East African Medical Journal Vol. 94 No 10 October 2017

OUTCOMES OF KENYAN CHILDREN UNDER FIVE YEARS OF AGE, INITIATED ON ISONIAZID PREVENTIVE THERAPY FOLLOWING EXPOSURE TO BACTERIOLOGICALLY CONFIRMED PULMONARY TUBERCULOSIS, 2013-2016

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ABSTRACT

Background: **Isoniazid preventive therapy (IPT) is one of the key interventions in achieving the End TB Strategy of 90% reduction in Tuberculosis (TB) incidence by 2030 compared with 2015. One of the key pillars in achieving this is preventive treatment of persons at high risk of contracting TB. This group includes children less than five years exposed to bacteriologically confirmed TB. Despite Kenya national IPT roll out in 2015, there still exists limited information on its programmatic coverage, outcomes and missed opportunities for initiation of IPT.**

Objective: **To determine the coverage, outcomes and missed opportunities for initiation of IPT among children under-five years in contact with bacteriologically confirmed pulmonary tuberculosis (PTB) in Kenya.**

Design: **Cross sectional descriptive study.**

Setting: **All the 47 counties in Kenya.**

Subjects: **Children under-five years exposed to bacteriologically confirmed PTB initiated on IPT and notified between 2013and 2016.**

Results: **During the study period (2013-2016), a total of 6,507 children aged less than five years who were exposed to bacteriologically confirmed PTB were initiated on IPT. The number of children initiated on IPT increased from 721 in 2013 to 3306 in 2016.The number of counties notifying cases increased from 26 in 2013 to 47 in 2016.**

Treatment completion was 78%, 87% and 82% for 2013, 2014 and 2015 respectively. Of the 1390 children who had completed the 6 month-course of IPT during the study period, 9%had no TB, 7% were not accessed while84% had no documentation of outcomes by the end of the follow up period of 24 months. Missed opportunities for initiation of IPT reduced from 90% (7109) in 2013 to 60% (4872) in 2016.

Conclusion: **IPT coverage and completion rates have improved from 721 in 2013 to 3306 in 2016 and 78% in 2013 to 82% in 2015 respectively. Despite this, Kenya is yet to meet the targets set by the World Health Organization (WHO). Sustainable measures need to be put in place to achieve the WHO targets.**

INTRODUCTION

Tuberculosis (TB) remains a major public health problem globally and it ranks among the top ten causes of mortality worldwide. According to the 2015 World Health Organization (WHO) global report, it was estimated that 6million cases of TB were notified, out of whom 1.5million died. Approximately 17% of the notified cases were children under 14 years of age with 170,000 reported deaths(1).

In 2008, multi-disciplinary experts drawn from WHO-HIV/AIDS and TB departments resolved to reduce the impact of tuberculosis as a public health concern. This was to be effected by three strategies: i)Isoniazid Preventive Therapy (IPT), ii)Intensive case finding and iii) Infection prevention and control(2). Further, the 2015 Global TB report emphasizes that prevention of new infection of *Mycobacterium tuberculosis* and its progression to TB disease is critical in reducing the burden of disease and death caused by TB and in achieving the End TB Strategy which targets 80% reduction in TB incidence by 2030 and further 90% reduction by 2035 compared with 2015. This strategy was approved by World Health Assembly in 2014 as part of the Sustainable development goals to end the global TB epidemic(3).

IPT has previously been reported to be safe and effective in reducing the risk of TB by 33 – 62% among People Living with HIV (PLHIV) for up to 2 years. Children under five years who are household contacts of bacteriologically confirmed PTB are initiated on 6 month course of IPT to prevent progression of latent TB infection (LTBI) to TB disease. Persons infected with TB have a possibility of transmitting Mycobacteria to 10-15 people per year. Persons in contact with individuals with PTB have higher chances of progression to TB disease if the contact is a child under five years, undernourished, TB patient living in crowded and poorly ventilated rooms or having unsafe cough etiquette(8).An estimated 1.2 million children aged below five years in 2015 were household contacts of bacteriologically confirmed pulmonary tuberculosis (PTB) cases and thus were eligible for IPT. However, only 87236 children were initiated on IPT(7.1%)(3).

Previously among the 22 high TB burden countries since 1998, Kenya is currently listed in the new WHO 2016 – 2020 reclassification with 13 other countries facing high drug susceptible TB, Multi Drug resistance (MDR)TB and TB/HIV burdens(4). In 2015,81518 people were notified with TB out of whom 8.5% were children under 14 years(5). Kenya started implementation of IPT in 2011in line with WHO guidelines. This was piloted in some selected sites with a national rollout in 2015 mainly targeting patients living with HIV and asymptomatic TB, as well children under-five years(6).Kenya National IPT standard operating procedure guidelines, 2015, recommend a 6-month course of IPT for the following groups: children living with HIV who are >12 months of age, children living with HIV who are <12months of age who have contact with bacteriologically confirmed TB case, all HIV negative children under 5 years who have contact with a bacteriologically confirmed TB case, all People living with HIV(PLHIV) above 12 months of age and prisoners, irrespective of HIV status; all of the above who screen negative for TB using the Intensive Case

Finding (ICF) tool(7) .Kenya had approximately 23 000 child contacts in 2015 with 1256 started on IPT(5.6% coverage)(3).In Kenya, child contacts are presumed to be 20% of the notified bacteriologically confirmed pulmonary tuberculosis cases. However, no studies have been done to document this phenomenon(9). This study therefore aims to determine the geographic coverage, outcomes and missed opportunities for IPT among under-five children exposed to bacteriologically confirmed PTB initiated on isoniazid preventive therapy in Kenya for the period between 2013 and 2016.

MATERIALS AND METHODS

Study design: This was a descriptive cross sectional study using routinely collected programmatic data between 2013 and 2016.

Setting: Kenya had an estimated population of 43 million in 2014 of whom 28% were children under 14 years of age. Children under five years of age are approximately 6.8 million with 11% of being underweight. Under five mortality rate in Kenya is52 deaths per 1000 live births(10).The proportion of fully immunized children at 12 months is 67%(11) Study site and study population: This study was done on retrospective data of patients initiated on IPT in all the 290 TB control zones distributed within the 47 counties in Kenya.

Data collection: Kenya TB Program utilizes Tuberculosis Information for Basic Units (TIBU) data management system as a central database of the National Tuberculosis and Leprosy Program (NTLD-P). TIBU is a web based solution integrated with mobile/tablet technology developed and introduced in Kenya in the year 2012 with inter-sector support. Patients with TB upon diagnosis, are notified, treated and followed up with primary record capture obtained from TB patient records cards, IPT care screening tools and Multi drug resistance (MDR) log book before being entered into facility registers. Electronic data entry is then done at Sub–County level into TIBU by sub-county TB coordinators using mobile computer tablets Data variables, Data variables included clinical demographics such as age, sex and HIV status, geographical coverage of cases per county, outcomes (at 6th, 12th, 18th and 24th months of IPT initiation) and number of bacteriologically confirmed TB cases reported between 2013 and 2016.Data validation: TIBU has internal consistency checks to ensure that data entry errors are minimized. The NTLD program has quarterly data quality audits at the county level and biannually at the national level.

Data analysis: Aggregated data for all children under five years exposed to bacteriologically confirmed pulmonary TB initiated on IPT, outcomes, follow up and all bacteriologically confirmed TB cases reported in TIBU between 2013 and 2016. Additionally, missed opportunity for IPT among children under five years exposed to bacteriologically confirmed PTB was calculated as 20% of the total number of bacteriologically confirmed cases registered during the study period as per communication from NLTP-Kenya which in turn was used to estimate the missed opportunity for IPT among children under-five years of age.

Data was exported to excel database and analyzed using Stataversion 12. Categorical data were analyzed using frequencies, proportions and presented using line and bar graphs. Continuous data were presented as median (interquartile range (IQR).ArcMap 10.3 was used to create chloropleth maps on coverage of IPT.

Ethical approval: This study was approved by the Moi University College of Health Sciences (MU/CHS) and Moi Teaching & Referral Hospital (MT&RH) Institutional Review Board (IREC).

RESULTS

A total of 6,507 children under five years exposed to bacteriologically confirmed TB were initiated on IPT between 2013 and 2016. The median age of these children was 3 (IQR 2-4) years. Demographic and clinical characteristics as well as the treatment outcomes are shown in Table 1.

Children who were less than two years of age comprised 36% of the children initiated on IPT during the study period. Half (50%) of the children initiated on IPT were males. Overall, 84% of the children were tested for the average proportion of children who completed IPT therapy between 2013 and 2016 was 61% with a range of40%to 87%. Analysis of unfavorable outcomes during the study period showed that 14(0.2%) died, 111 (2%) defaulted, 65(1%) transferred out and 60 (1%) had the therapy discontinued. The outcomes of 2303 children (35%) were not documented. Most of these, 1923 (84%) were those registered in 2016 since some had not completed the six month course.

Table 1:

Demographic, clinical characteristics and treatment outcomes of children under-five years initiated on Isoniazid Preventive Therapy in Kenya, 2013-2016

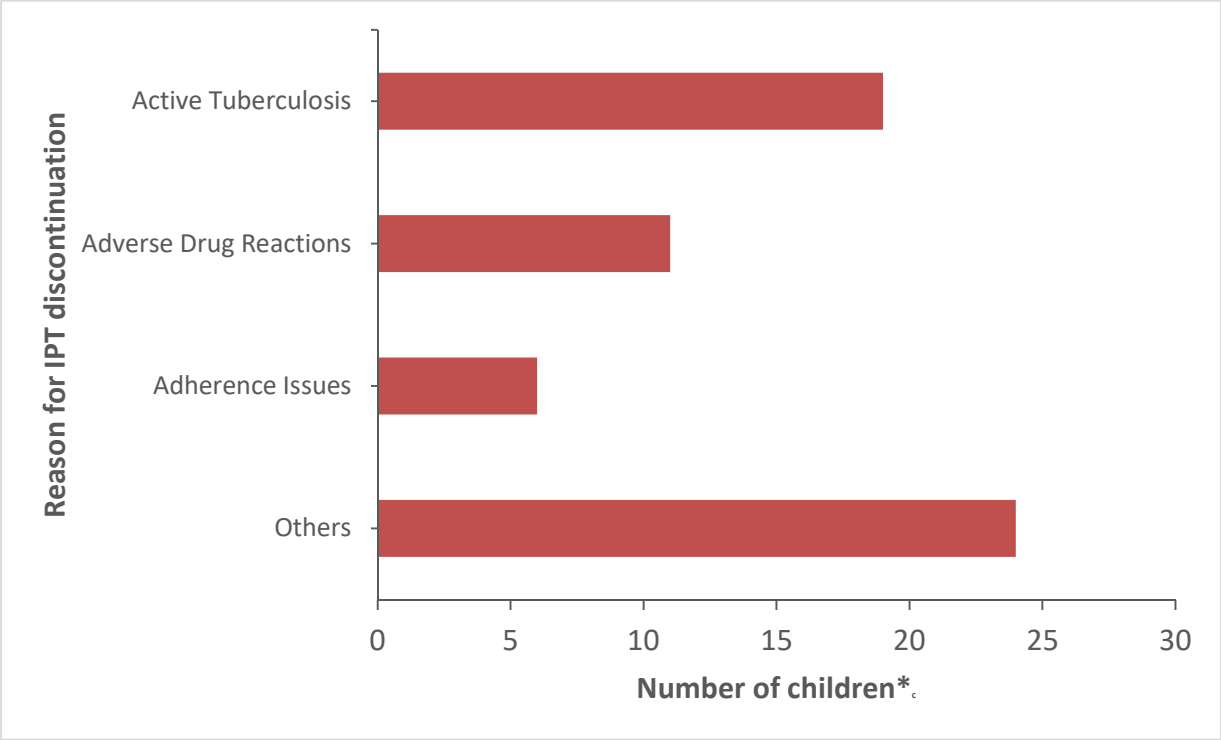
Variables	2013	2014	2015	2016	Total
	n (%)	n (%)	n (%)	n (%)	n (%)
Age					
≤23 months	235 (33)	231 (35)	691 (38)	1189 (36)	2346(36)
2- ≤ 5years	486 (67)	438 (66)	1120 (62)	2117 (64)	4161(64)
Gender					
Female	353 (49)	335 (50)	894 (49)	1696 (51)	3278(50)
Male	368 (51)	334 (50)	917 (51)	1610 (49)	3229(50)
HIV Status [a]					
Negative	614 (98)	504(98)	1423 (98)	2689 (95)	5230(96)
Positive	16 (3)	9 (2)	30 (2)	146 (5)	201(4)
Treatment Outcomes [b]					
Completed	563 (78)	585 (87)	1492 (82)	1314 (40)	3954(61)
Died	3 (0.4)	3 (0.4)	7 (0.4)	1 (0.0)	14(0.2)
Discontinued	8 (1)	14 (2)	17 (1)	21 (1)	60(1)
Defaulted	26 (4)	27 (4)	28 (2)	30 (1)	111(2)
No outcome	102 (14)	31 (5)	247 (14)	1923 (58)	2303(35)
Others	19 (3)	9 (1)	20 (1)	17 (1)	65(1)

a -Excludes those not done or declined

b -most of those initiated on treatment in 2016 were still on treatment, thus no outcomes

The reasons for discontinuation of IPT were active TB disease 19(0.3%), poor adherence 11(0.2%), and adverse drug reactions 6(0.1%). The reasons for discontinuation of IPT in 24 children (0.4%) were not documented as shown in Figure 1.

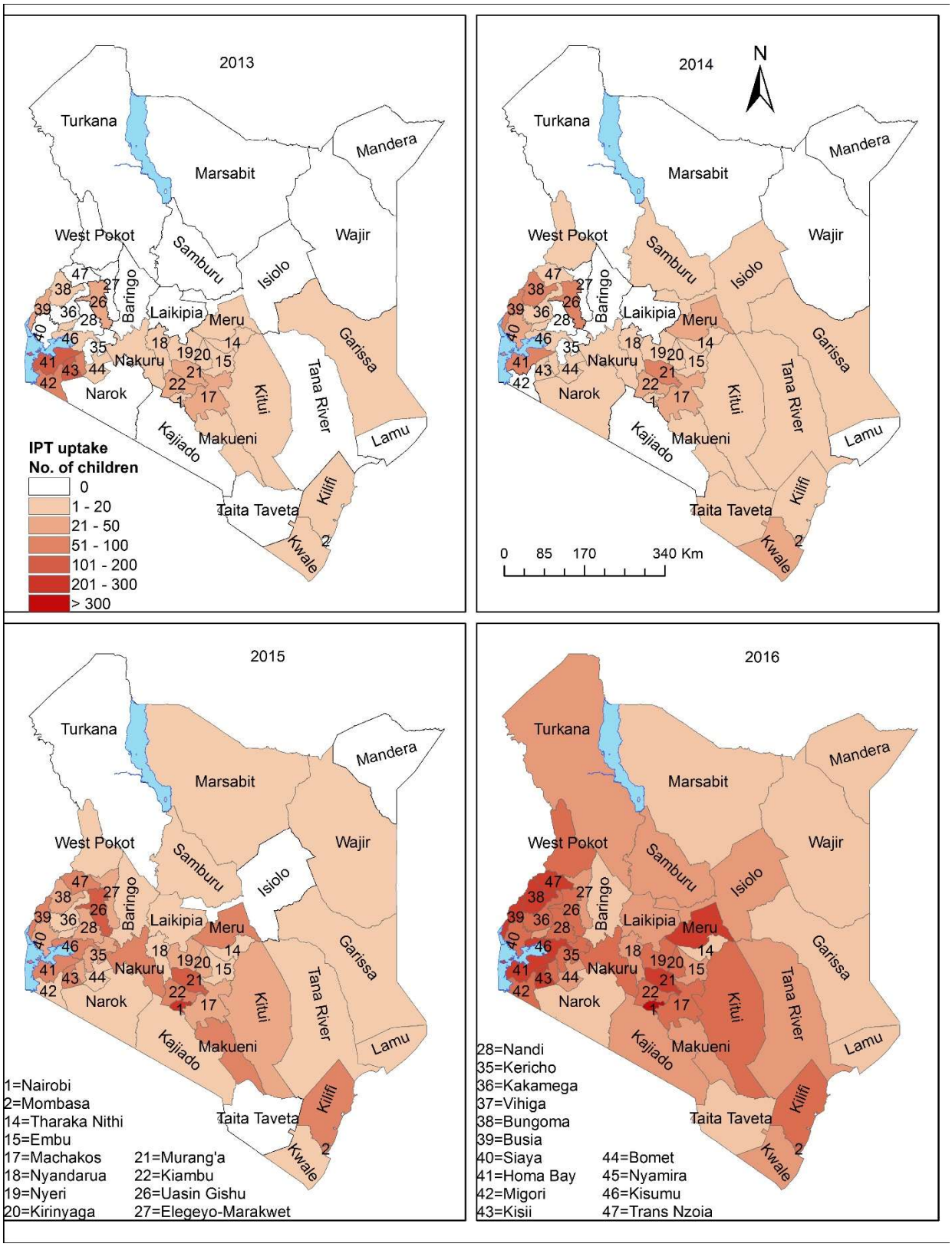
Figure1.
Reasons for discontinuation of IPT



**Some children had not completed the 6 month-course of IPT*

There was approximately nine fold increase in the number of children under five years initiated on IPT between 2013 and 2016. In 2013, 26 counties had at least one initiated case on IPT while in 2014 and 2015, 35 and 43 counties had initiated respectively. In 2016, all the 47counties had initiated IPT as shown in Figure 2. Counties located within 4 regions (Central, Eastern, Nyanza and Western) of Kenya contributed 71% of all the notified cases in the year 2016

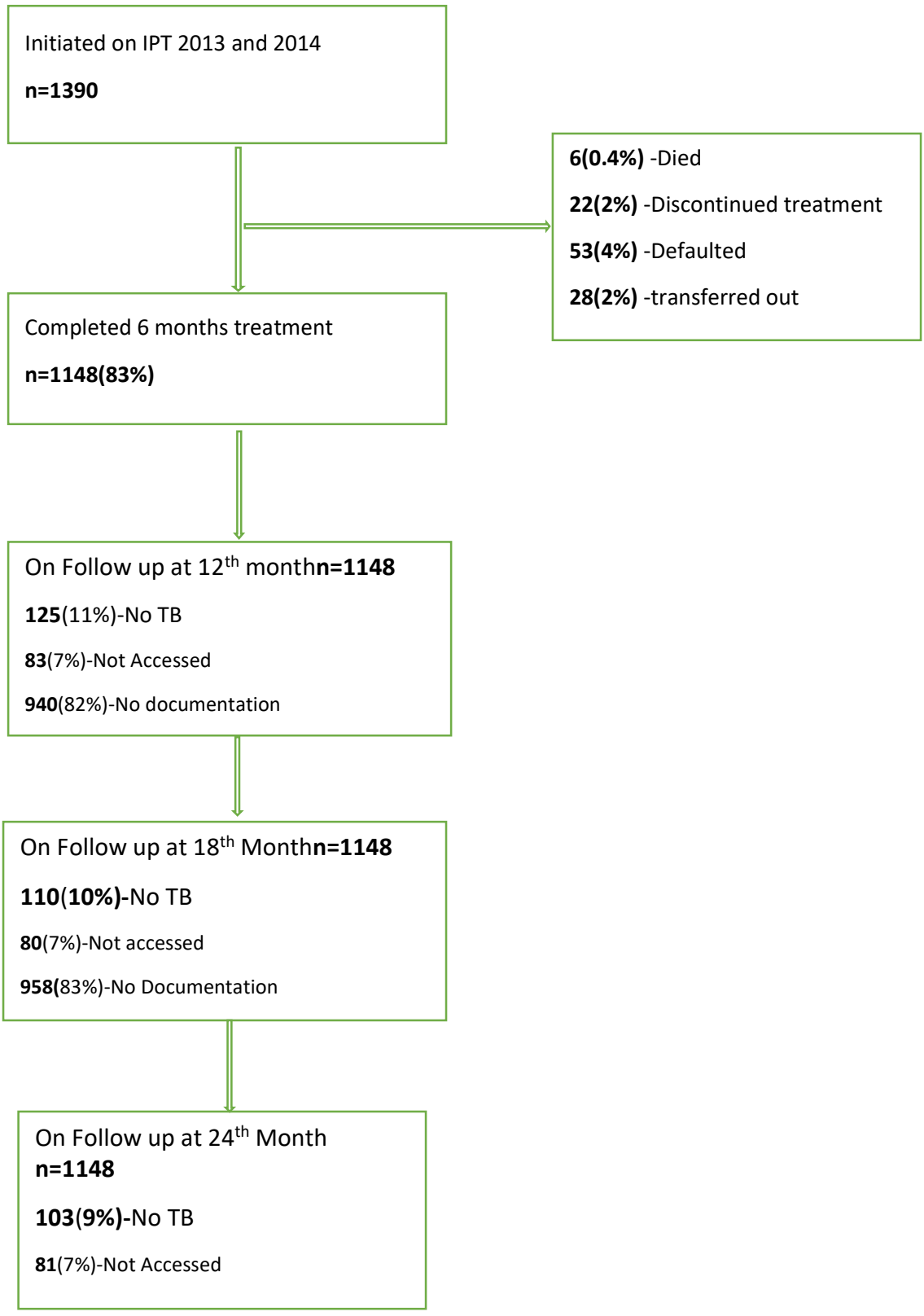
Figure 2:
Geographic coverage of IPT in Kenya 2013-2016



Isoniazid Preventive therapy follow-up

A total of 1390 children were initiated on IPT in 2013 and 2014. At 6th month of follow up, 86% of the children had successfully completed treatment, 4% had defaulted, 0.4% had died, while IPT had been discontinued in 2% of the children. Further, 2%of the children had transferred out and10% had no could not be accessed, while the outcomes of 82% of the children were yet to be documented. Follow up done at the18thmonth showed that 10% of the children had no TB, 7% were not accessed and 82% had no documentation of outcomes. By the end of 24th month of initiation of IPT,9% of the children turned up for TB screening, 7% were not accessed while 84% had no documentation (Figure 3).

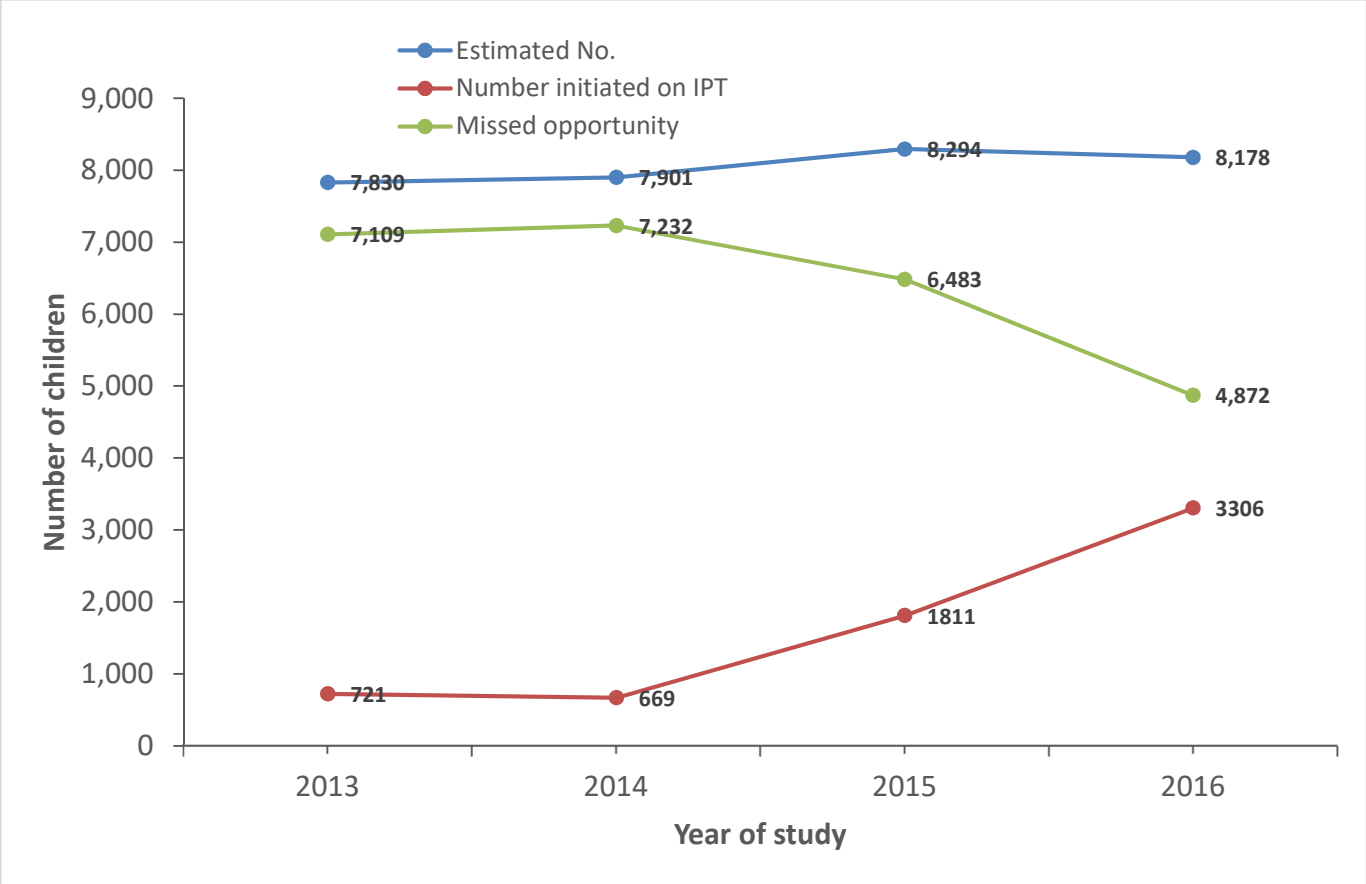
Figure 3:
Flow diagram on follow ups done at the 6th, 12th, 18th and 24th month of IPT initiation in 2013 and 2014



In 2016, 3306 children were initiated on IPT compared with 721 in 2013. The ratio of missed to number initiated was approximately10:1to 2:1.Cumulatively, between 2013 and 2016, 80% of the children under-five years exposed to bacteriologically confirmed PTB were not initiated on IPT. This represented missed opportunities (Figure 4).

Figure 4

Trends in IPT initiation among children under-five years exposed to bacteriologically confirmed PTB in Kenya, 2013-2016



DISCUSSION

This study showed that Kenya had a progressive increase in national IPT coverage between 2013 and 2016.This could be attributed to the National roll out of IPT in 2015 with increased sensitization of healthcare workers; and the development, dissemination and implementation of IPT standard operation guidelines. The variation in absolute numbers among counties was attributed to several factors including; the number of index cases of bacteriologically confirmed cases, initial capacity building of staff in these regions on IPT and established use of IPT among PLHIV. In addition, most of these regions had facilities which were pilot sites before national rollout thus health systems were more equipped for IPT initiation. A steady decline in missed IPT opportunities was observed. However,

our findings were not in agreement with the WHO estimates that reported 5.5% coverage in 2015 while this study estimated it to be at 22%.This huge discrepancy could be attributed to the differences in methodologies used to determine the estimates of missed opportunities. For instance the WHO provided formula uses estimates based on parameters such as ;proportion of children under five years and average household size per country(12).*Osman et al*., in Cape Town in South Africa faced similar challenge in his study while trying to estimate the number of child contacts. He also observed an average of 0.7 child contacts per infectious adult case(13).This was also observed by Lisa, who recommended further research to assess different IPT delivery interventions and operational challenges(14).Completion rates of IPT have been increasing. As a country, we are yet to achieve the 90% WHO target(3). A slight drop in IPT completion was observed in 2015, the year the country launched national rollout. There was a significant number of undocumented outcomes in the same year. This lack of documentation could be attributed to system challenges either in disseminating guidelines or slow service providers, improved logistical support and enhanced supervision and monitoring (18). Some of the limitations in our study included, (i) A missing link between IPT TIBU data and that of the TB index client and number of child contacts in the client's household, there was a lack of documentation of outcomes of some of the children initiated on IPT and those due for follow up. The undocumented figure was however not significant to affect the results of the study. (iii), there is no harmonized method to estimate child contacts among patients with PTB. Despite the limitations, this study had several strengths. Firstly, it is the first national study to focus on children under five years exposed to bacteriologically confirmed TB cases. This study used a large national sample size. The TIBU has existing internal quality checks In addition, the study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for quality reporting of scientific findings (19). There is need for a standardized or validated pace of setting up systems in implementing facilities after the roll out(7).A Gambian study reported 78% completion rate in a home based IPT program study but concluded that system rather than patient factors were the main determinants of success in IPT(15).A South African study in 2013 reported completion rates of 13% (13). Two studies done in Kenya, one on outcomes of IPT in HIV infected children under five years and another by Okwaro et al., on challenges IPT as a child preventive strategy, showed higher completion rates of 92 and 88% respectively(16,17).A large proportion of children who had completed 6 months of IPT had no 24th month TB status screening documentation. The reasons for this lack of documentation are unknown. Further research needs to be done to find out if it is lack of documentation, children not being brought back due to inadequate health education or other factors. A study done in India showed that National TB program guidelines were not being followed by clinicians' offering IPT. This hindered the implementation of the IPT program. The researchers observed and recommended that the provision of IPT could be improved through the training of method of estimation of child contacts to avoid the discrepancy between the country and the WHO estimates. This can be done by creating an entry in TIBU data base to record all children under five years in contact with bacteriologically confirmed PTB cases. Emphasis on documentation of all under five contacts of bacteriologically confirmed TB patients will address the issue of non- documented and transferred out outcomes and might increase IPT completion rates leading to better outcomes and outcome data. For county coverage, more focus should now be on coverage per proportion of bacteriologically confirmed cases reported in that county.

Finally, there is need to come up with standardized outcome case definitions and have system checks to avoid wrong outcome being assigned to a child initiated on IPT.

CONCLUSION

This study shows that Kenya is almost achieving the WHO target of IPT completion rate. Documentation needs to be enhanced to address undocumented outcomes and transferred out. Coverage of IPT in counties needs to be based on the number of identified child contacts. The monitoring for TB should not stop at the 6th month but should continue for 24 months as this population has the greatest likelihood of developing active TB disease following infection within the first two years. Finally, factors that lead to discontinuation of IPT need to be identified and mitigated.

Conflict of Interest: None.

FUNDING/ ACKNOWLEDGEMENT STATEMENT

This research was conducted through the Structured Operational Research and Training Initiative (SORT IT), a global partnership led by UNICEF/UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR) based at the World Health Organization. The model is based on a course developed jointly by the International Union Against Tuberculosis and Lung Disease (The Union) and Médecins sans Frontières (MSFOCB). The specific SORT IT programme which resulted in this publication was led by the Department of Obstetrics and Gynaecology, University of Nairobi and the National Tuberculosis, Leprosy and Lung Disease Program's (NTLD-P).

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