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Trends in Tuberculosis Epidemiology among Children in the Democratic Republic of Congo

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Abstract

Setting: The epidemiology of tuberculosis (TB) among children in the Democratic Republic of Congo (DRC) is not well known. **Objective:** This study aimed to describe the trends in TB epidemiology among children in the DRC and to compare these trends in children and adults. **Design:** Data from the National TB program, the WHO Global TB Report, and a demographic survey of health in the DRC were retrospectively analyzed. The study period was from 1995 to 2014. The notification rate, absolute incidence and incidence rate of TB per 100,000 population were reported. **Results:** In 2014, 12,785 (12.6% of adult cases) TB cases were reported in children and 101,303 in adults. Among children, 3438 (26.89%) had PTB+; 2828 (22.11%) had PTB−; and 6519 (50.98%) had extrapulmonary TB (EPTB). Children under 5 years had a lower reported prevalence of TB (184 cases). The incidence rate per 100,000 population was 10 in children and 181 in adults. The TB incidence decreased between 2010 (11.47) and 2014 (10.46). The proportion of children in overall cases of PTB+ was 4% to 5% in all districts. **Conclusion:** Caring for childhood TB remains a challenge in the DRC. Improved diagnostic procedures and effective training of providers who care for childhood TB are needed.

Keywords

Childhood Tuberculosis, Epidemiology, Africa

1. Introduction

Tuberculosis (TB) is an important contributor to maternal and child's morbidity and mortality [1] [2]. TB is highly prevalent in some countries in Asia and Africa and is the 3rd leading cause of mortality worldwide [3]. The Democratic Republic of Congo (DRC) has the 3rd highest prevalence of TB in Africa [3]. In 2014, the incidence and case notification rates of TB in the DRC were estimated to be 325 (295 - 356)/100,000 population (pop) and 155/100,000 pop, respectively [3]. Among children less than 15 years old, approximately 3138 microscopy smears were positive for TB in a recent DRC national report [4]; however, the incidence and epidemiologic trends in TB among children remain unknown. This lack of knowledge could contribute to a poor control of TB among children, limiting advances to attain the "End TB" objectives.

Indeed, the vision of the "End TB Strategy" is to have a world free of TB by 2035, meaning zero deaths, diseases and suffering due to TB [5]. In countries with a high TB prevalence, strategic plans have been adopted following the World Health Organization (WHO) recommendations. The objectives of these plans cannot be attained without understanding the epidemiologic evolution of the disease in adults and children, as childhood TB is an indicator of poor TB control in adults [6].

Therefore, there is an urgent need to address the lack of epidemiological data on TB in children in high-burden countries and to understand the differences in epidemiology between children and adults; this information could contribute to a reduction in the TB burden.

The present study aimed to describe the trends in childhood TB epidemiology in the DRC and to compare these trends to those in adults.

2. Materials

This study conducted a retrospective analysis of data collected from the WHO Global TB Report and the National Tuberculosis Program (NTP), specifically data concerning the DRC's districts. The NTP houses the central processing unit for the fight against TB in the DRC. This program is organized into 3 levels of activity: data from the Centers for TB Diagnosis and Treatment (CDST) are sent to provincial coordinating centers for the fight against TB (CPLT) and are then consolidated at the national level. The study period was from 1995 to 2014. Data regarding the notification rates for total TB cases, new TB cases, and cases by form of TB, district, and age group were collected. Children were divided into two groups: children aged 0 - 4 years and those aged 5 - 14 years. District-specific population data were obtained from the 2014 national survey on health demography in the DRC (EDS) [7].

2.1. Indicators of TB

Data were available from 1995 for new TB case notifications in children and adults, from 1999for new smear-positive pulmonary TB (PTB) cases by age group and sex, and from 2010 for year- and district-specific cases by sex, age and type of TB. These data

were collected until 2014. For practical reasons, we used the previous 11-district organization of the DRC for data analysis.

The number of case notifications was defined as the number of cases registered during a given period. TB incidence was calculated using the number of new cases divided by the total population within a reporting area or age group. Rates of notified and incident cases were expressed per 100,000 pop. The rate of detection was defined as the ratio of the number of cases registered during a given period and the number of cases tested during the same period multiplied by 100 [8].

The number of new cases was defined as the number of cases detected and treated for the first time during a given period. The proportion of pediatric TB cases was defined as the number of cases in children aged 0 to 14 years old divided by the total number of cases [8].

Cases of smear-positive PTB, smear-negative PTB, and extra pulmonary TB (EPTB) and type of patient (new cases and retreatment) were defined according to the WHO criteria [9].

2.2. Data Analysis

Data were collected and analyzed using Excel. The calculation of incidence and the generation of graphs were performed using the same software. Frequencies and average values were reported for the variables of interest. Chi-square test was performed to evaluate the differences in trends between different DRC districts from 2010 to 2014. A p-value < 0.05 was considered statistically significant. Density maps depicting the TB case notification rate per 100,000 pop by DRC district were produced using Geographic Information System software (QGIS), version 1.6. This study was approved by the Ethics Committee of the School of Public Health (Permit Number: ESP/CE/042/2015, part B). The procedures used in the study were in accordance with the recommendations of the Declaration of Helsinki. Informed consent was not obtained from the patients because this was a retrospective study and we worked exclusively with data obtained from documents.

3. Results

3.1. Cases Reported in Children in 2014 by Form of TB, Sex, and Age

In 2014, a total of 12,785 TB cases were reported in children, and this prevalence was 12.6% of the cases in adults (101,303 adults). Of the cases in children, 3438 (26.89%) were smear-positive PTB (1582 boys and 1856 girls), 2828 (22.11%) were smear-negative PTB, and 6519 (50.98%) were EPTB. The distribution by age showed that 184 children aged 0 - 4 years (99 boys and 85 girls) and 3254 aged 5 - 14 years (1483 boys and 1771 girls) had smear-positive PTB, 1441 children aged 0 - 4 years and 1387 aged 5 - 14 years had smear-negative PTB, and 2251 children aged 0 - 4 years and 4268 aged 5 - 14 years had EPTB (**Figure 1**).

A total of 75,339 new smear-positive PTB cases (42,735 males and 32,604 females, sex ratio of 1.31) were identified in 2014: 3,438 were children, and 71,901 were adults. The

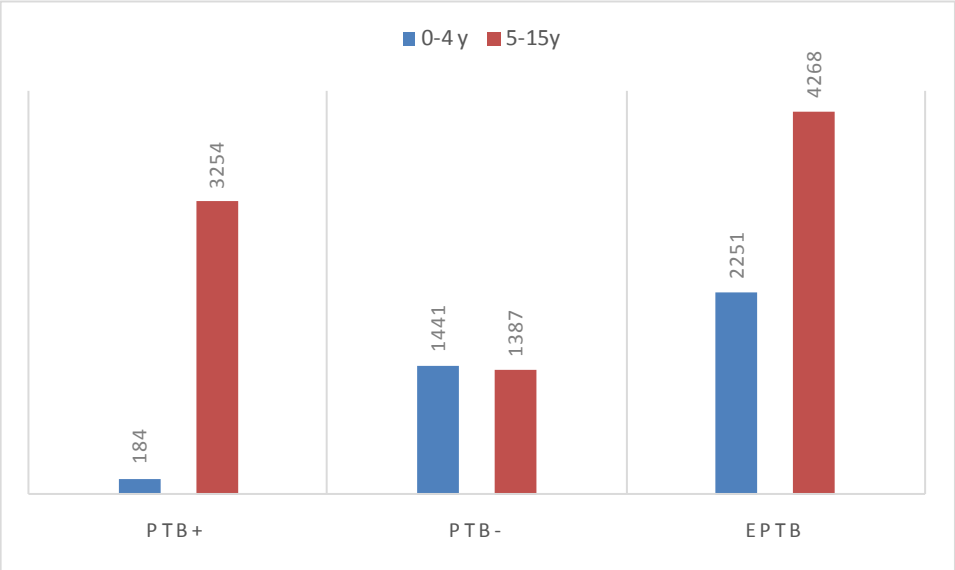

Figure 1. Distribution of children by form of TB in 2014.

distribution by age group was as follows: 184 (0.24%) were 0 - 4 years old, 3254 (4.31%) were 5 - 14 years old, 13,638 (18.01%) were 15 - 24 years old, 19,009 (25.23%) were 25 - 34 years old, 16,401 (21.76%) were 35 - 44 years old, 11,813 (15.68%) were 45 - 54 years old, 7256 (9.63%) were 55 - 64 years old, and 3784 (5.02%) were 65 years and older (**Figure 2**).

3.2. Comparison of TB Case Notification and Incidence Rates per 100,000 Pop in Children and Adults in 2014

In 2014, the overall TB case notification rate was 162/100,000 pop, and the overall incidence was 104/100,000 pop. The incidence rate was 10/100,000 pop in children and 181/100,000 pop in adults. The district-specific distribution of cases among children in the DRC showed that the highest incidence rates were in Bandundu (16/100,000 pop), Maniema (15/100,000 pop) and Katanga (14/100,000 pop). The lowest incidence rates were reported in North Kivu (5/100,000 pop), Bas-Congo and Province Orientale (each 6/100,000 pop). In adults, the highest incidences were observed in Kinshasa, Katanga and Maniema (255, 229 and 213 cases/100,000 pop, respectively), and the lowest incidence was in North Kivu (91/100,000 pop) (**Figure 3**).

3.3. Trends in TB Case Notification for Adults and Children from 1995-2014 and 2010-2014

The trends in new TB case notifications in adults and children from 1995 to 2014 are presented in **Figure 4** and **Figure 5**. In 1995, there were 13,365 new notifications of adult TB cases, followed by a decrease in notifications in 1996-1997 (11,067 in 1996 and 12,662 in 1997); the notification rate then began to increase, reaching 71,901 cases in 2014. This trend exhibited an increasing linear curve.

In children 0 to 15 years old, the number of new case notifications in 1995 was 704,

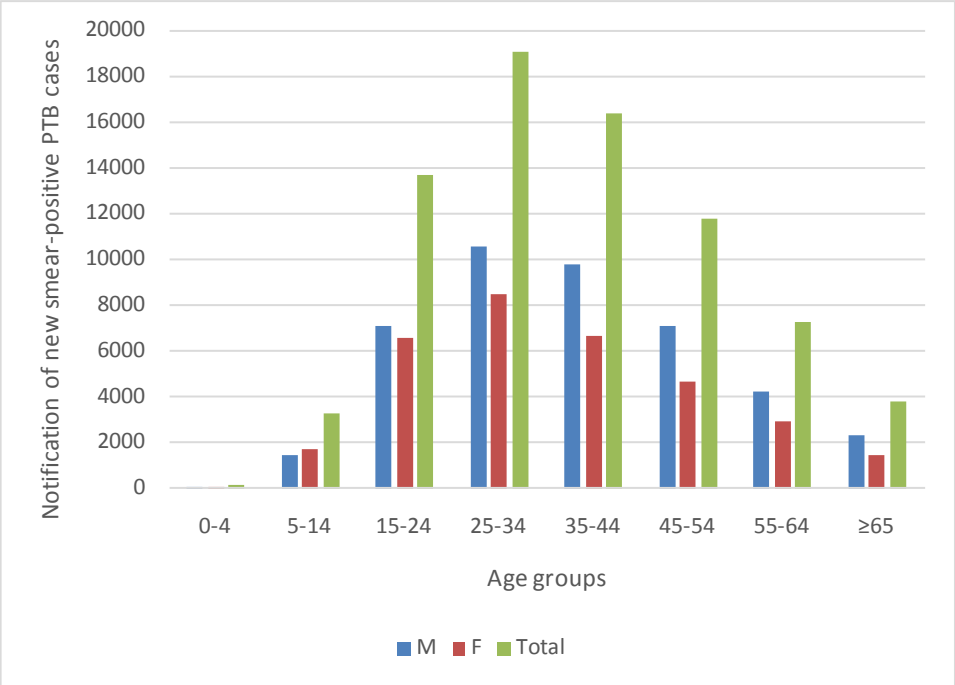

Figure 2. Age distribution of new smear-positive PTB cases in the DRC in 2014.

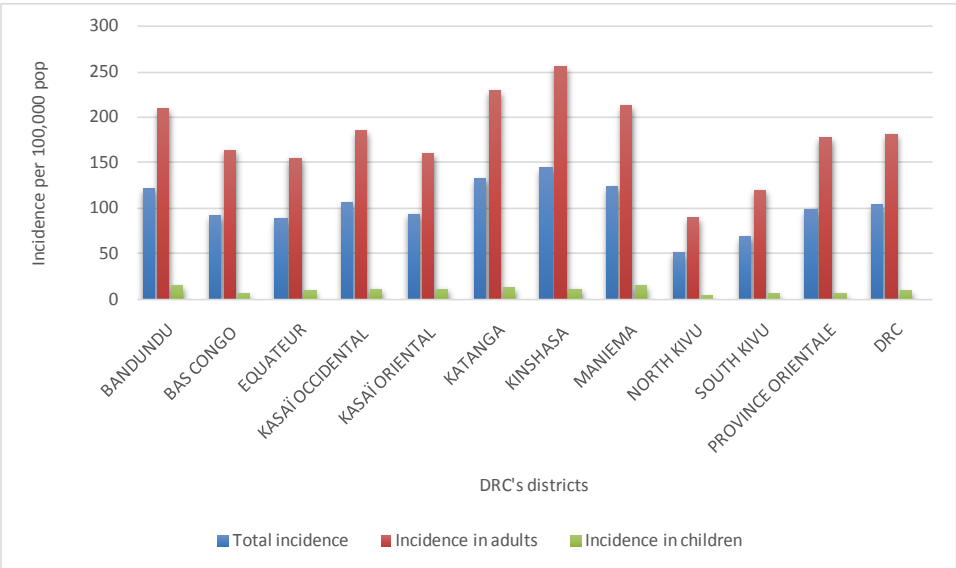

Figure 3. Distribution of TB incidence overall and in children and adults in 2014.

followed by a decrease from 1996-1997 (520 in 1996 and 580 in 1997) and then an increase to 3438 cases in 2014.

From 2010 to 2014, the incidence rate in children/100,000 pop indicated a decreasing trend: from 11.47 in 2010, to 10.17 in 2011, 8.90 in 2012, 8.28 in 2013, and 10.46 in 2014. This variation was statistically significant ($p < 0.01$) in DRC overall based on chi-square tests. The five-year trends in case notification among children during the

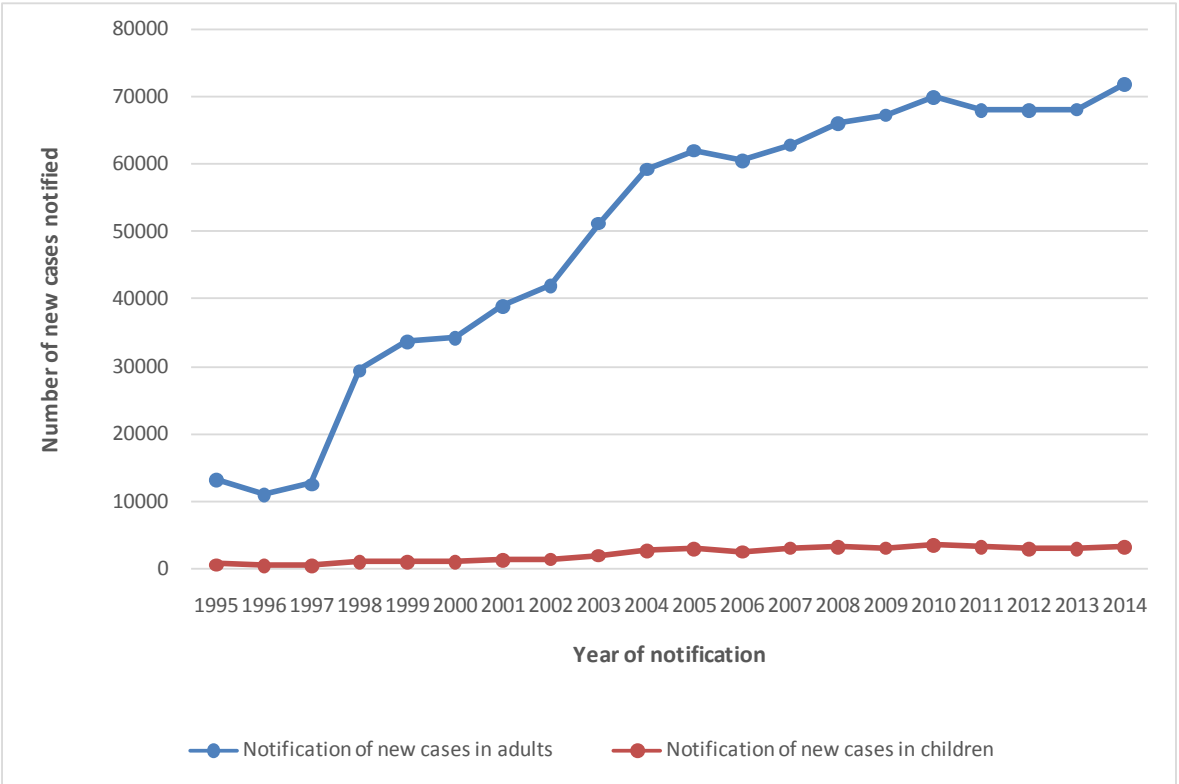

Figure 4. Trends in new TB case notifications in adults and children from 1995 to 2014 (Source: www.who.int/tb/data/).

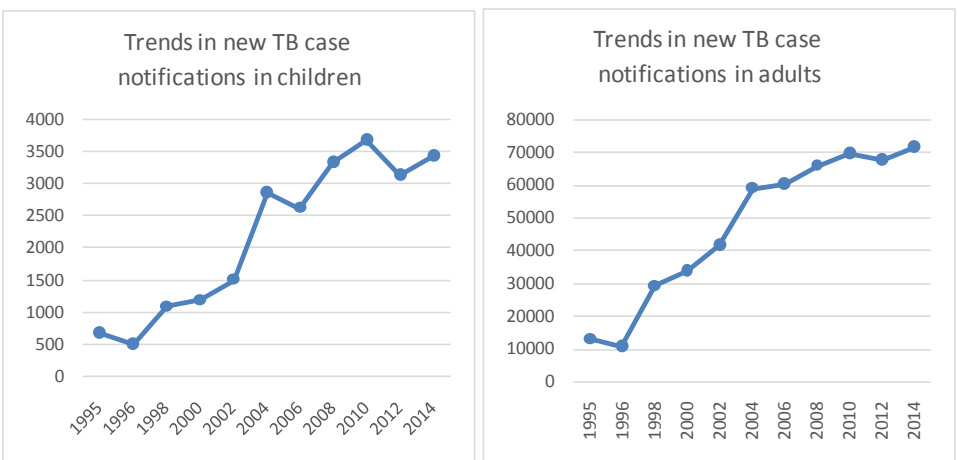

Figure 5. Trends in new TB cases notifications in children and adults from 1995 to 2014. Legend: Number of new TB cases reported annually from 1995 to 2014 in children (left) and adults (right).

study period indicated the highest numbers in Kasaï Oriental (3246 in 2010 and 1765 in 2014), Kinshasa (2884 in 2010 and 2075 in 2014), and Katanga (2103 in 2010 and 1,499 in 2014). A progressive reduction in reported cases occurred in almost all districts, Kasaï Occidental in particular (1181 in 2010 and 545 in 2014), with the exception of North Kivu, where the number of reported cases slightly increased (767 in 2010 and 860 in

2014). Detailed data from all districts during the 5-year study period are presented in the in Table 1.

3.4. Trends in the Age, Gender, and Proportion of TB Case Notifications and in the Distribution of TB Forms in Children and Adults

The trends in the age and gender distribution of new smear-positive PTB cases during 1999-2014 indicated that the highest TB incidence occurred in the 25- to 34-year-old age group, followed by the 35- to 44-year-old and 15- to 24-year-old age groups (Figure 6). After 2011, a progressive decrease in new cases of smear-positive PTB among children (0 to 14 years) was identified. The female sex was predominant in cases younger than 25 years old, whereas males were more prevalent in those aged 25 years and older (Table 2).

From 2010 to 2014, the proportion of TB notification rates in children in terms of the overall TB cases ranged between 10 and 15%. The lowest proportion of children was

Table 1. Trends in TB case notification rates per 100,000 pop in children from 2010 to 2015 in the DRC.

DISTRICT	2010	2011	2012	2013	2014
BANDUNDU	28.88	28.60	24.02	31.70	19.65
BAS CONGO	19.84	16.27	16.36	27.14	16.30
EQUATEUR	29.87	28.02	24.52	22.51	18.52
KASAÏ OCCIDENTAL	49.92	49.01	44.32	30.83	17.65
KASAÏ ORIENTAL	116.82	99.76	85.80	56.25	45.00
KATANGA	45.69	45.38	39.05	39.72	31.74
KINSHASA	68.93	63.30	55.17	90.77	70.36
MANIEMA	64.57	75.38	61.74	55.96	36.28
NORTHKIVU	30.98	27.45	25.10	29.54	32.41
SOUTHKIVU	33.40	30.84	28.00	27.24	27.14
PROVINCE ORIENTALE	32.26	24.72	28.61	26.27	19.67
DRC	46.90	43.12	38.47	39.29	30.93

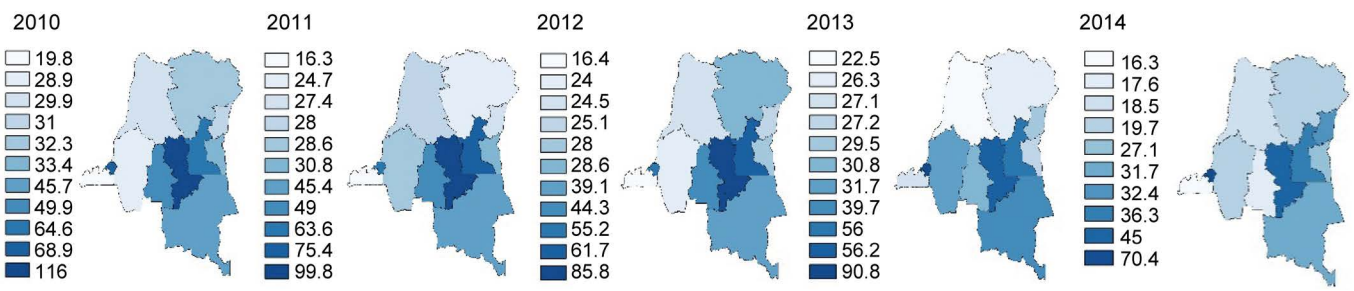

Figure 6. Trends in TB case notification rates per 100,000 pop in children in the DRC from 2010 to 2015. Legend: The number of cases per 100,000 pop, with lighter colors corresponding to a lower number and a darker color corresponding to a higher number of case notifications per 100,000 pop.

Table 2. Trends in smear-positive PTB cases by age group and sex from 1999 to 2014.

	0 - 14		15 - 24		25 - 34		35 - 44		45 - 54		55 - 64		≥65	
	M	F	M	F	M	F	M	F	M	F	M	F	M	F
1999	474	708	4061	4472	5886	4991	4191	3117	2250	1725	1279	836	626	305
2000	485	718	4042	4418	5822	5135	4147	3304	2544	1719	1291	853	601	351
2001	581	842	4651	4922	6794	5586	4817	3704	2876	2057	1384	1042	724	470
2002	649	874	4965	5378	7414	6230	4994	3939	3065	2262	1388	1055	791	476
2003	853	1233	5886	6630	8426	7711	6194	4827	3776	2866	1836	1457	1046	592
2004	1201	1682	7057	7662	9560	8623	7134	5542	4426	3439	2355	1855	1226	720
2005	1320	1694	6661	7550	9800	8487	7571	5825	5017	3894	2631	2049	1499	951
2006	1122	1517	6391	7236	9486	8522	7321	5621	5011	3762	2657	2019	1504	975
2007	1343	1842	6485	7130	9548	8415	7925	5939	5341	4127	2801	2352	1752	1099
2008	1495	1811	6497	7304	9888	8895	8452	6293	5706	4064	3121	2516	1686	1212
2009	1556	1940	6993	7362	10037	9191	8746	6586	6316	4757	3401	2669	1827	1325
2010	1707	1987	6859	7199	10412	9120	9134	6721	6464	4579	3641	2612	1907	1311
2011	1579	1800	6640	6802	9872	8742	8932	6541	6415	4537	3584	2671	1911	1295
2012	1439	1699	6612	6598	10274	8406	9361	6471	6612	4131	3698	2625	1941	1257
2013	1380	1706	6776	6376	10218	8352	9280	6472	6587	4402	3841	2551	2016	1263
2014	1582	1856	7098	6540	10540	8469	9771	6630	7123	4690	4294	2972	2337	1447

identified in Bas-Congo (7%), and the highest rates were observed in Kasaï Oriental (17%), Maniema and North Kivu (each 15%).

From 2010 to 2014, the trends in TB forms suggested a very large gap between the number of cases reported in children and adults. The proportion of children in overall cases of smear-positive PTB was 4% to 5% in all districts. Nearly a third (26% to 33%) of smear-negative PTB cases occurred in children, and approximately half (50% - 55%) of EPTB cases were in children. The 5-year trends showed a decrease in cases in both adults and children (Figure 7).

4. Discussion

The present study was the first to analyze the epidemiologic trends in childhood TB in the DRC and to compare them to the trends in overall cases and in adults.

The main results of this study showed an overall difference between children and adults in the trends in TB epidemiology. In children, the incidence of TB in 2014 was 10/100,000 pop. This rate varied between 5 and 16/100,000 pop in specific DRC districts. Cases in children represented approximately 9.6% of the overall incident TB cases and 5.5% of the incidence in adults. The incidence in the DRC districts showed a decreasing trend from 2010 to 2013. Additionally, in adults, the trends in new TB case notifications showed a decrease from 13,365 to 12,662 cases from 1995 to 1997; this de-

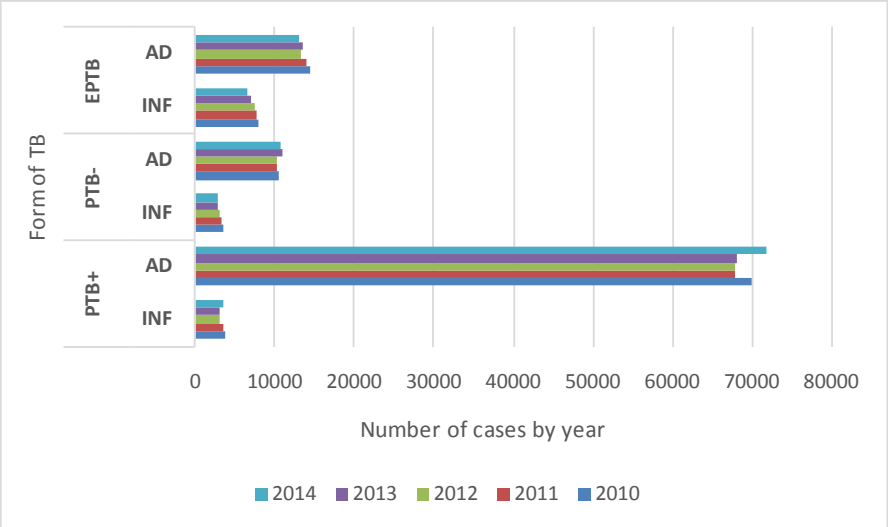

Figure 7. Distribution of smear-positive PTB, smear-negative PTB and EPTB cases in children and adults from 2010 to 2014 in the DRC. Legend: PTB+ (smear-positive pulmonary TB), PTB– (smear-negative pulmonary TB), EPTB (extrapulmonary TB).

crease was followed by a slight increase from 1998 to 2000 and a substantial increase from 2002 to 2005, doubling the number of reported cases to reach 62,024 in 2005. The number of cases reported in 2014 was 5.4 times higher than in 1995 in adults and 4.7 times higher in children (**Figure 3**). The proportion of TB cases that occurred in children was 10% - 15%, and we observed a majority of EPTB cases, followed by smear-negative PTB, then smear-positive PTB cases in children. In adults, the distribution of TB forms differed; there was a predominance of smear-positive PTB cases, followed by EPTB and then smear-negative PTB cases.

In the DRC, the gap in the incidence between children and adults and the low incidence in children were likely due to an underestimation of TB cases in children; a similar underestimation has previously been indicated worldwide, particularly in countries with limited resources [10]. This under estimation is likely explained by the challenges in diagnosing TB as well as by the difficulties correctly implementing the anti-TB program in some parts of the country that are affected by tribal conflict. The incidence of TB among children in Northern countries has shown increasing trends as countries approach the Mediterranean Sea, with the exception of the Balkan countries, where the incidence of TB is particularly high [11]-[19] (**Table 3**).

The decrease in TB incidence suggests better control of the disease in these countries. In areas with a high burden of TB, although we would expect an increase in TB incidence, our findings showed a slight variation in children, likely because of the challenges managing TB in children in these countries [20] [21]. However, there is good reason to believe that the effects of vaccination and the improvements in patient care could influence the trends observed in these data [22]. The decrease in TB observed from 1995 to1997 may be due to the country's ongoing war and changing political system. The increase in incidence from 2002 was likely associated with the interventions of

Table 3. Global epidemiologic data for TB in children.

Country and study period	Incidence in children/ 100,000 pop	Notification in children/year	Proportion of TB cases in children	Trends	Authors
Denmark 2000-2009	**1.9** (2009)	323 cases (2009)	**7.6%** (2009)	↓ incidence 4.1/100,000 in 2000 1.9/100,000 in 2009	Hatleberg CI *et al.*, 2014 [12]
Greece 2000-2009	**5.37** (2009)	321 cases		No significant difference (p = 0.194)	Syridou G *et al.*, 2012 [13]
Spain 2005-2009	**8.1** (2009)	2690 cases (2009)	**6.76%** (2009)	↓ incidence in children and adults Children (y = 0.15x + 7.8) Adults (y = −2.8x + 20.2)	Elena Rodriguez *et al.*, 2012 [14]
Kosovo and the Balkans 2012	**39** Kosovo **7.5** Slovenia **13** Albania **20** Serbia **83** Romania				Xhevat Kurhasani *et al.*, 2014 [15]
Brazil (Sao Paulo) 2001-2005 2006-2010	**3.23** **2.13**	2881 cases 2513 cases			Venancio TS *et al.*, 2014 [16]
Australia 2003-2012		538 cases	**4.6%**		Teo SS *et al.*, 2015 [17]
Israel 1999-2010	**1.05** (2010)	405 cases (2010)	**8.4%** (2010)		Mor Z *et al.*, 2013 [18]
Ethiopia, (Sidama Zone) 2003-2012		4656 cases (2012)	**13%** (2012)	No variations overall However, ↑ in incidence from 2010 to 2011	Dangisso*et al.*, 2015 [19]
Benin (Cotonou) 2009-2011	**13** (2011)	73 (2011)	**4.9%** (2011)	↑ incidence in children 13.2/100,000 in 2009 13.8/100,000 in 2011	Ade S *et al.*, 2013 [20]
The DRC 1995-2014	**10** (2014)	3438 cases	**12%** (2010-2013)	↓ incidence in children 11.47/100,000 in 2010 10.46/100,000 in 2014	Present study

the Global Fund and its partners to enable a better coverage of activities in the country and a better detection of cases [23].

Approximately 30% - 40% of close contacts are estimated to be infected at the time of diagnosis for each identified case of TB [24], and children have been identified as being most vulnerable to this disease. The proportion of TB cases reported in children should be higher than the rate identified in this study; this gap demonstrates that childhood TB has historically been neglected [25], and surveillance is additionally challenged by the difficulty diagnosing TB in children [26]. Furthermore, the previous directives of the WHO (before 2014) proposed treated cases of smear-positive TB as tool of the epidemic control [27]; however, this condition may be difficult to identify in children. Fortunately, the WHO developed new guidelines for children that accounted for this difficulty [28].

Regarding the incidence in DRC districts, in general, the most affected districts were Kasaï Oriental, Kasaï Occidental and Katanga, probably because of the influx in population to the mining zones in these areas, resulting in a high rate of TB transmission in mining camps. Subsequently, from 2010-2011, the NTP increased the number of CDSTs in these districts, and a decrease in the TB case notification rate has been observed in recent years.

The distribution of smear-positive PTB cases showed an increase by age, particularly in those aged 15 - 44 years (peak in 24- to 34-year-olds), corresponding to the period of increased social and sexual activity. A study previously conducted in the DRC with children from 0 to 15 years old also reported an increase in the number of cases with age [29]. This unusual distribution supports the difficulty diagnosing TB in younger children [30] [31]. However, other authors, particularly those in developed countries, have demonstrated that the age group of most concern is those less than 4 years [32].

The low number of new smear-positive PTB cases in children can be explained by a slight increase in case detection during the 5 study years. This observation differed from findings previously reported in developed countries, where PTB was the most frequently identified clinical form of TB [33], probably because of the difficulty obtaining sputum and other organic products from children to identify bacillus of Koch (BK), as reported above. Diagnosis in young children is often based only on clinical and radiological evidence. The Xpert MTB assay can improve the diagnosis of TB, especially in children [34] [35]. However, the implementation of the WHO recommendations [28] regarding the use of the Xpert MTB assay in children has not occurred widely throughout the DRC.

The observations by district showed a decreased number of smear-positive PTB cases in Katanga; however, the number of smear-negative PTB and EPTB cases increased. This trend indicated fewer cases of bacteriologically confirmed TB and more clinically diagnosed cases, which could likely be explained by the conflict between tribes in this district that occurred in the last years of the study. In the Bandundu district, a continuous increase in the rate of new smear-positive PTB cases in children was observed. The intervention of several partners in this district's various health programs could have contributed to the improvement observed in the rate of detection. Partner support has had a major impact on disease control in the DRC, particularly in conflict zones such as the east districts, where war has raged for several years.

This study is the first to describe the epidemiological profile of TB in the DRC. Another strength of the study was the description of the epidemiologic trends in childhood TB, as this understanding can contribute to a better control of the disease by the application of new strategies.

Some limitations should be acknowledged; few data were available for more specific age groups of children, and this scarcity may have limited some understanding of the TB trends in subgroups of children. Additionally, there are potential biases inherent to retrospective studies. Some specific data were not available before 2010, and this lack of data limited some analyses. The difficulty in diagnosing TB from sputum in young

children, particularly the difficulty in obtaining expectorate samples or gastric aspirates, the low sensitivity of the scoring system, and the difficulty confirming smear-negative cases based on clinical signs and chest X-rays could also be considered limitations of this study.

5. Conclusion

In 2014, the incidence of TB among children in the DRC was 10/100,000 pop. The proportion of children with TB was approximately 12% of total cases. The highest incidence occurred in the Bandundu district (16/100,000 pop). Globally, an increase in new TB case notifications in adults and children was observed from 1995 to 2014, but a decrease in notification rate occurred in children in 2014. These findings showed that childhood TB remains a challenge in the DRC. The rate of TB notification remains low compared with the rates targeted by the WHO. The identification of BK must be performed on all suspected TB cases. Control efforts should be increased to achieve the rate of TB infection recommended by the WHO and WHO guidelines for children. Specific strategies must be implemented to improve the diagnosis, monitoring, and reporting of cases, especially in children.

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