range: 27 - 40) years and 63.3% were males. A total of 246 (47.3%) samples were susceptible to all the first-line anti-TB drugs. The rest 274 (52.7%) were resistant to at least one first-line anti-TB drug. One hundred and two (19.6%) were resistant to one anti-TB drug only, 37 (7.1%) were multi-drug resistant and 79 (15.2%) were poly-drug resistant. Monoresistance to Streptomycin 33 (32.4 %) was the highest followed by multiple resistance to Streptomycin, Isoniazid and Rifampicin combination for 21 (4.0%) of the cases. **Conclusion:** The high proportion of resistance to anti-TB drugs calls for improved surveillance and the need to understand the factors fueling TB drug resistance in the country.

Introduction

Tuberculosis (TB) is among the top ten causes of death in low and middle-income countries [1]. Despite the remarkable progress made over the years in the fight against TB worldwide, the disease remains the top infectious disease killer alongside Human Immunodeficiency Virus Acquired Immune Deficiency Syndrome (HIV/AIDS), claiming 1.5 million lives every year and causing morbidity to millions more [2]. In 2016, there were an estimated 10.4 million new TB cases worldwide, 10% of which were co-infected with HIV. Achieving the third goal of the Sustainable Development Goals (SDGs) might be a mirage if the current trend in the burden of TB persists [3].

An estimated 1.7 million people died from TB, and seven countries accounted for 64% of the total TB global burden in the year 2016, including Nigeria [2,4]. More than 80% of TB cases and 78% of deaths from the disease occurred in developing countries [5]. In 2018, an estimated 484,000 incident cases of Rifampicin resistant TB (RR-TB) and 377,520 cases of multi-drug resistant TB (MDR-TB) were reported globally. Among the MDR-TB about 2.14 per 10 million deaths occurred [6]. Mono-resistant and poly-resistant TB remain undiagnosed in resource-limited settings due to the limited drug susceptibility testing (DST) availability outside of a few designated testing centres for high-risk patients [4]. Thus, these undiagnosed mono-and poly-resistant TB cases are often treated with first-line drug regimens leading to suboptimal treatment and increased risk of development of further resistance.

In 2020, Nigeria ranked 8th among the 30 high Multi-Drug Resistance (MDR) burden countries with a drug resistance TB prevalence of 4.3% among new cases and 25% among previously treated cases [7]. The rising prevalence of resistance to anti-TB drugs has been a major public health obstacle to achieving the goal of effective global TB control. Each country, therefore, needs to maintain active surveillance of the level and pattern of anti-TB drug resistance in its territory to provide useful evidence to mount effective control measures. We described the pattern of resistance to first-line anti-TB drugs among patients tested at the National Tuberculosis and Leprosy Control Program (NTBLCP) reference laboratory in Abuja, Nigeria.

Methods

Study setting

The study was conducted at Zankli Medical Hospital Laboratory in the Federal Capital Territory, Abuja, Nigeria. The hospital is a private secondary-level hospital that served as one of the reference sites for TB laboratory testing. It provides advanced testing for TB including GeneXpert, culture and drug sensitivity testing. It also provides TB treatment services for patients diagnosed with TB. It receives referrals from all six geopolitical zones of Nigeria in addition to providing outpatient and inpatient care services in various specialties of medicine, surgery, paediatrics, and orthopaedics.

Study design and data source

We conducted a secondary data analysis of TB laboratory tests done at Zankli Medical Hospital from January 2009- December 2012. Records of patients newly diagnosed with TB cases were extracted from the reference laboratory register.

Sample size and variables of interest

A total of 857 records were extracted for this study. Of these, 520 records with complete information on TB drug resistance testing were included in the analysis. The variables of interest included patient´s sociodemographic characteristics (age, sex, location, occupation), HIV status, DST results, nature of case, number of tests conducted and resistance pattern to anti-TB drugs. The first-line anti-TB drugs used for treatment of newly diagnosed TB cases were Rifampicin, Isoniazid, Ethambutol and Streptomycin.

Laboratory Procedure

We observed that the reference Laboratory analyzed sputum samples collected from each patient microscopically for Acid Fast Bacilli (AFB) using Ziehl Neelsen (ZN) method. The sputum sample of each positive patient was cultured using modified Petroff´s method onto Lowenstein Jensen (LJ) medium slope incubated at 37oC for 4-6 weeks. The laboratory used In-house well-known strain of Mycobacterium tuberculous strain (H37Rv) as a positive control while sterile LJ medium as negative control done under biosafety level II hood. The growth and morphology of the colonies were noted,

and biochemical test performed on the colonies and confirmed with ZN method to identify Mycobacterium tuberculosis [8-9]. All culture-positive M. tuberculosis identified colonies were subjected to drug sensitivity test using the proportional method as described by WHO [2]. The concentration of Streptomycin 4 μg/ml, isoniazid 0.2 μg/ml, rifampicin 40 μg/ml and ethambutol 2 μg/ml were incorporated into LJ medium slope and 1.0ml of the cell suspension for 2-4 weeks at 37°c. The critical proportion was taken at 1% for all drugs. If the bacteria growth on the medium with the specific drug was >1% compared to the control, the strain was identified as resistant to the specific drug but sensitive to the drug if the growth rate was <1% compared to the control. The in-house strain and H27RV Standard Mycobacterium tuberculosis strain was used as positive control while inoculated slope without drugs was used as a negative control. Internal quality control was routinely performed.

Operational definitions We employed the standard definition for drug resistance from WHO [4]. Monoresistance was defined as resistance to one first-line anti-TB drug only; poly-resistance as resistance to more than one first-line anti-TB drug, other than both isoniazid and rifampicin; MDR was defined as resistance to at least both isoniazid and rifampicin. Rifampicin resistance. (RR) was resistance to rifampicin detected using phenotypic or genotypic methods, with or without resistance to other anti-TB drugs. It includes any resistance to rifampicin, in the form of mono resistance, poly-resistance, MDR or Extensively drug-resistant (XDR); pan drug resistance (PDR) is resistance to all first-line anti-TB drugs and pan sensitive (PS) as sensitivity to all the first-line anti-TB drugs.

DST: If the bacteria growth on the medium with the specific drug was >1% compared to the control, the strain was identified as resistant to the specific drug but sensitive to the drug if the growth rate was <1% compared to the control.

Data analysis

Laboratory data were retrieved on Microsoft Excel and analyzed using Epi Info version 7.2. The demographic characteristics were summarized in frequencies and proportions. The proportion of the different forms of resistance was determined.

Ethical Consideration

The approval to use the data was obtained from the hospital management and exemption was granted by the Federal Capital Territory Administration, Abuja. We protected all health information of participants got for this study.

Results

A total of 520 records were analyzed. The median age of the patients was 32 years (interquartile range: 27 - 40 years) and the age group 25-34 years constituted 37.9% (197/520) of the population. There were 329 (63.3%) males and 108 (20.8%) patients were co-infected with HIV while another 77 (14.8%) did not know their HIV status **Table 1**. Students constituted 18.1% (94/520) of the population.

274/520 (52.7%) of the participants had at least one form of drug-resistant TB. Among them, mono drug resistance was 19.6% (102/520); polydrug resistance was 15% (79/520) and Multi-drug-resistant TB was 7.1% (37/520) **Figure 2**.

For TB monoresistance, resistance to Streptomycin was 32.4% (33 /102), resistance to Isoniazid was 29.4% (30/102) and resistance to Rifampicin was 15.7% (16/102), **Figure 2**. Resistance to all the first-line drugs (Pan-resistance) was seen in 10.8% (56/520) cases. Among the multi-drug resistant cases, 56.8% (21/37) were also resistant to Streptomycin whereas 29.7% (11/37) were also resistant to Ethambutol. Resistance to both Isoniazid and Ethambutol was the commonest form of poly-resistance at 30.4% (24/79) **Table 2**.

Discussion

The study provides some insight into the pattern of resistance to first-line anti-TB drugs among patients presenting with symptoms of Tuberculosis at a reference TB treatment centre. We found a high level of resistance among the patients. More than half of the patients had at least one form of resistance to first-line anti-TB drugs. This high level of resistance though observed from a hospital with a reference laboratory that receives referrals from a wide catchment area is still higher than expected. The

high prevalence is of great concern to the TB control program because these cases could transmit the infection to the susceptible individuals in their communities. The high prevalence of resistant TB strain also supports the call to conduct resistance testing on all newly diagnosed TB cases before initiating treatment to guide the choice of effective treatment to use.

The overall resistance to one or more drugs found in the present study was lower than the study carried out in Ethiopia [10], but our finding corroborates the result observed in a study conducted earlier in Nigeria [11]. A high prevalence of resistance to one or more drugs has also been reported by other studies [6,12-13]. and suggests a high rate of primary drug resistance among new TB cases. The prevalence of MDR-TB and pan-resistance found in this study was high. The value was higher than the reported national [7], and global levels [1-2]. The level was also found to be higher than reported in earlier studies [5,9,14]. This has serious public health implications. On one hand, it might be an indication of hidden yet undetected epidemics of MDR ongoing in the population due to a low index of suspicion or limited capacity to test for the existence of the resistance in the population. On the other hand, it could signal some challenges either in the supply of first-line drugs for the treatment of TB or in the adherence of patients already on treatment. Either way, this calls for an urgent need to quickly review the TB treatment program, institute a surveillance system for TB drug resistance and review the existing data on TB resistance nationwide to have a holistic picture of the problem.

The highest mono resistance to anti-TB drugs was observed in Streptomycin. This agreed with the findings in previous studies [9,15], however, another study had reported the highest mono resistance in Ethambutol [16]. The high prevalence of Streptomycin resistance was an indication of extensive use of the drug in the TB control programme in the previous years and the use of the drug for other bacterial infections in the population may have exacerbated the problem.

High Poly and Mono resistance to anti-TB drugs compared to MDR was observed. Poly-drug resistance may be an indication of a larger epidemic. Although the presence of MDR-TB in the country is widely suspected in clinical practice, most diagnoses of drug resistance are not confirmed because few centres in Nigeria are equipped for TB DST.

Forty-seven per cent of DST conducted on samples was susceptible to all the first-line drugs. This was lower than the outcome of a study previously conducted in Nigeria[8], and higher than what was found in India [12]. The low prevalence of DST observed in this study may be due to poor supervision of short course chemotherapy regime with very few followup tests being conducted. It could also be because our study site was a reference laboratory with a higher risk of receiving samples with a higher risk of resistance compared to the other laboratories providing services for TB testing.

Study Limitation

Our study has some limitations which need to be taken into consideration while interpreting the result. First, this was a secondary data analysis from a reference hospital laboratory with limited variables available to explore more relationships (like occupation, clinical presentation, disease category, etc.) so we focused on the descriptive analysis of the resistance pattern and could not examine the risk factors nor the genetic characteristics of the resistant organisms. Second, we could not also examine information on the prior treatment history (drug, duration and outcome), and the sample size available was small. However, despite these limitations, our study presents an important detail on the extent of resistance to first-line anti-TB drugs among this unique population and the pattern of the resistance to guide further study.

Conclusion

There is a high level of drug-resistant TB among patients tested. The pattern of resistance observed calls for the need to institute a surveillance system for TB drug resistance and encourage drug sensitivity testing of all newly diagnosed TB prior to commencing anti-TB treatment.

What is known about this topic

- TB drug resistance exists in Nigeria. MDR has been known as an emerging problem in Nigeria.
- All newly diagnosed TB patients are placed on standard first-line TB regiment and no testing is routinely conducted to ascertain the drug sensitivity pattern.

What this study adds

- The high prevalence of poly-resistance indicates that there might be an ongoing outbreak of resistant TB in the population
- There is need to institute active surveillance for anti-TB drug resistance
- There is need to commence drug sensitivity testing for all newly diagnosed TB patients prior to treatment initiation.

Competing interests

The authors declare no competing interests.

Authors' contributions

Conceptualization: Chukwuemeka A, Ajumobi O, Balogun M and Nguku P. Methodology: Chukwuemeka A, and Balogun M. Data Analysis: Chukwuemeka A, Umeokonkwo C,D. Writing original draft: Chukwuemeka Anthonia and Nguku P. Writing reviews and editing: Chukwuemeka A, Adebowale A, Lovette Lawson and Umeokonkwo C, D. Resources: Chukwuemeka A and Lawson L. Validation: Balogun M, Nguku P , Lawson L and Adebowale A.

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Tables and figures

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Figure 1: Pattern of drug resistance in patients whose samples were diagnosed in Zankli Medical Services, Abuja January 2009- December 2012

Figure 2: Pattern of Mono drug Resistance for participants diagnosed in ZanKli Medical Services January 2009- December, 2012

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Table 1: Socio demographic characteristics of TB patients diagnosed in Zankli Medical Services, Abuja, January, 2009-December, 2012

Characteristics	Frequency n=520	Percentage (%)
Age (years)		
<15	6	1.2
15-24	86	16.5
25-34	197	37.9
35-44	129	24.8
45-54	60	11.5
55+	42	8.0
Sex		
Female	191	36.7
Male	329	63.3
Work status		
Employed	360	69.2
House wife	21	4.0
Student	94	18.1
Unemployed	45	8.7
HIV status		
Negative	335	64.4
Positive	108	20.8
Unknown	77	14.8
Region of residence		
North Central	239	46.0
North West	3	0.6
South East	183	35.2
South South	15	2.9
South West	80	15.4

Table 2: Patterns of resistance to anti-Tuberculosis drugs among patients tested for TB, 2009 - 2012		
Pattern of Drug resistance	**Frequency**	**Percentage (%)**
Pan –Resistance	56/520	10.8
Mono Resistance		
Streptomycin	33/102	32.4
Isoniazid	30/102	29.4
Rifampicin	16/102	15.7
Ethambutol	23/102	22.5
Multi-Drug Resistance		
Rifampicin + Isoniazid	5/37	13.5
Streptomycin + Isoniazid + Rifampicin	21/37	56.8
Ethambutol+ Isoniazid +Rifampicin	11/37	29.7
Poly-Resistance		
Streptomycin + Isoniazid + Ethambutol	19/79	24.1
Isoniazid + Ethambutol	24/79	30.4
Streptomycin + Ethambutol	8/79	10.1
Streptomycin + Isoniazid	12/79	15.2
Streptomycin + Rifampicin	12/79	15.2
Ethambutol + Rifampicin	4/79	5.1

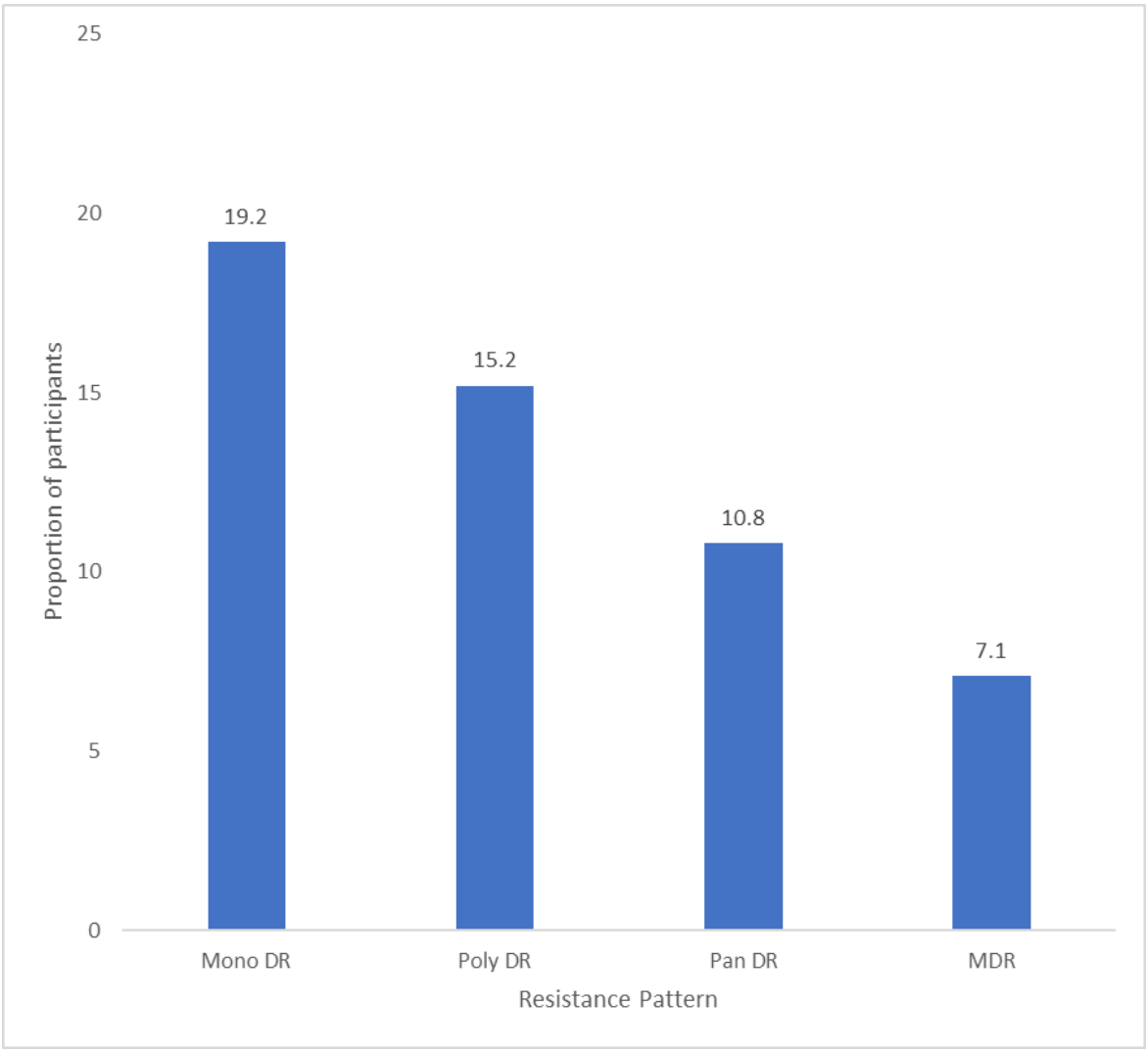

Figure 1: Pattern of drug resistance in patients whose samples were diagnosed in Zankli Medical Services, Abuja January 2009- December 2012

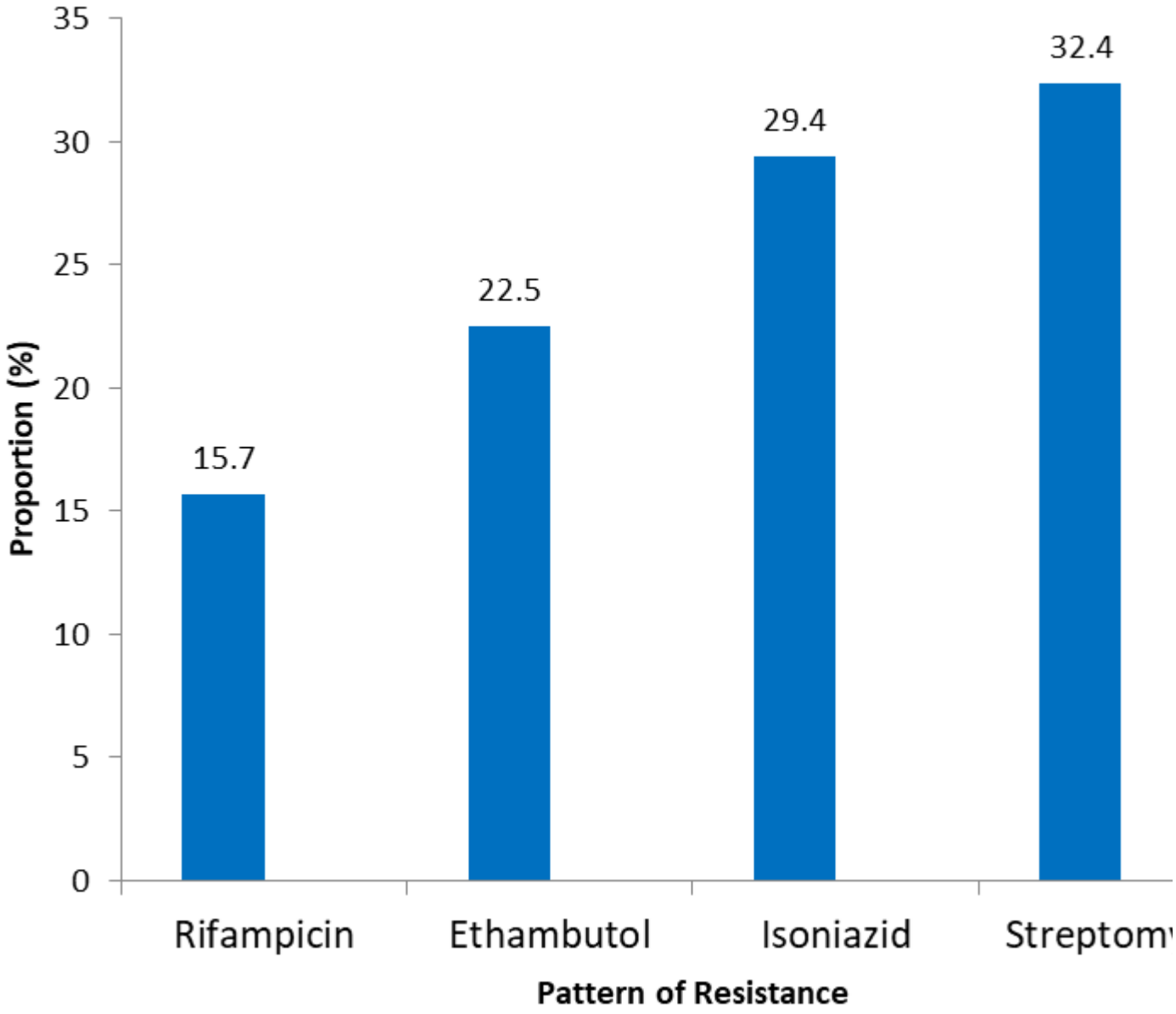

Figure 2: Pattern of Mono drug Resistance for participants diagnosed in ZanKli Medical Services January 2009-December, 2012