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Interruption of tuberculosis detection and care during the Ebola virus disease epidemic (2014–2015) in Liberia: time-series analyses for 2013–2017

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ABSTRACT

Objective: Interrupted time-series analyses, using 5 years of routinely collected health information system data, were conducted to estimate the magnitude of impact of the 2014–2015 Ebola virus disease (EVD) epidemic and determine trends in tuberculosis (TB) care services in Liberia.
Methods: A segmented linear regression model was used to generate estimates and predictions for trends for three TB service indicators before, during, and after EVD, from January 2013 to December 2017.
Results: It was found that the number of presumptive TB cases declined significantly at the start of the EVD outbreak, with an estimated loss of 3222 cases (95% confidence interval (CI) −5691 to −752; $P = 0.014$). There was also an estimated loss of 709 cases per quarter post-EVD (95% CI −1346 to −71; $P = 0.032$). However, over the post-EVD period, quarterly increases were observed in the proportion of smear-positive to presumptive cases (1.45%, 95% CI 0.38% to 2.5%; $P = 0.011$) and the proportion of treatment success to TB cases evaluated (3.3%, 95% CI 0.82% to 5.79%; $P = 0.013$).
Conclusions: These findings suggest that the EVD outbreak (2014–2015) negatively affected TB care services. Rigorous quantitative analyses can be used to assess the magnitude of interruption and advocate for preparedness in settings with limited healthcare capacity.

1. Introduction

Tuberculosis (TB) is a major public health problem in Liberia, where the annual incidence (including HIV+TB) is 308/100 000, yet treatment coverage is 54% (38%–84%) (WHO, 2018). Liberia is identified by the World Health Organization (WHO) as a high burden country for TB and HIV-associated TB. The Ebola virus disease (EVD) outbreak from March 2014 to May 2015 in Liberia severely impacted the already fragile healthcare system, leading to disruption of health services in many of the country's 15 counties.

During the outbreak, the establishment of Ebola treatment centers and the consequential re-deployment of healthcare workers to these centers, led to understaffing of routine services. In parallel, population-level intervention measures, such as curfews, border closures, and impaired free movement, made accessing medical services or continuing drug treatments arduous (Parpia et al., 2016). Drug stockouts further impaired consistent and reliable treatment for TB patients. TB treatment in Liberia is focused on facility-based drug administration, especially at the beginning of treatment, where direct observation is performed to maintain strict adherence (Ortuno-Gutierrez et al., 2016). Increased transmission

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and decreased TB patient survival probability were attributed to such factors (Ortuno-Gutierrez et al., 2016).

Several studies have examined the effects of the EVD outbreak on the health system in Liberia. EVD was found to negatively impact service delivery around antenatal care and delivery (Shannon et al., 2017), immunization (Wesseh et al., 2017), malaria diagnosis (Dunbar et al., 2017), HIV testing and care linkage (Jacobs et al., 2017), TB case finding and treatment (Konwloh et al., 2017), and primary healthcare in general (Wagenaar et al., 2018). The majority of these studies used routinely collected data and did not analytically account for issues such as the similarity in consecutive observations, the display of secular trends in data series, and seasonal effects (Bernal et al., 2017; Lagarde, 2012). Moreover, some of these studies covered short post-Ebola periods (Konwloh et al., 2017), or did not consider pre-EVD trends as a counterfactual for evaluating EVD and post-EVD trends. One study (Wagenaar et al., 2018) with a more robust analysis of 10 primary health care indicators did not examine the impact of EVD on TB care services and did not cover the entire country.

Recognizing the added value of a more rigorous time-series analysis, an interrupted time-series analysis was conducted to robustly estimate the direct impact of the EVD outbreak (2014–2015) on TB care services in Liberia and reveal trends over a 5-year study period, using routinely collected national TB data.

2. Methods

2.1. Ethics

Ethical approval for this study was obtained from the Pacific Institute for Research and Evaluation (UL-PIRE) (Monrovia, Liberia) of the University of Liberia and the Ethics Board of the London School of Hygiene and Tropical Medicine (London, UK; reference 15637). As this study only used anonymous aggregate data, informed patient consent was not required. The Ministry of Health (MOH) additionally approved the use of the data.

2.2. Study design

As a retrospective secondary analysis of routinely collected aggregate health information system data, the study involved an interrupted time-series (ITS) analysis where the 'interruption' was defined as the EVD (2014–2015) outbreak.

2.3. Study population

All presumptive and confirmed TB cases were recorded nationally and reported centrally to the MOH, Republic of Liberia. These included patients who were examined and treated from January 1, 2013, through December 31, 2017. As per WHO definitions, a presumptive case refers to a patient who presents with symptoms or signs suggestive of TB.

2.4. Data source and variables

Data were abstracted from the headquarters of the MOH into a Microsoft Excel spreadsheet (Microsoft Corporate Headquarters, Redmond, WA, USA). The data collected for TB care services contained aggregated data for the following variables on a quarterly basis: the quarter of the year; number of presumptive TB patients assessed; the sputum smear result; the frequency of patients for whom a smear was not done; the anatomical distinction of TB stratified by age (0–4 years, 5–14 years, and ≥15 years); the result of complementary HIV testing, the frequency of patients started on co-trimoxazole preventive therapy (CPT) and antiretroviral therapy (ART); and the treatment outcomes (cured, complete, defaulted, failed, died) of patients with both new and relapse smear-positive TB (Konwloh et al., 2017). This study evaluated three outcome variables: (1) presumptive TB (proxy measure of functioning health centers), measuring the number of patients who presented at a health facility with symptoms or signs suggestive of TB per quarter; (2) the proportion of smear-positive cases to presumptive cases (a measure of the case detection effort at the health facility), i.e. the percentage of smear-positive cases (investigated by smear microscopy) diagnosed out of presumptive cases assessed per quarter; (3) the proportion of treatment success to TB cases evaluated for bacteriological evidence of cure (measure of the program's capacity to retain patients on a full course of treatment), i.e. the percentage of treatment success out of the total number of TB cases evaluated per quarter. Smear-negative TB and extrapulmonary TB cases for which treatment was finished were classified as treatment completed (Ortuno-Gutierrez et al., 2016).

2.5. Time

The three outcomes were evaluated over three time periods. The first was the pre-EVD epidemic period, before the EVD outbreak, which comprised 15 months (January 1, 2013 to March 31, 2014). As EVD was first diagnosed in Liberia on March 30, 2014 (World Health Organization. Media Centre: WHO Statement. Geneva: World Health Organization; 9 May 2015), the pre-EVD period included the month of March 2014. Also, TB data are aggregated quarterly. The second was the EVD epidemic period. This covered a period of 15 months (April 1, 2014 to June 30, 2015) starting from the beginning of the first major EVD outbreak, which began March 30, 2014, officially, through May 9, 2015, when Liberia was first declared Ebola-free. The third was the post-EVD epidemic period, covering 30 months (July 1, 2015 to December 31, 2017), from the end of the first and most significant outbreak (ending May 9, 2015) through December 31, 2017. Liberia subsequently experienced 12 cases (clusters of 6, 3, 3) and was last declared Ebola-free on June 9, 2016 (WHO, 2016). As these subsequent cases were few and localized, they did not disrupt health services across the country; hence, these clusters were considered in the post-EVD period.

2.6. Data analysis

The abstracted Microsoft Excel dataset was imported into Stata 15 IC (StataCorp, College Station, TX, USA) for cleaning and analysis. The dataset was set as time-series data and explored for missing observations. One missing value for registered TB cases was discovered in the dataset. As data are aggregated quarterly, attempts to recover the missing value from the data source proved futile. For this reason, only complete quarterly records were used in the analyses. Descriptive analyses were done, which included summary statistics of the three key indicators by periods and quarters, and two-way plots of TB services indicators and EVD cases over time. The Pearson Chi-square test for independence, or Fisher's exact test in the case of small counts (<5), was run to test for associations between period and yearly quarters. With no significant association between the periods and quarters per year, a parametric segmented linear regression model was used to generate mean estimates, control for secular trends, and adjust for potential serial correlation of the data (Lagarde, 2012; Linden, 2015; Wagner et al., 2002). To adjust for autocorrelation in the data, a Prais–Winsten estimation, autoregressive (AR) model was fitted to the model, for a multiple period interrupted time-series analysis with the pre-EVD period used as a control group to explore counterfactual scenarios of no change during the EVD and post-EVD pe-

Table 1
Time series indicating the three time periods and the three outcome variables and Ebola virus disease (EVD) cases, 2014–2016

Yearly quarters	Time (*T*)	Period (*X*)	Presumptive TB cases (*Yt*)	Proportion of smear-positives/presumptive cases (*Yt*)	Proportion of treatment success/ cases evaluated (*Yt*)	EVD cases[a]
01/01/2013	1	0	5436	16.98	74.61	
01/04/2013	2	0	6765	10.66	82.12	
01/07/2013	3	0	9876	10.52	75.25	
01/10/2013	4	0	5432	15.67	88.18	
01/01/2014	5	0	7650	9.69	74.49	8
01/04/2014	6	1	5651	12.32	69.62	43
01/07/2014	7	1	4307	12.98	73.27	3407
01/10/2014	8	1	5890	7.15	66.75	4560
01/01/2015	9	1	6989	10.40	67.02	1694
01/04/2015	10	1	7898	10.08	64.05	954
01/07/2015	11	2	6810	8.21	73.49	6
01/10/2015	12	2	6780	8.51	71.06	3
01/01/2016	13	2	9876	8.04	86.60	0
01/04/2016	14	2	5432	12.15	88.62	3
01/07/2016	15	2	7650	9.35	85.63	
01/10/2016	16	2	6652	11.24	84.90	
01/01/2017	17	2	5307	16.32	85.79	
01/04/2017	18	2	7890	10.08	78.42	
01/07/2017	19	2	6989	9.72	89.98	
01/10/2017	20	2	7898	11.29	86.12	

[a] Source: https://www.cdc.gov/vhf/ebola/history/2014-2016-outbreak/case-counts.html (WHO Situation Reports). These EVD cases include all suspected, probable, and confirmed cases for Liberia from 2014 to 2016 aggregated quarterly. *X* is a dummy variable: 0, pre-EVD period; 1, EVD period; 2, post-EVD period. *T* is the unit time. *Yt* is an indicator variable.

riods (Linden, 2015). The following model equation was applied:

$$Yt = \beta_o + \beta_{pe}T_t + \beta_e X + \beta_e XT_t + \beta_{poe}X + \beta_{poe}XT_t + \varepsilon t,$$

where *Yt* is the outcome variable measured at each equally spaced time point (*t*); β_n represents the intercept, the starting level of the outcome variable; *X* indicates a dummy variable for the three time-periods (pre-EVD, EVD, and post-EVD); *Tt* is the time since the start of the study; $\beta peTt$ represents the pre-EVD period slope; βeX represents a change in the level of outcome that begins at the start of the EVD period; $\beta eXTt$ represents the slope of the EVD period; $\beta poeX$ represents the change in the level of the outcome at the start of the post-EVD period; $\beta poeXT$ represents the slope of the post-EVD period; εt is a random error term for a variation. Model coefficients were used to generate mean estimates and trends, and the magnitude of impact was calculated as a difference of model predictions and actual quarterly data. A linear posttrend model table was included for each outcome indicator to demonstrate trends after the pre-EVD and EVD periods. Statistical significance was set at $P < 0.05$.

3. Results

Data analyzed over the 5 years generated 20 time-points with a total number of 10 678 suspected, probable, and confirmed cases of Ebola registered from 2014 to 2016 (Table 1).

3.1. Presumptive cases

As shown in Figure 1, the maximum number of presumptive cases ($n = 9876$) occurred in the pre- and post-EVD periods, with the minimum number of presumptive cases coinciding with the peak periods of the EVD outbreak. By the regression model, at the beginning of the pre-EVD period, the estimated number of presumptive cases was 6651, with a quarterly increase of 249 cases (95% confidence interval (CI) −382 to 881; $P = 0.412$). However, at the beginning of the EVD outbreak, there appeared to be a marked decline in the number of presumptive cases presenting to health centers by 3222 (95% CI −5691 to −752; $P = 0.014$). This decline was followed by a gradual increase in presumptive cases by 411 per quarter (95% CI −461 to 1236; $P = 0.329$) in the EVD period. At the beginning of the post-EVD period, there was an increase in the number of presumptive cases, followed by a significant decreasing trend of 709 presumptive cases (95% CI −1345 to −71; $P = 0.032$) per quarter over the post-EVD period, when compared to the EVD period, as shown in Table 2a. On further evidence, separate posttrend estimates for the EVD period showed a significant increasing trend over time of 660 presumptive cases (95% CI 24 to 1296; $P = 0.042$) per quarter in the period (Table 2b). Also, the post-EVD trend estimates showed a declining trend in the number of presumptive cases per quarter when compared to the EVD period. The impact of EVD can be seen in Figure 2, and the magnitude of impact quantified during the EVD and post-EVD periods is reported in **Supplementary Material** Table S1.

3.2. The proportion of smear-positive cases to presumptive cases

The lowest proportion (7.5%) of smear-positive to presumptive cases occurred at the peak of the EVD outbreak, while the highest proportion (16.9%) was seen at the beginning of the pre-EVD period (Figure 3). The regression model estimated the proportion of smear-positive to presumptive cases at the beginning of the pre-EVD period to be 14% (Table 2a). A decline of 0.68% was estimated per quarter over the pre-EVD period. At the beginning of the EVD period, there was an increase in the detection of smear-positive cases of 1.78% (95% CI −3.61% to 7.18%; $P = 0.490$) per quarter. This was followed by a similar decreasing trend in the proportion of smear-positives to presumptive cases in the EVD period, when compared to pre-EVD trends. However, this trend was reversed with a significant increase in the proportion of smear-positives to presumptive cases over the post-EVD period at 1.45% per quarter (95% CI 0.38% to 2.5%; $P = 0.011$) when compared to the EVD period. Figure 4 shows the trends in the proportion of smear-positive/presumptive cases. Evidence of this significance is further demonstrated in the separate post-EVD trend table (Table 2b) (the difference in post-EVD coefficient of 0.30 and EVD coefficient of −1.15 is 1.45%, as shown in the main results; Table 2a). Also, the impact of EVD on case detection is quantified in **Supplementary Material** Table S2.

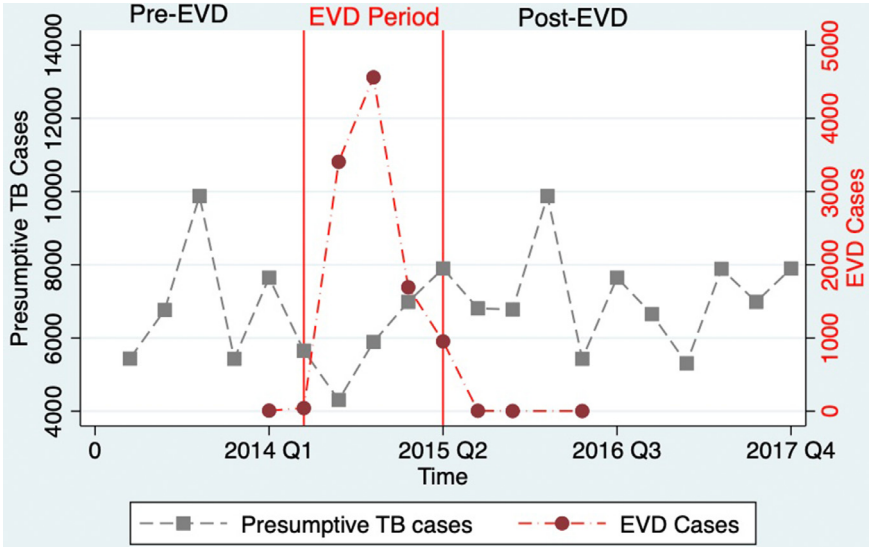

Figure 1. Two-way plot of presumptive cases and Ebola virus disease (EVD) cases over time (in yearly quarters).
EVD period, denoted with vertical red lines, begins April 1, 2014 and ends June 30, 2015.

Table 2a
Model regression AR(1) analysis of presumptive cases, proportion of smear-positive/presumptive cases, and proportion of treatment success/cases evaluated over the three time periods

Time	Presumptive TB cases Coefficient (95% CI)	*P*-value	Proportion of smear-positive/ presumptive cases Coefficient (95% CI)	*P*-value	Proportion of treatment success/ cases evaluated Coefficient (95% CI)	*P*-value
Secular trend ($\beta_{pe}T_t$)	249.14 (−382.41, 880.68)	0.412	−0.68 (−2.10, 0.73)	0.318	0.61 (−3.03, 4.25)	0.724
Level change (β_eX)	−3222.1 (−5691.73, −752.47)	0.014*	1.78 (−3.61, 7.18)	0.490	−9.60 (−25.56, 6.36)	0.218
Change in trend (β_eXT_t)	410.96 (−461.12, 1283.03)	0.329	−0.47 (−2.04, 1.10)	0.532	−2.19 (−6.12, 1.74)	0.251
Level change (β_eX)	94.64 (−1818.99, 2008.27)	0.917	1.22 (−2.20, 4.64)	0.458	7.79 (−1.06, 16.65)	0.080
Change in trend ($\beta_{poe}XT_t$)	−708.57 (−1345.93, −71.19)	0.032*	1.45 (0.39, 2.52)	0.011*	3.31 (0.83, 5.80)	0.013*
β_n (Constant)	6651.48 (4647.55, 8655.41)	<0.001	13.99 (9.98, 17.99)	<0.001	77.82 (71.30, 84.34)	<0.001

CI, confidence interval; TB, tuberculosis. *P-value <0.05.

Table 2b
Posttrend, presumptive cases, the proportion of smear-positive/presumptive cases, and the proportion of treatment success/cases evaluated

Period	Presumptive TB cases Coefficient (95% CI)	*P*-value	Proportion of smear-positive/ presumptive cases Coefficient (95% CI)	*P*-value	Proportion of treatment success/ cases evaluated Coefficient (95% CI)	*P*-value
EVD	660.10 (24.31, 1295.87)	0.042*	−1.15 (−2.17, −0.14)	0.02*	−1.58 (−3.60, 0.44)	0.115
Post-EVD	−48.48 (−214.62, 117.67)	0.5415	0.30 (−0.05, 0.65)	0.09	1.73 (0.47, 3.00)	0.010*

CI, confidence interval; EVD, Ebola virus disease; TB, tuberculosis. *P-value <0.05.

3.3. The proportion of treatment success to TB cases evaluated

The highest proportion (90%) of treatment success to TB cases evaluated occurred in the post-EVD period, whereas the lowest proportion (64%) of successful treatment occurred within the terminal stages of the EVD outbreak (Figure 5). The proportion of treatment success to cases evaluated as estimated by the regression model was 78% at the beginning of the pre-EVD period. The quarterly increase in the proportion of treatment success/TB cases evaluated before the start of the EVD period was less than 1%. At the start of the EVD period, the direction of the trend reversed and a decreasing trend in proportion continued, with a 2.2% (95% CI −6.1 to 1.7%; $P = 0.25$) decline per quarter in the EVD period. In contrast, the post-EVD period was notable for an increasing trend in the proportion of treatment success to TB cases evaluated. There was a 3.3% (95% CI 0.83% to 5.79%; $P = 0.013$) increase in the proportion of treatment success to TB cases evaluated over the entire post-EVD period. Figure 6 shows the changes in trends over the three periods. Separate post-EVD predictions further demonstrated this increasing trend in the post-EVD period when compared to the EVD period, with a difference in coefficients of 3.3%, as reported in Table 2a. See **Supplementary Material** Table S3 for the magnitude of impact of EVD on the proportion of treatment success to cases evaluated.

4. Discussion

This study provides a robust analysis of the impact of the EVD epidemic on three TB care service outcomes using routine health information system (RHIS) data, with an interrupted time-

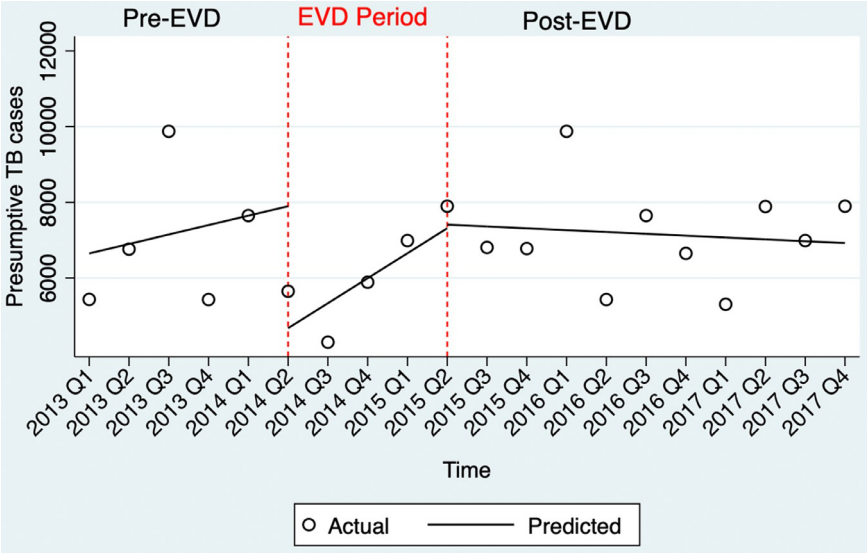

Figure 2. Interrupted time-series graph generated from an AR(1) linear segmented regression model, adjusting for autocorrelation, showing level and slope changes across the Ebola virus disease (EVD) and post-EVD periods for presumptive cases.
EVD period, denoted with vertical dashed red lines, begins April 1, 2014 and ends June 30, 2015. The pre-EVD period begins January 1, 2013 and ends March 31, 2014; the post-EVD period begins July 1, 2015 and ends December 31, 2017. The black lines are estimates generated from AR(1) model regression.

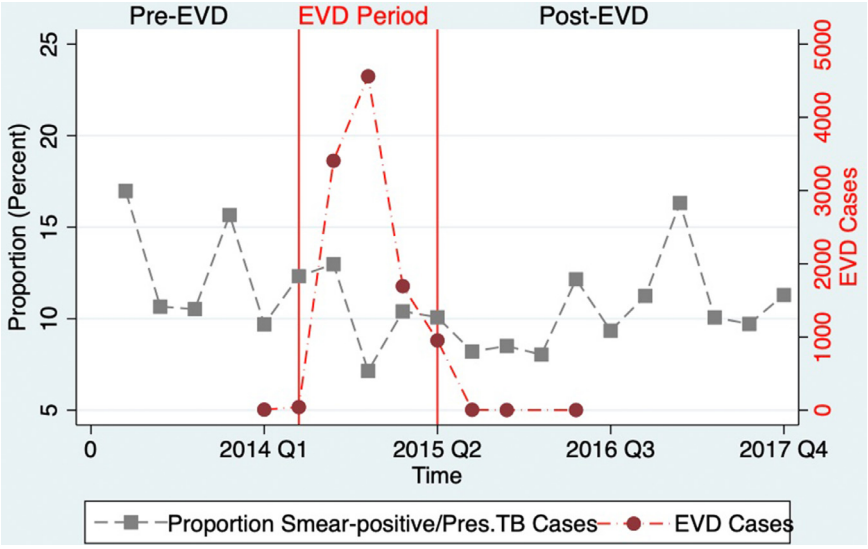

Figure 3. Two-way plot of the proportion of smear-positives/presumptive cases and Ebola virus disease (EVD) cases over time (in quarters).
EVD period, denoted with vertical red lines, begins April 1, 2014 and ends June 30, 2015.

series analysis. Previous studies have suggested that presumptive TB cases declined in the EVD period but increased in the post-EVD period (Desta et al., 2019; Konwloh et al., 2017). One study reported a significant decline in case detection in the EVD and post-EVD periods (Konwloh et al., 2017), and treatment success was significantly reduced during the EVD epidemic with improvement post-EVD. In the present study, it was found that the number of presumptive cases dropped significantly at the beginning of the EVD outbreak. Whilst there was some recovery during the EVD period, in the post-EVD period there was a trend of further decline, reversing a trend to increased presumptive cases in the pre-EVD period, in contrast to previous reports (Konwloh et al., 2017). It was also found that the proportion of smear-positives to presumptive cases had been in decline before the EVD outbreak and that this trend continued but more sharply through the EVD period. Contrary to previous findings (Konwloh et al., 2017), it was found that there was a significant increase in the proportion of smear-positive to presumptive cases in the post-EVD period. Finally, the model showed that in contrast to trends in the pre-and post-EVD periods, the proportion of treatment success to TB cases evaluated declined throughout the EVD period. Together these results show that the EVD epidemic likely impeded TB care services in Liberia, by reducing the number of patients presenting for assessment, increasing the number of late presentations, and reducing the likelihood of treatment success during the EVD period.

The number of presumptive cases declined by nearly one-fifth at the beginning of the EVD outbreak. This decline was consistent with previous studies in Liberia (Desta et al., 2019; Konwloh et al., 2017) and Sierra Leone (Bah et al., 2017) that compared annual aggregates and monthly means, respectively. Rather than being identified as presumptive TB cases, patients may instead have been triaged as suspected EVD cases and promptly isolated due to similarities in presentation to EVD, with symptoms such as fever and hemoptysis. Further, the fear of contracting EVD from a health fa-

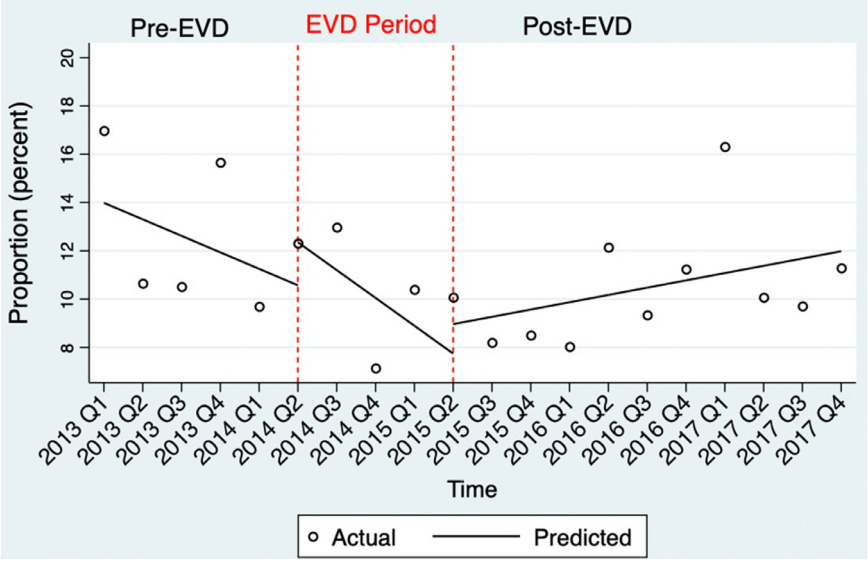

Figure 4. Interrupted time-series graph generated from an AR(1) linear segmented regression model, adjusting for autocorrelation, showing level and slope changes across the Ebola virus disease (EVD) and post-EVD periods for the proportion of smear-positives/presumptive cases.
EVD period, denoted with vertical dashed red lines, begins April 1, 2014 and ends June 30, 2015. The pre-EVD period begins January 1, 2013 and ends March 31, 2014; the post-EVD period begins July 1, 2015 and ends December 31, 2017. The black lines are estimates generated from AR(1) model regression.

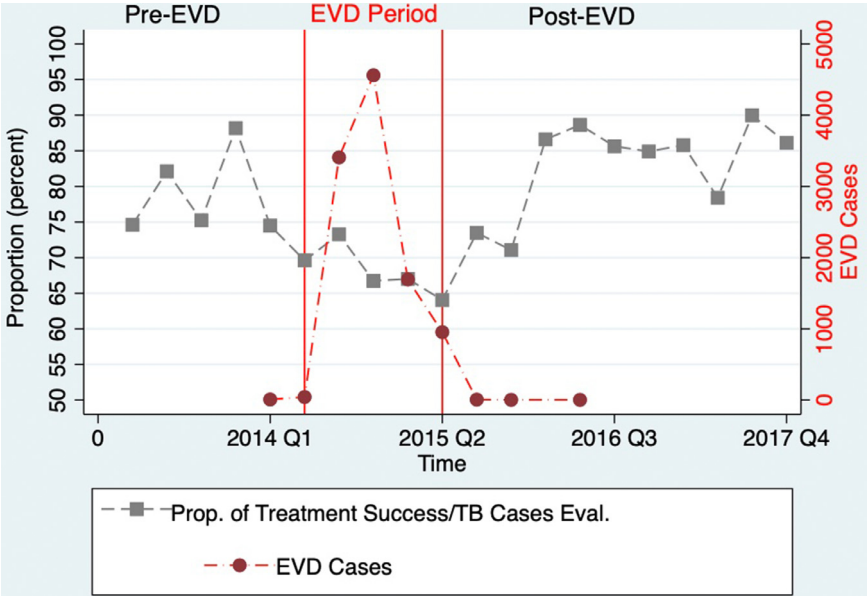

Figure 5. Two-way plot of the proportion of treatment success/tuberculosis (TB) cases evaluated and Ebola virus disease (EVD) cases over time (in quarters).
EVD period, denoted with vertical red lines, begins April 1, 2014 and ends June 30, 2015.

cility and the closure of health facilities due to health worker infections, the lack of personal protective equipment (PPE), and the lack of isolation facilities may have prevented care-seeking. This decline, however, did not persist throughout the EVD period. This change may have been due to several factors. By October 2014, Liberia's diagnostic capacity for EVD had improved (Raftery et al., 2018), thus allowing patients to access care after being screened for EVD. Also, by the end of 2014, the epidemic was restricted to several hot spots around the country, allowing less affected areas to resume full essential health services. It is important to note the decline in presumptive cases over the post-EVD period, reversing the pre-EVD trend. This highlights the potential lingering impact of EVD on the country's healthcare delivery system. The explanation for this trend is not clear; however it highlights the challenge the national TB program still faces in effectively reducing the burden of TB in Liberia.

This study demonstrated a decline in the proportion of smear-positive to presumptive cases from the pre-EVD period, and a similar decline during the EVD period compared to previous studies (Desta et al., 2019; Konwloh et al., 2017; Ortuno-Gutierrez et al., 2016). A lower proportion of smear-positive to presumptive cases may indicate a decline in samples submitted for testing, a decline in laboratory capability, or an increase in patients presenting with TB symptoms, whether or not they really have TB. It seems more likely to be one of the former explanations. A reduction in the number of sputa collected for case ascertainment may be due to a moratorium on invasive procedures and handling of bodily fluids during the peak of the epidemic. Another reason may be a 'no

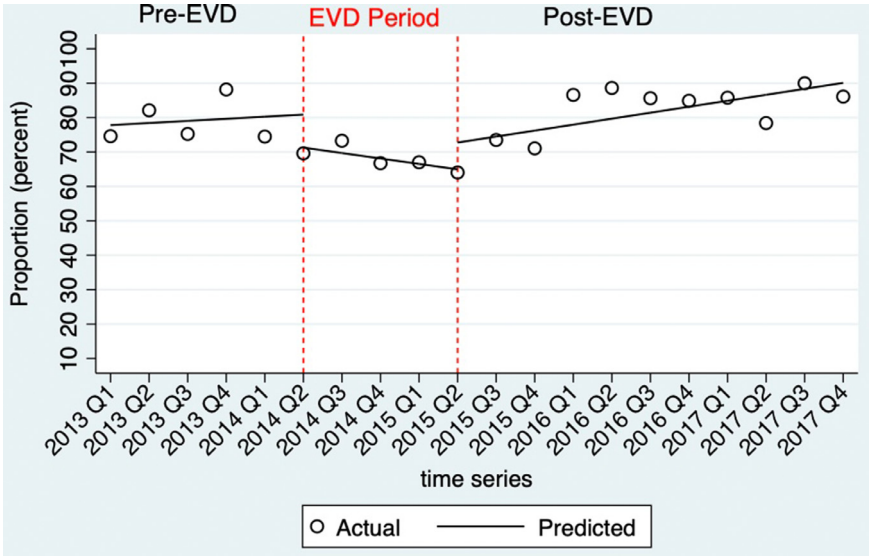

Figure 6. Interrupted time-series graph generated from an AR(1) linear segmented regression model, adjusting for autocorrelation, showing level and slope changes across the Ebola virus disease (EVD) and post-EVD periods for the proportion of treatment success/tuberculosis (TB) cases evaluated.
EVD period, denoted with vertical dashed red lines, begins April 1, 2014 and ends June 30, 2015. The pre-EVD period begins January 1, 2013 and ends March 31, 2014; the post-EVD period begins July 1, 2015 and ends December 31, 2017. The black lines are estimates generated from AR(1) model regression.

touch' policy that was being carried out. This policy may have resulted in more patients being treated presumptively and recorded as smear-not-done pulmonary cases. However, the proportion of smear-positives to presumptive cases increased significantly following the start of the post-EVD period. This increase in proportion may be the direct result of an increase in late presentations with smear-positive disease or due to an increase in the actual number of smear-positive cases remaining constant while presumptive cases declined. Facility-level data are needed to ascertain this further.

In alignment with previous findings (Desta et al., 2019; Konwloh et al., 2017), the present study found that the EVD outbreak adversely impacted treatment outcomes, i.e., the proportion of treatment success to cases evaluated. As TB cases are generally evaluated towards the end of treatment, the impact of an interruption in treatment was profound in the latter part of the EVD outbreak. This was likely the consequence of a higher loss-to-follow-up due to the temporary closures of health facilities in response to an escalating EVD epidemic. Drug stockouts and the stigmatization of health centers and health workers may have likewise contributed. Moreover, deaths from EVD may also have contributed to attrition. Evidence has shown that EVD transmission was high in impoverished communities, which is where TB in Liberia is most prevalent (Fallah et al., 2015).

Despite the challenges for retention in care, it is notable that the post-EVD period saw a trend of increasing proportions of treatment success to TB cases evaluated. These improvements may have been due to community mobilization to encourage treatment-seeking behavior, the influx of resources to bolster the health system, and a move towards early treatment initiation in HIV-co-infected patients. Overall, it is encouraging to see that the decline in proportions of patients achieving treatment success found during the EVD period was not sustained post-EVD. This may reflect to some extent health service recovery. Investigations into how a more sustained impact of such interventions could have been attained could be instrumental in reducing the impact of an epidemic response on routine health services going forward.

The strengths of this study include the use of an interrupted time-series to analyze national TB data over 5 years using national program indicators and time trends to accurately estimate the magnitude of the EVD outbreak on TB care services. This strong quasi-experimental design provides a robust method of measuring the effect of an intervention without a control group or randomization (Bernal et al., 2017; Lagarde, 2012). Using the Student *t*-test to compare means for time-series data has become limited and may lead to a biased result (Box and Tiao, 1975; Lagarde, 2012). Additionally, the study used 5 years of routine TB data that were collected from both public and private facilities across the country and aggregated across multiple administrative levels. Five years of routine data increases the accuracy of the estimation of trends over the three time periods and the predictions generated to estimate the impact of EVD on various TB care services outcomes, improving generalizability. Previous studies (Dunbar et al., 2017; Jacobs et al., 2017; Konwloh et al., 2017; Shannon et al., 2017; Wesseh et al., 2017) in Liberia investigating the effects of EVD on various health programs using routine health data and shorter periods did not account for temporal trends or autocorrelation commonly found in routinely collected data.

Notwithstanding, this study has several limitations. First, routinely collected data are not always reliable and lack consistent quality. Health system disruption may have affected data recording and collection, as limited resources were shifted towards stopping the epidemic. Also, new tools that have been in use, such as GeneXpert, culture, and drug susceptibility testing (DST), were not reflected in the DHIS2 database, such that data did not capture cases detected with these tools. Second, with this design, it is challenging to infer direct causality because concomitant unrelated activities may be responsible directly or indirectly for changes in TB care services (Lagarde, 2012). Third, this study used an overlapping outcome variable (presumptive TB cases) that could have influenced the results of the proportion of smear-positive to presumptive cases. Fourth, a power calculation methodology for time-series data has not been formally developed, especially for studies using routine data (Bhaskaran et al., 2013). Due to the retrospective nature of the study and despite the use of all available case data during the periods of interest, the study may lack the power to detect small changes in trends or trends over a shorter period, and estimates of the impact will have to be interpreted with caution.

In conclusion, this study adds quantitative insights into the magnitude of the impact that the EVD epidemic (2014–2015) had on the delivery of TB care services. A stringent estimation of the detrimental impact of the Liberian EVD outbreak on national TB services and the trends in the recovery period are provided, suggesting an overall reduction in case detection. Even with the health system returning to normalcy, a significant decline in presumptive cases and increase in the proportion of smear-positives in the post-EVD period is concerning. Much still needs to be done to improve health system resilience against unprecedented pandemics, like EVD and COVID-19, in order to reduce the collateral damage of future epidemics, particularly important for addressing the 'long tail' of impact after such health emergencies, to meet global 'End TB' targets.

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Declarations

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Ethical approval: Ethical approval for this study was obtained from the Pacific Institute for Research and Evaluation (UL-PIRE) of the University of Liberia (Monrovia, Liberia) (protocol # 18-05-06) and the Ethics Board of the London School of Hygiene and Tropical Medicine (London, UK) (reference 15637). As this study only used anonymous aggregate data, informed patient consent was not required. The Ministry of Health additionally approved the use of the data.

Conflict of interest: The authors have declared that no conflicts of interest exist.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2021.08.041.

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