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Coinfection of Tuberculosis and HIV in Nigeria: A Systematic Review and Meta-analysis

Eleazar E. Reward[1,2], Anthony C. Ike[1], Sophia O. Muo[1], Busola F. Soga-Oke[3], and Emmanuel M. Mbaawuaga[4]*

[1]*Department of Microbiology, University of Nigeria, Nsukka, Enugu State, Nigeria;* [2]*Department of Biological Sciences, Wayne State University, Detroit, Michigan, United States;* [3]*Department of Microbiology, Federal University of Agriculture, Abeokuta, Ogun State, Nigeria;* [4]*Department of Biological Sciences, Benue State University, Makurdi, Benue State, Nigeria*

Abstract

Tuberculosis (TB) and HIV/AIDS are major public health issues globally. The burden of these diseases is particularly significant in Nigeria due to the high TB and HIV/AIDS prevalence. This meta-analysis for the 1st time addressed the TB/HIV coinfection prevalence in Nigeria at the regional level. A total of 58 relevant publications comprising 80 studies (n = 44,508) were obtained from PUBMED, ScienceDirect, African Journals Online, and Cochrane Library databases using carefully constructed keywords combinations. The PRISMA guideline was followed for this meta-analysis. Two independent reviewers conducted the publication screening, data extraction and methodological quality appraisal with a third reviewer serving as arbitrator. The pooled estimates were calculated using the random effects model. Heterogeneity was assessed using Cochran's Q and I^2 statistic. Univariate and multivariate meta-regressions were done to predict sources of between-study heterogeneity. Overall, the pooled prevalence of TB/HIV coinfection was 25.8%. The highest coinfection prevalence of 34.3% was recorded among the North Central States of Nigeria, while the least prevalence of 19.3% was recorded among the Southeastern states of Nigeria. There was a paucity of published articles from the Northeastern states of Nigeria. There was a significant heterogeneity between studies (I^2 > 90%, p < 0.001), but meta-regression analysis only explained < 10% of it. This study has shown that the prevalence of TB/HIV coinfection remains significantly high in Nigeria. Constant surveillance should be rigorously implemented with special attention given to the Northeast due to the ongoing crises that are compounding the problem. **(AIDS Rev. 2020;22:82-90)**

Corresponding author: Anthony C. Ike, anthonyc.ike@unn.edu.ng

Key words

HIV/AIDS. Tuberculosis. Coinfection. Systematic Review. Meta-analysis.

Introduction

The significant interaction between tuberculosis (TB) and HIV pathoepidemiological causal pathway and disease natural history within and across various populations is well established[1,2] and is one of the major global health challenges plaguing humankind in the 21st century[3]. In 2011, it was estimated that 13% of 8.7 million people who developed TB globally had HIV coinfection[4]. TB is reportedly responsible for 25% of all AIDS-related death and in the 2016 global TB/HIV coinfection statistics, 374,000 died as a result of the coinfection[3]. The prevalence of TB is currently increasing in developing countries, particularly in Sub-Saha-

Correspondence to:
*Anthony C. Ike
E-mail: anthonyc.ike@unn.edu.ng

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ran Africa due to the burden of HIV. At present, Africa accounts for 74% of the 1.2 million TB/HIV cases globally[5] with Nigeria being among the 30 high burden countries for TB/HIV coinfection[6]. She also ranks as the highest TB burdened country in Sub-Saharan Africa[7] with a prevalence and incidence of 322 and 338 per 100,000, respectively, according to the 2014 Global TB Control Report[8]. Kolade et al.[2] outlined the main militating factors of TB control measures to include "poor case detection, ineffective laboratory diagnosis, weak reporting system, lack of effective treatment, lack of political will, and the ever growing threat of drug resistance TB." On the other hand, Nigeria recorded a moderate reduction in the number of HIV-infected individuals from 5.8% in 2001 to 3.2% in 2013[2].

HIV has a debilitating effect on the immune system by depleting the CD4 cell counts making the body prone to invasion by opportunistic infections such as TB. HIV-positive individuals are 20 times at more risk of latent *Mycobacterium tuberculosis* infection reactivation and subsequent progression to active TB compared to HIV-negative people[2,5] – this risk increases by 2.5-fold in HIV-positive children[9]. TB has also been reported to lower the CD4 count and worsen the immunodeficiency caused by HIV[9] and increases diversity and replication of HIV due to the facilitation of transcription of HIV genes[5]. The incidence of coinfection is influenced by many factors such as family size, injectable drug use, anemia, clinical stage of HIV, and use of antiretroviral therapy[5].

Although studies have been conducted on the prevalence and associated risk factors of TB/HIV infection in Nigeria, there are no comprehensive data on the magnitude and risk factors at national and regional levels. This is the first study to pool the prevalence estimates for TB/HIV coinfection in Nigeria (at national and regional levels) where estimates have ranged from 0% to 50% in various regions of the country using a meta-analysis based on a systematic review of published studies. This meta-analysis is very critical to the Federal Ministry of Health to advance TB/HIV control program.

Objectives

The objectives of the study were to conduct a systematic review and meta-analysis of data in populations residing in Nigeria as reported in studies published to determine the prevalence of TB-HIV coinfection.

Materials and methods

Data sources and search strategy

PUBMED/MEDLINE, ScienceDirect, African Journals Online, and Cochrane Library databases were searched between December 1, 2018, and December 2, 2018. The keywords combination applied for the PUBMED database is contained in the supplementary file. There was emphasis on sensitivity over specificity to reduce the possibility of missing an eligible publication, thus the keywords applied were broad. The search strategy applied was modified to fit the peculiarity of each database. Furthermore, the reference list of the retrieved publications, proceedings of conferences, and other gray literature were investigated for eligible publications.

Study selection and inclusion/exclusion criteria

The titles and abstracts of the publications obtained from the database queries (after removal of duplicates) were assessed for their eligibility. The full texts of publications that met the inclusion criteria were retrieved for further screening. The assessments of the titles, abstract, and full text were independently carried out by two investigators; where there were discordant opinions, a third investigator reviewed the publication and had the final say on its eligibility. Studies deemed eligible for inclusion in the meta-analysis were cross-sectional or cohort studies addressing the prevalence of HIV infection among TB patients or the prevalence of TB among HIV/AIDS patients. There was no limitation in terms of diagnostic methods used. Furthermore, self-report of disease status (diagnosis based on questionnaires) was included. Reviews, correspondences, economic analyses, vaccine efficacy trials, perspectives, and studies that were carried out in Nigerian population not resident in Nigeria were excluded from the study.

The delineation used by Khadr et al.[10] to define publication, study, and measure is applied.

Appraisal of risk of bias

Risk of bias of included studies was evaluated using an adapted version of the tool applied in a previous meta-analysis[11]. A score of 1 (yes) or 0 (no) was assigned for each item, and scores summed across items to generate an overall quality score that ranged from 0 to 10. Studies were then classified as having a

low (8-10), moderate (5-7), or high (0-4) risk of bias. Two investigators independently assessed study methodological quality, with disagreements resolved by consensus or arbitration of a third investigator.

Data extraction and statistical analysis

A data extraction tool was implemented using excel. One investigator extracted the region, year of publication, setting, sample population, number in sampled population, and prevalence of TB-HIV coinfection for each study. A second investigator independently crosschecked the data for correctness.

The meta-analyses were carried out using MetaXL software version 5.3. The pooled prevalence estimates were calculated using the variance stabilizing Freeman-Tukey double arcsine transformation[12]. The Wilson method was employed to calculate 95% confidence intervals (CIs) around the estimates. Heterogeneity was calculated in this study using the Cochrane *Q* (reported as Chi-square and p values) which determined the existence of heterogeneity in effect size ($p < 0.10$ indicated heterogeneity)[13] and the I^2 heterogeneity measure which estimated the percentage of between-study variation in effect size that is due to actual differences in effect size rather than chance[14]. Unlike *Q*, I^2 does not inherently depend on the number of studies included; values of 25%, 50%, and 75% show low, moderate, and high degrees of heterogeneity, respectively. Because heterogeneity was high ($I^2 > 75\%$), the summary statistics were estimated using the DerSimonian-Laird random effects model. This method accounts for sampling variation and heterogeneity in effect size[13].

To determine the source of heterogeneity, groups of studies were arranged according to potentially relevant characteristics and by meta-regression. The independent variables specified priority include: region, sex, number of sample population (≤ 500 vs. > 500), and screening (HIV from TB vs. TB from HIV). Factors associated with prevalence at $p \leq 0.10$ in univariable analysis were included in the final multivariable analysis. Factors associated with prevalence at $p \leq 0.05$ in the final multivariable analysis were deemed statistically significant. The meta-regression was done using STATA version 15.1.

Results

Search results and scope of evidence

A total of 481 publications were identified through the search in the four databases aforementioned, adjusted to 479 when duplicates were removed. Another 420 publications were eliminated after the titles and abstracts were screened. The full texts of 59 publications were retrieved for further screening and additional 23 publications were included from scanning the reference lists of the retrieved full texts. After examining full texts of the 82 publications, 24 were found ineligible (summary of the reasons for their exclusion is shown in Fig. 1). Overall, 58 publications reporting the findings of 80 studies (n = 44,508) were included for the final systematic review and meta-analyses. Supplementary Table 1 shows the characteristics of each study and table 1 includes number of studies, ranges, and medians for the different stratified population types.

Pooled prevalence overview

The overall pooled mean prevalence for TB/HIV coinfection was 25.8% (n = 44,508; 95% CI, 21.6%-30.2%). Stratified by sex, the pooled mean was 26.5% (n = 10,752; 15.9%-38.6%) and 24.0% (n=9206; 16.5%-32.4%) for females and males, respectively. For region specific meta-analyses, the pooled mean prevalence was not computed for North-East since only one study was available for the region; for North-Central, South-South, and South-East, it was 34.3% (n = 9291; 26.6%-42.4%), 27.7% (n = 3800; 18.2%-38.3%), and 19.3% (n = 9923; 11.0%-29.2%), respectively (Table 1). There was strong evidence of heterogeneity in the prevalence in all the meta-analyses ($p = 0.000$; Table 1). The variation was due to true variation in prevalence rather than sampling variation ($I^2 > 75\%$). The forest plot for the overall pooled prevalence is shown in figure 2, while the geographical distribution of the pooled prevalence by region is shown in figure 3.

Predictors of prevalence and sources of between-study heterogeneity

The results of the meta-regression are shown in table 2. In univariate meta-regression, setting (population based vs. hospital based), sex, and year of publication were not statistically significant ($p > 0.10$). Only region, sample size, and screening (HIV from TB vs. TB from HIV) had $p < 0.10$ and thus were included in the final multivariable analysis and they were still significant after the multivariate meta-regression.

Risk of bias assessment

Five (6.25%) studies from four publications[15-18] had moderate risk of bias and the remaining 75 studies from 53 publications[2,7,8,19-67] had low risk of bias.

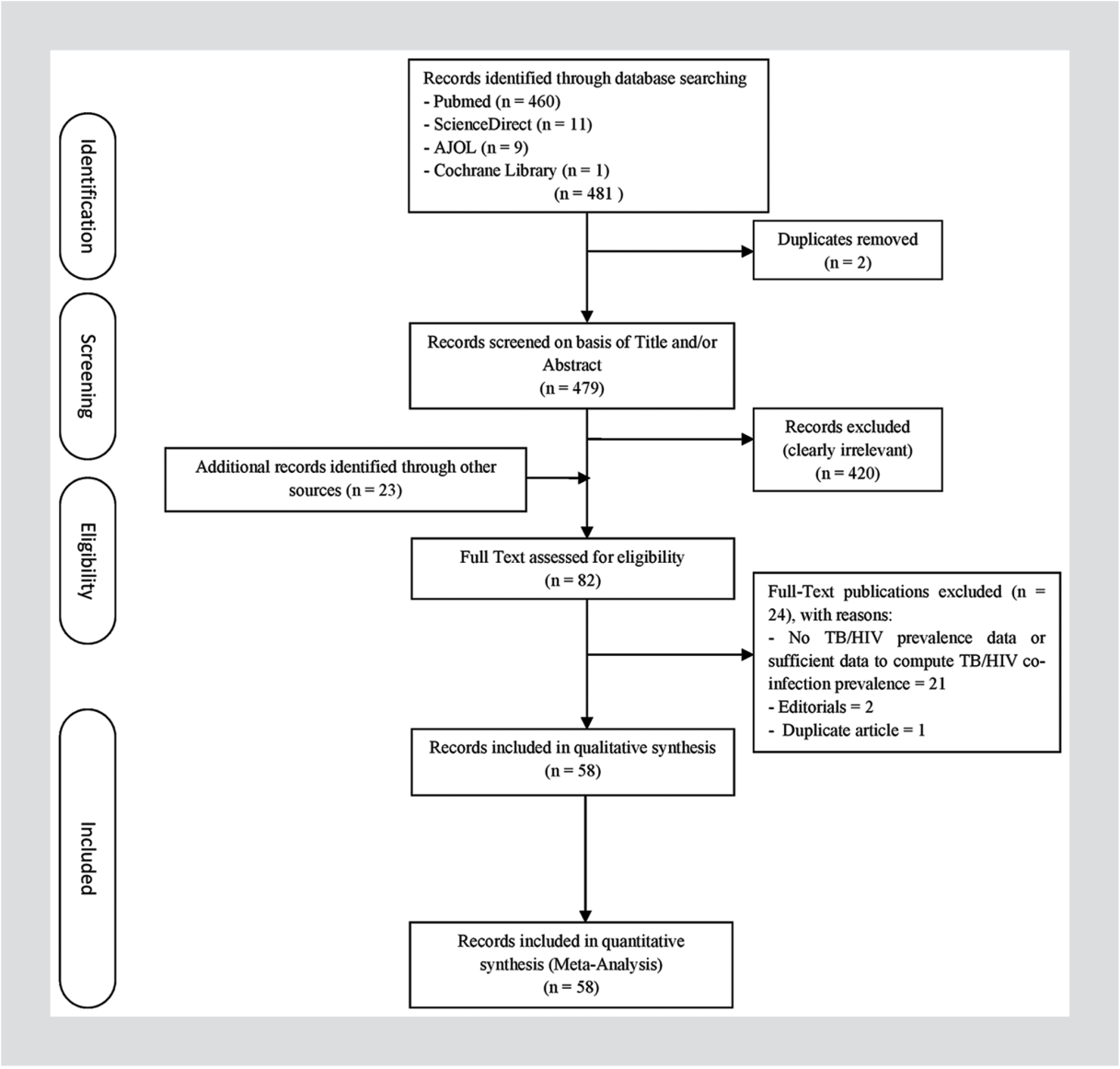

Figure 1. *Process of identification and selection of studies for inclusion in the review.*

Discussion

This systematic review and meta-analysis of TB/HIV coinfection identified 80 studies of 44,508 individuals resident in Nigeria. The overall prevalence of TB/HIV coinfection of 25.8% (95% CI, 21.6%-30.2%) estimated in this review indicates a considerable high prevalence of TB/HIV coinfection in Nigeria.

The pooled TB/HIV prevalence estimated in this study is higher than the findings in Ethiopia (22%)[5], China (11%), European countries (20.1%), the USA (14.8%), and in a global study (23.5%)[4]. It is also higher than the estimate (13%) reported by the WHO in 2011[68]. This may be attributed to the lower standard of living in Nigeria compared to the other regions. It is well documented that poverty and low standard of living are risk factors for TB infection. Furthermore, overcrowding in most of the households in Nigeria encourages the spread of TB[9]. Furthermore, variation in prevalence may be attributed to the differences in monitoring systems and collaboration on TB/HIV control programs across countries and regions[3]. The high prevalence of TB/HIV coinfection in Nigeria can also be ascribed to the high HIV seroprevalence in the country (accounting for the second largest HIV epidemic in the world).

Our pooled TB/HIV coinfection prevalence is congruent with the prevalence in Latin American countries

Table 1. Pooled mean estimates for TB/HIV prevalence among different populations in Nigeria

Population type	Studies, total no.	Samples, total no.	TB/HIV prevalence		Pooled mean TB/HIV prevalence, mean (95% CI)	Heterogeneity		
			Range	Median		I^2 (95 % CI), %	Q	p value
Sex								
Male	21	9206	4.1-62.4	19.4	24.0 (16.5-32.4)	98.6 (98.4-98.7)	1471.8	< 0.001
Female	22	10,752	0.0-84.4	26.0	26.5 (15.9-38.6)	99.4 (99.3-99.5)	3444.9	< 0.001
Mixed	37	24,550	3.5-73.0	25.0	25.9 (20.5-31.7)	98.9 (98.8-99.0)	3351.9	< 0.001
Region								
South-East	14	9923	5.5-73.0	17.9	19.3 (11.0-29.2)	99.2 (99.1-99.3)	1644.0	< 0.001
North-East	1	58	NA	NA	NA	NA	NA	NA
South-West	23	18,176	0.0-60.0	23.8	22.4 (16.2-29.2)	98.9 (98.7-99.1)	2051.9	< 0.001
North-West	6	3098	9.6-49.7	22.6	23.1 (10.8-38.3)	98.7 (98.1-99.1)	379.3	< 0.001
South-South	15	3800	5.9-57.7	23.1	27.7 (18.2-38.3)	97.9 (97.3-98.3)	652.2	< 0.001
North-Central	20	9291	6.1-84.4	36.5	34.3 (26.6-42.4))	98.2 (97.8-98.5)	1053.5	< 0.001
Screening								
TB patients	49	27,344	3.5-84.4	26.8	28.7 (23.9-33.7)	98.7 (98.5-98.8)	3608.0	< 0.001
HIV patients	31	17,164	0.0-61.1	14.4	21.1 (13.6-29.7)	99.4 (99.3-99.4)	4760.8	< 0.001
Setting								
Hospital based	72	42,029	3.2-84.4	23.6	26.9 (22.3-31.7)	99.1 (99.1-99.2)	8267.4	< 0.001
Population based	8	2479	0.0-29.2	16.4	16.7 (10.8-23.7)	93.1 (88.7-95.8)	101.4	< 0.001
Sample size								
≤ 500	55	10,012	0.0-84.4	22.8	27.3 (22.6-32.3)	96.6 (96.1-97.1)	1608.0	< 0.001
> 500	25	34,496	3.2-73.0	23.3	22.5 (15.4-30.4)	99.6 (99.6-99.7)	6571.7	< 0.001
All studies	80	44,508	0.0-84.4	23.2	25.8 (21.6-30.2)	99.1 (99.0-99.1)	8368.8	< 0.001

TB: tuberculosis; NA: not applicable.

Table 2. Univariate and multivariate meta-regression for the prevalence of TB/HIV coinfection

	Meta-regression coefficient (%)	95 CI (%)	p
Univariate meta-regression	1.10	1.01-1.20	0.023
Region	0.77	0.42-1.40	0.381
Setting (population based vs. hospital based)	1.02	0.84-1.26	0.806
Sex	0.69	0.49-0.97	0.035
Screening (HIV from TB vs. TB from HIV)	0.74	0.52-1.06	0.098
Sample size (≤ 500 vs. > 500)	1.02	0.98-1.06	0.412
Year			
Multivariate meta-regression			
Region	58.5	12.35-277.66	< 0.001
Screening (HIV from TB vs. TB from HIV)	3.84	1.75-8.46	0.001
Sample size (≤ 500 vs. > 500)	0.20	0.09-0.46	< 0.001

CI: confidence interval.

(25.1%) but lower than the 31.3% prevalence estimate for Africa[4].

In the subgroup analyses, the coinfection was lowest in the South-East 19.3% (11.0%-29.2%) and highest in the North-Central 34.3% (26.6%-42.4%). Subgroup analysis was not done for the North-East region as only one study was available but the prevalence in this region from the single study was 19.0% (n = 58). This is a loophole that should be filled by future research, and it is even more critical considering the humanitarian

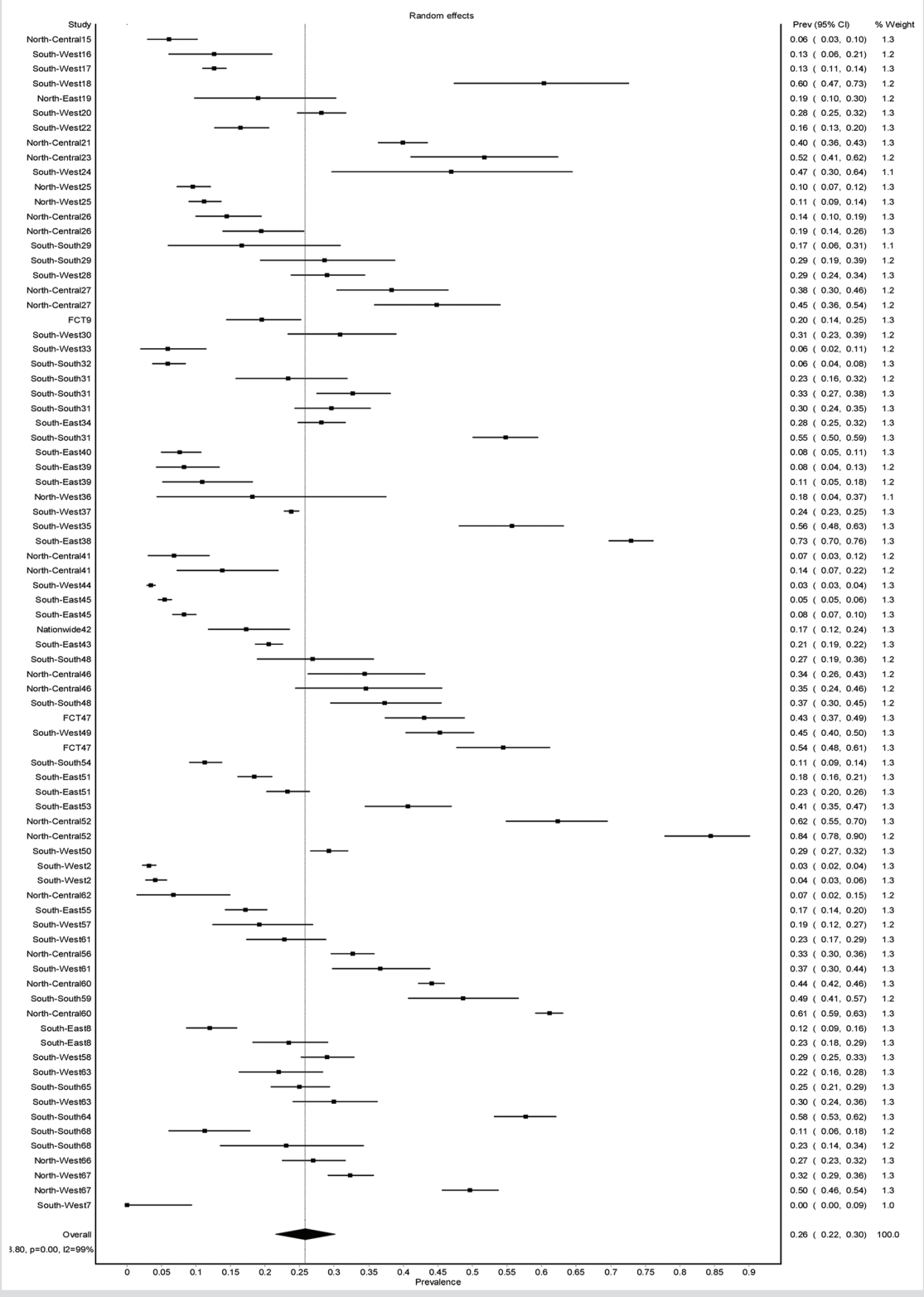

Figure 2. *Forest plot of overall TB-HIV coinfection prevalence.*

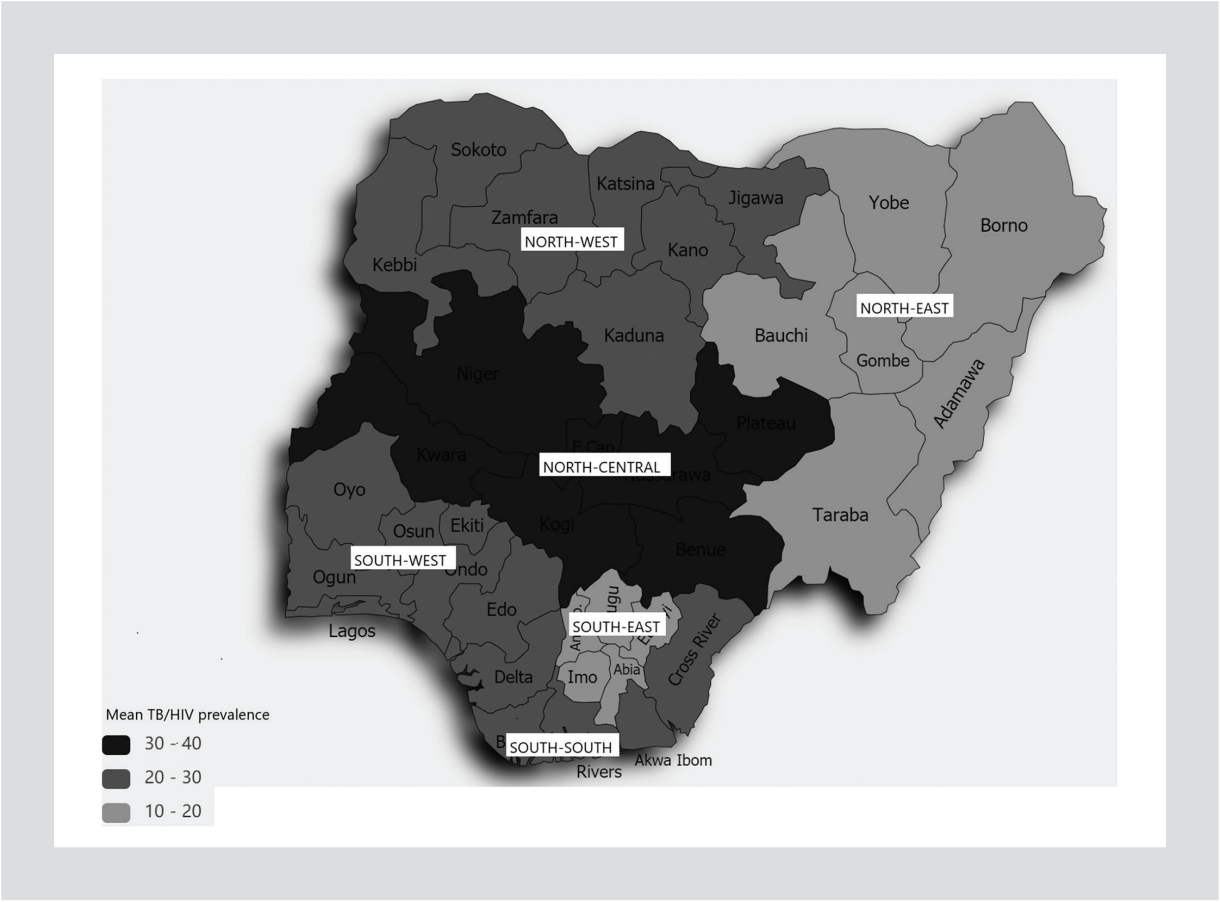

Figure 3. *Map of Nigeria showing the pooled prevalence of TB-HIV coinfection according to region.*

crises currently raging in the region due to activities of insurgence. The incessant attacks by the terrorist groups and constant reprisals and advances by the Nigerian army have led to millions of people being displaced and housed in internally displaced persons camps. This forced displacement camp exposes the displaced people to new hazards, vulnerability, and results in greater risk of TB and HIV monoinfection, on the one hand, and TB/HIV coinfection on the other.

The higher coinfection prevalence in South-South 27.7% (18.2%-38.3%) and North-Central 34.3% (26.6%-42.4%) compared to North-West 23.1% (10.8%-38.3%), South-West 22.4% (16.2%-29.2%), and South-East 19.3% (11.0%-29.2%) is consistent with the HIV seroprevalence pattern in Nigeria reported in a study published in 2018[69]. In their national epidemiological study of Nigeria, 60% of the states with HIV prevalence > 8% were in the South-South and North-Central region. Another explanation that can be put forward for the regional disparities is the urban versus rural residence variation in the different regions, as urban populations have been shown to have higher vulnerability to TB/HIV coinfection compared to rural populations[3].

In the subgroup analysis based on sex, the pooled TB/HIV prevalence was slightly higher in females 26.5% (15.9%-38.6%) compared to males 24.0% (16.5%-32.4%) but the meta-regression analysis did not show any significant variation in the pooled means based on sex (p = 0.806). Furthermore, almost half (46.3%) of the studies did not report sex stratified coinfection prevalence.

Since Nigeria is among the high burden countries for both TB and HIV, the high prevalence of TB/HIV coinfection reported in this review is not completely surprising. However, it is still significantly higher than the coinfection estimate by the WHO (8%) report for 2017[70]. High prevalence of coinfection estimated in this review is a cause of concern considering the emerging risk due to multiple drug-resistant TB cases recorded in Nigeria[6]. Similarly, high coinfection prevalence is alarming considering the efforts made by the Federal Government of Nigeria through the Ministry of Health toward reducing the HIV and TB associated morbidity and mortality.

Hence, there is a need to review policy strategies so as to intensify prevention, early detection, and comprehensive management of cases[5]. This is more so as 90% of the studies included in this meta-analysis were hospital-based screening of HIV, TB, or HIV/TB, with only 10% being population based. If Nigeria is to achieve its National HIV and AIDS Strategic Plan (2017-2021), more efforts should be geared toward contact household screening for both HIV and TB. Increased status awareness and early detection play a key role in early initiation of antiretroviral treatment and significantly increase the success of TB treatment in HIV patients[5].

Furthermore, TB/HIV coinfection is reported to have increased deleterious effects on the patient compared to TB or HIV monoinfection due to accelerated progression of disease[5] and TB is the single most important opportunistic infection in People Living With HIV (PLWHIV)[3].

Limitations of the study

This study is limited by the high heterogeneity observed in the studies (I^2 > 90%) and the meta-regression could only explain < 10% of the between-study heterogeneity. Second, the selection of subjects may have been prone to selection bias due to the specific high-risk behaviors of TB and HIV infections. Furthermore, due to the differences in the design and population of the studies, analysis of the trends of prevalence over the years was not done.

Conclusion

This meta-analysis has shown that the prevalence of TB/HIV coinfection is high in the Nigerian population and requires urgent attention. Constant surveillance through intensive case finding, preventive therapy, and infection control should be carried out by clinicians and concerned institutions. Furthermore, community-based efforts should be integrated with the facility-based efforts and strengthened to mitigate the spread of the double burden infections. Finally, the North-East region should be given special attention due to the ongoing crises as it poses a significant risk of derailing the country's HIV and TB control program.

Supplementary data

Supplementary data are available at AIDS Reviews online (http://www.aidsreviews.com/). These data are provided by the corresponding author and published online for the benefit of the reader. The contents of supplementary data are the sole responsibility of the authors.

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