

## **The challenge of estimating tuberculosis mortality accurately in England and Wales**

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## SUMMARY

### Background

Accurate estimates of TB mortality are required to monitor progress towards the WHO END TB goal of reducing TB deaths by 95% by 2035. We compared TB death data for England and Wales from the national surveillance system (ETS) and the vital registration system from the Office for National Statistics (ONS).

### Methods

TB cases notified in ETS were matched to deaths in ONS with ICD-10 codes indicating TB caused/contributed to the death (A15-A19). Deaths captured in one but not both systems were assessed to identify if ONS captured all TB deaths and if there is under-notification of TB in ETS. We stratified deaths into: active TB, TB sequelae, incidental deaths and not TB.

### Results

There were fewer deaths in ETS (4,207) than ONS with ICD-10 codes A15-A19 (6,560) between 2005 and 2015. 57% of ETS were recorded as ONS and 53% of ONS were notified to ETS. 9,289 deaths were identified in total from ETS and ONS; 64% were active TB, 23% were TB sequelae, 6% were incidental and 7% were not TB.

### Conclusions

TB deaths in ETS and ONS differ substantially. Almost one third of TB deaths recorded by ONS are not due to active TB, amendable through coding changes.

## INTRODUCTION

An estimated 1.8 million people died from TB in 2015, making TB one of the leading causes of death globally.<sup>1</sup> The ambitious WHO END TB target is a 95% reduction in the number of deaths **from active TB** between 2015 and 2035.<sup>2</sup> It is methodologically challenging to estimate TB mortality at a population level. Estimates have been calculated using multiple data sources of varying quality including mortality surveys, national or sample vital registration (VR) systems, verbal autopsy, ecological modelling or indirectly by calculating the case fatality rate (CFR). The advantages and disadvantages of different data sources and subsequent estimation errors in tuberculosis mortality have been described.<sup>3,4</sup> There has been a concerted effort to invest in strengthening VR systems, particularly in high burden TB countries, many of which do not collect accurate country-wide mortality data.<sup>1,5</sup> Treatment outcomes including death from all causes are also collected through TB surveillance. In the absence of reliable VR data from all countries, the CFR will be used to monitor progress towards the mortality END TB goal.<sup>1</sup>

The UK Office for National Statistics (ONS) compiles mortality statistics using the VR system, collected from death certificates, where the causes of death are assigned ICD-10 codes. TB mortality data in England and Wales have been collected and analysed since 1901.<sup>6</sup> The automated coding system IRIS has been used since 2014 to assign ICD-10 codes from text on death certificates and determine the underlying cause of death.<sup>7,8</sup> ICD-10 codes for TB include active TB (A15-A19) and sequelae of TB (B908-B909).<sup>9</sup> The UK and global WHO TB mortality estimates use data from the ONS VR system. In addition to data collected in the VR system, TB outcomes at defined times (12,24,36 months) including death, are recorded for notified TB cases within the web-based Enhanced Tuberculosis Surveillance system (ETS) and are reported in the TB Annual Report.<sup>10</sup>

An accurate estimate of mortality enables us to understand the burden and cost of TB in England and Wales and informs TB control strategies to reduce mortality. We matched the data from the two systems to help determine how best to use the available data to estimate TB mortality in England and Wales.

## STUDY POPULATION AND METHODS

We matched TB cases notified to ETS between 2000 and 2015 in England and Wales to TB deaths from ONS reported between 2005 and 2015 (see supplementary methods for statutory requirements for notifying TB or reporting deaths and matching methods used). ETS cases notified between 2000 and 2005 were included in the matching as TB deaths may occur several years after notification and the time between active TB and death were used to identify deaths due **to** active TB or TB sequelae.

### *Data from Notification system ETS*

We included demographic (sex, age, country of birth), clinical (notification date, site of disease), microbiological (smear and culture results) and treatment outcomes including dates. We included data on the relationship between TB and death as recorded by case managers (caused, contributed, incidental).

### ***TB death data from ONS***

We included deaths recorded in the VR system at ONS that occurred between 2005 and 2015, where TB caused/contributed to death. ONS had ICD-10 codes A15-A19 assigned at ONS using text from death certificates. We included date of death, text from death certificate, ICD-10 codes, and relationship between TB and death (caused/contributed). In addition, ONS with ICD-10 codes B90\* (sequelae of TB) were included at an aggregate level, as individual level data were not available (see supplementary methods for definition of sequelae of TB).

### ***Deaths reported in ETS***

As outcomes for TB cases are collected up to 12 months after notification, the most recent year of notification with complete outcomes was 2014. To report on the number of deaths by year, we included cases notified between 2005 and 2014 to capture cases that had died by the end of 2015. Deaths reported in ETS between 2005 and 2015 were identified in ONS to assess if ONS captured all notified TB deaths. ETS were stratified into those that were not ONS, ONS where TB caused death (according to ONS) and ONS where TB contributed. We compared the relationship between TB and death recorded in ETS and ONS.

### ***Deaths reported in ONS***

ONS with ICD-10 codes A15-A19 were identified in ETS data to assess if all deaths where TB caused/contributed had been notified between 2000 and 2015. ONS were stratified into: active TB, TB sequelae and those who did not have TB using the following data: denotification information, outcomes, timing of notification, treatment and death from ETS, and text from death certificates used to assign ICD-10 codes (see supplementary materials for details).

### ***Statistical analysis***

To identify factors associated with ETS not in ONS, we conducted univariable **logistic regression analysis** to compare demographic, clinical and microbiological characteristics of deaths reported to ETS only with those in both systems. We also identified factors associated with ONS who were not notified to ETS, comparing demographic characteristics in deaths only in ONS and those in both systems. We conducted multivariable logistic regression including all factors from the univariable analyses to calculate adjusted odds ratios (aORs). Analysis was conducted using Stata 13.1.

### ***Ethics statement***

Public Health England has authority under the Health and Social Care Act 2012 to hold and analyse national surveillance data for public health and research purposes.

## **RESULTS**

### ***Death as outcome in notified TB cases (ETS)***

Between 2005 and 2014, a total of 78,243 TB cases were notified and not subsequently denotified in ETS. Of these, 5.4% (4,207) were ETS from all causes. The number and proportion of ETS decreased from 470 in 2005 (6.0%) to 364 in 2014 (5.5%) (**Figure 1A**). The relationship between TB and death was known in 53.2% (2,238) of deaths; **in those with known relationship**, TB caused death in 17.6% (395), contributed in 41.5% (929), and was incidental in 40.8% (914) (**Figure 2**).

### ***TB deaths reported by ONS***

There were a higher number of ONS reported (2005: 654, 2014: 587) with a similar decrease observed over time (**Figure 1B**). TB was recorded as the underlying cause of death in 52% (3,389/6,560) of ONS.

### ***ETS as TB deaths in ONS***

Of the 4,207 notified TB cases that were reported to have died from all causes at the last known outcome (ETS), 56.8% (2,389) matched to ONS (**Figure 2**). Of the deaths where TB caused/contributed, 76% (1,006/1,324) matched to ONS. For cases where TB caused/contributed to the death in ETS that were matched to ONS, the relationship between TB and death was often different in ETS and ONS; 11.1% (36/323) of deaths where TB caused the death in ETS had TB contributing in ONS and 60.5% (413/683) of deaths where TB contributed in ETS had TB as the cause of death in ONS. For those deaths in ETS where TB was reported as incidental to the death, a **notable** proportion had TB caused (17.2%, 157/914) or TB contributed (25.5%, 233/914) in ONS. For deaths where the relationship was not reported on ETS, over half matched to ONS (50.4%, 993/1,969).

### ***ONS notified in ETS***

53.2% (3,487/6,560) of ONS from 2005 to 2015 coded A15-A19 where TB caused/contributed to the death were notified to ETS between 2000 and 2015 (**Figure 3**). Ten percent (664) of ONS were identified as not having TB; 220 of the matched cases had been denotified in ETS as they didn't have TB, and 412 had text that indicated they did not have active TB (non-tuberculous mycobacteria, latent tuberculosis, BCGosis, spinal/sacral/psoas abscess

without TB, or lung cavities without TB). A further 20% (1,290) of ONS were identified as TB sequelae deaths; 425 had matched to ETS cases more than a year before the death with an outcome that was not death, a further 865 were not matched to ETS cases but had text indicating their TB had occurred in the past and was not active at death.

Of the remaining 70% (4,606) of ONS, 61.0% (2,810) matched to ETS notifications and 39.0% (1,796) did not. Of those that matched, 2,587 had an outcome of death in ETS and the remaining 223 had another outcome though the date of death was less than a year since start date of treatment/notification (**Figure 3**).

Identification of TB deaths in ONS that were incorrectly assigned active TB ICD-10 codes from text on death certificates highlights that changes to the coding algorithm of IRIS could improve accuracy (see supplementary material)

#### ***Total deaths 2005-2015 in ONS and ETS***

A total of 9,289 deaths were identified from ETS and ONS (**Figure 4, Figure 5**); and stratified into: reported in both systems, reported in ETS but not ONS (ETS only), and reported ONS but not in ETS (ONS only). 7.1% (664) were not TB, 6.1% (571) were incidental deaths, 22.5% (2,093) were TB sequelae deaths and 64.2% (5,961) were active TB deaths.

Out of those that were recorded as active TB deaths, 22.7% (1,355) were not matched to ONS, 47.1% (2,810) were in both ETS and ONS and a further 30.1% (1,796) were not notified in ETS.

Multivariable analysis identified that ETS not recorded as ONS were almost 3 times more likely not to have culture confirmation or be smear positive (aOR 2.86, 95% CI 2.24-3.66, aOR 3.04, 95% CI 2.38-3.87 respectively) and were 4 times (aOR 3.93, 95% CI 2.82-5.47) more likely to have been diagnosed post-mortem (**Table 1**).

ONS not notified to ETS were 1.5 times (aOR 1.45, 95% CI 1.23-1.65) more likely to be female, 2.5 times (aOR 2.38, 95% CI 1.87-3.04) more likely to be aged over 65 years and 3 times (2.99, 95% CI 2.61-3.42) more likely to be UK born (**Table 2**).

#### **DISCUSSION**

TB deaths recorded in ETS and ONS differ **substantially**. We have shown that the ONS VR system does not capture all deaths notified to ETS where TB caused/contributed to the deaths, and ETS does not have notifications for all deaths recorded as due to TB on death certificates.

A **notable** proportion of deaths in TB cases notified to ETS were not captured by ONS. This may be due to: TB not having caused/contributed to death (relationship between TB and death poorly completed in ETS), TB not recorded on death certificate despite death being due to TB, or ONS coding system not assigning a TB ICD-10 code from death certificate text. We found that smear or culture positive TB cases were more likely to be captured in the VR system, suggesting clinicians may be reluctant to record TB on death certificates without laboratory diagnosis. We found TB cases diagnosed post-mortem were 4 times less likely to be recorded as a TB death, suggesting that death certificates may have been completed before the diagnosis was made and not subsequently amended. Future work to better understand this group could include matching deaths to all ONS deaths (not just TB deaths) to review cause of death; and auditing deaths with clinicians to understand why TB was not mentioned on death certificates.

Thirty percent of active TB deaths recorded by ONS appear not to be due to active TB, with 23% due to TB sequelae and 7% not due to TB at all. Capturing TB sequelae is useful for long term monitoring of TB mortality trends, but should not be conflated with deaths from active TB. Combining deaths we identified as TB sequelae from text on death certificates (assigned A15-A19 incorrectly) and those assigned as TB sequelae (B90\*) showed 62% of TB sequelae deaths were miscoded, the majority could be rectified through changes to the IRIS coding system used both at ONS and internationally.

After excluding TB sequelae deaths identified in this analysis, we found a **substantial** proportion of the remaining ONS deaths were not notified to ETS. Anyone with active TB should be notified to ETS, even if the diagnosis is made post-mortem. We found that deaths not notified to ETS were more likely to be female, aged over 65 and UK born. An audit to understand if these deaths are really due to active TB is required.

Although we found a striking difference between the systems, it is important to note that whilst ETS aims to capture all incident cases of active TB, including those diagnosed post-mortem, and records short term outcomes including deaths from all causes; the ONS VR system aims to assign the cause and contributory factors to all deaths, recording deaths from active TB and deaths where TB caused/contributed to the death at a later stage (coded as TB sequelae).

ETS and ONS differ in recording the relationship between TB and death. This indicates there may be a problem in the definitions, their interpretation by clinicians, a lack of training on how to determine and record the relationship, or difficulty in deciding if TB caused/contributed to the death. An audit to clarify why these differences occur, followed by development of clear guidance should improve reporting.

Previous studies have shown that mortality statistics from death certificates can be inaccurate due to lack of training or knowledge of physicians in how to assign and record cause of death, complex cases which do not easily fit into the ICD-10 classification system where codes are often more relevant for morbidity than mortality, or coding practices.<sup>11-13</sup> In the US small studies have shown that data recorded on death certificates relating to tuberculosis is often inaccurate; a third of patients assigned an ICD-10 code of TB had no evidence of TB on the death certificate were not notified and that concordance between death certificates and TB notifications was at best 60%.<sup>14,15</sup>

Our study has several strengths: we matched two large datasets from two independent systems over a ten year time period and reviewed the text on death certificates in combination with data recorded in ETS. This enabled us to highlight deficiencies in the systems and identify potential solutions to improve both of them. Limitations include: missing data on cause of death in ETS, and not having access to all ONS deaths to analyse cause of death in ONS where TB was not mentioned.

## **CONCLUSIONS:**

This study has important implications. Firstly, it is essential that we can accurately estimate TB mortality in order to monitor our progress towards decreasing TB mortality. Currently, neither the data from ONS, nor ETS is complete, requiring information to be combined to calculate estimates. Secondly, we show that well-established VR systems in high resource settings contain inaccurate data, requiring improvements in collection and coding. Thirdly, when setting up new VR systems in developing countries, careful consideration is required to ensure accurate data collection and coding so the issues we report here are not replicated. Work is underway to consider coding changes at ONS and to plan an audit of deaths reported in one but not the other system. If ONS make coding changes, ONS data will more accurately assess long term mortality, while ETS might be best placed to provide reliable data on deaths in active TB. Revised estimates of both active TB and TB sequelae are being calculated based on the combined data presented in this paper, with the aim to produce accurate, informative and reproducible national mortality estimates between now and 2020.

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### **Authors' contributions**

MKL conceived and designed the study. MKL, TM, TU collected data for the study. MKL and TM carried out the analysis and MKL wrote the manuscript. All authors contributed to the design of the analysis and commented on manuscript versions. All authors read and approved the final manuscript.

**Conflicts of interest**

The authors declare that they have no competing interests.

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Table 1: Factors associated with **active** TB deaths notified in ETS not being recorded as a TB death in ONS

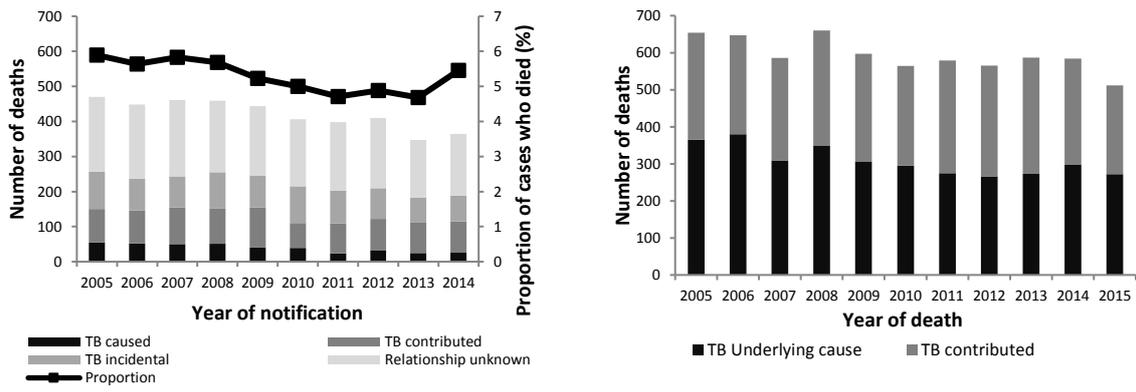
	ETS and ONS		ETS Only		Total N	P value	OR (95% CI)	aOR* (95% CI)
	n	%	n	%				
All <b>active deaths</b>	2,810	67.5	1,355	32.5	4,165			
Sex								
Male	1,823	68.3	848	31.7	2671	0.180	1	
Female	984	66.2	502	33.8	1486		1.10 (0.96-1.26)	
Age								
0-14	14	58.3	10	41.7	24	0.611	1	
15-44	398	68.0	187	32.0	585		0.66 (0.29-1.51)	
45-64	662	68.6	303	31.4	965		0.64 (0.28-1.46)	
65+	1,736	67.0	855	33.0	2591		0.69 (0.31-1.56)	
Country of birth								
UK born	1,210	68.6	553	31.4	1763	0.997	1	
Non UK born	1,249	68.6	571	31.4	1820		1.00 (0.87-1.15)	
Site of disease								
Pulmonary (with or without EP)	2,292	71.6	910	28.4	3202	<0.0001	1	1
Extra-pulmonary (EP) only	511	54.4	429	45.6	940		2.11 (1.82-2.46)	1.09 (0.75-1.60)
Culture confirmation								
Yes	2,044	74.7	694	25.3	2738	<0.0001	1	1
No	766	53.7	661	46.3	1427		2.54 (2.22-2.91)	2.86 (2.24-3.66)
Sputum smear status								
Positive	920	84.8	165	15.2	1085	<0.0001	1	1
Negative	454	57.5	335	42.5	789		4.11 (3.31-5.11)	3.04 (2.38-3.87)
Postmortem diagnosis								
Yes	403	50.7	392	49.3	795	<0.0001	2.43 (2.08-2.85)	3.93 (2.82-5.47)
No	2,407	71.4	963	28.6	3370		1	1

\* adjusted ODDs Ratios (aORs) were calculated by including all factors from the univariable analysis in the multivariable logistic regression.

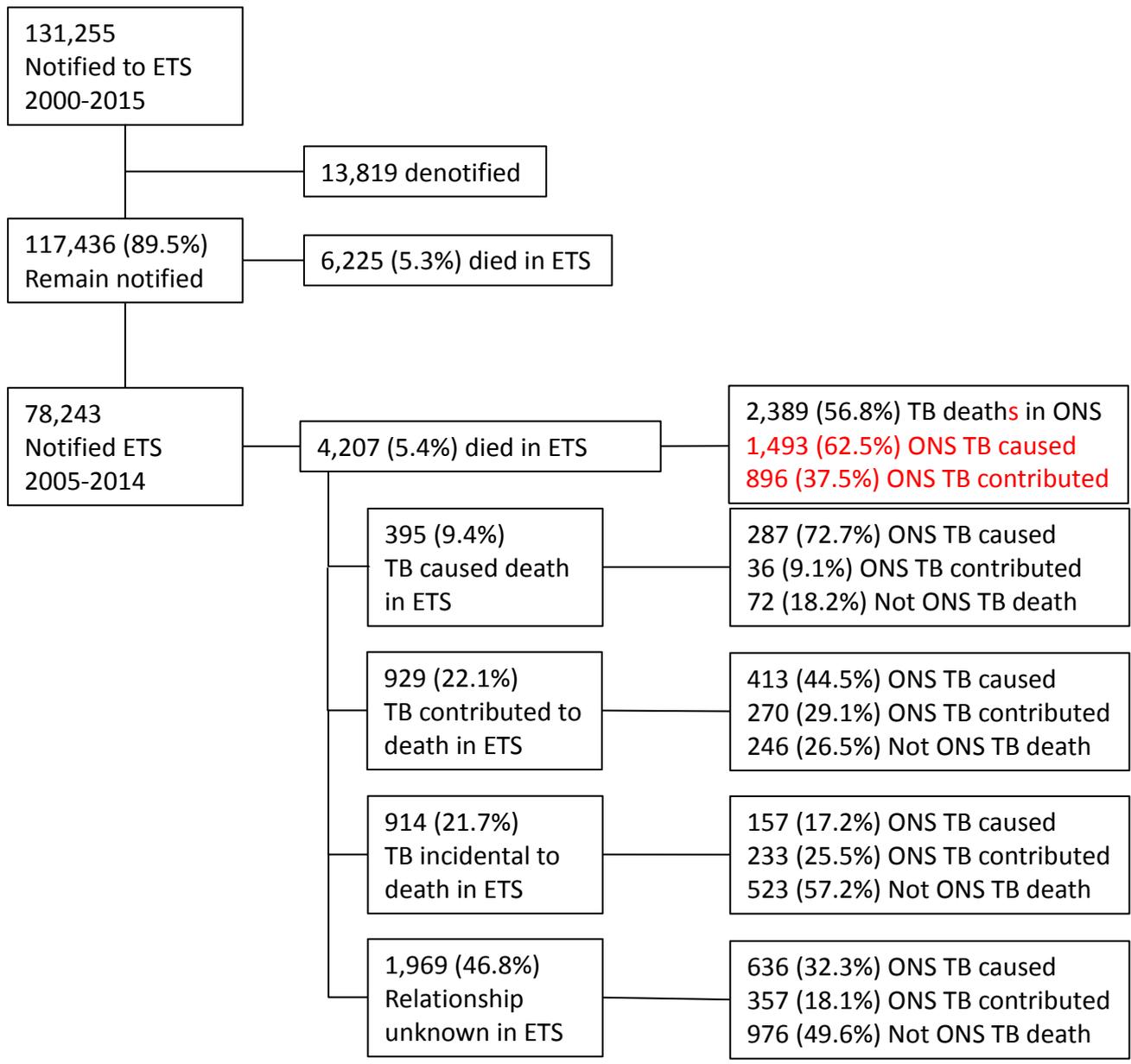
Table 2: Factors associated with **active** TB death recorded in ONS not being notified in ETS

	ETS and ONS		ONS Only		Total N	OR (95% CI)	aOR* (95% CI)
	n	%	n	%			
All <b>active deaths</b>	2,810	61.0	1,796	39.0	4,606		
Sex							
Male	1,827	64.2	1,021	35.8	2848	1	1
Female	983	50.0	983	50.0	1966	1.41 (1.25-1.59)	1.45 (1.23-1.65)
Age							
0-14	15	68.2	7	31.8	22	1.77 (0.70-4.46)	1.07 (0.42-2.77)
15-44	379	79.1	100	20.9	479	1	1
45-64	648	72.2	249	27.8	897	1.46 (1.12-1.90)	1.31 (0.99-1.72)
65+	1,757	55.0	1,437	45.0	3194	3.10 (2.46-3.91)	2.38 (1.87-3.04)
Country of birth							
UK born	1,357	50.2	1,348	49.8	2705	3.26 (2.86-3.72)	2.99 (2.61-3.42)
Non UK born	1,431	76.6	436	23.4	1867	1	1

\* adjusted ODDs Ratios (aORs) were calculated by including all factors from the univariable analysis in the multivariable logistic regression.



**Figure 1: A] Number and proportion of notified TB cases with death recorded as the outcome between 2005 and 2014 in the Enhanced Tuberculosis Surveillance system (ETS) B] Number of TB deaths by underlying cause reported by ONS between 2005 and 2015**



**Figure 2: Flow chart of notified TB cases with death reported as their outcome, stratified by the relationship between TB and death, and outlining those that matched to TB deaths recorded on ONS (A15-A19) notified to ETS, those reported to have died on ETS and the proportion that were reported as TB deaths by ONS, including detail on the relationship between TB and death**

\* Notified TB cases from 2000 to 2015 were matched to ONS deaths from 2005-2015 to identify all TB deaths that occurred between 2005 and 2015. ETS cases notified between 2000 and 2005 were included in the matching as TB deaths may occur several years after notification and the time between active TB and death were used to identify deaths due to active TB or TB sequelae for subsequent analysis.

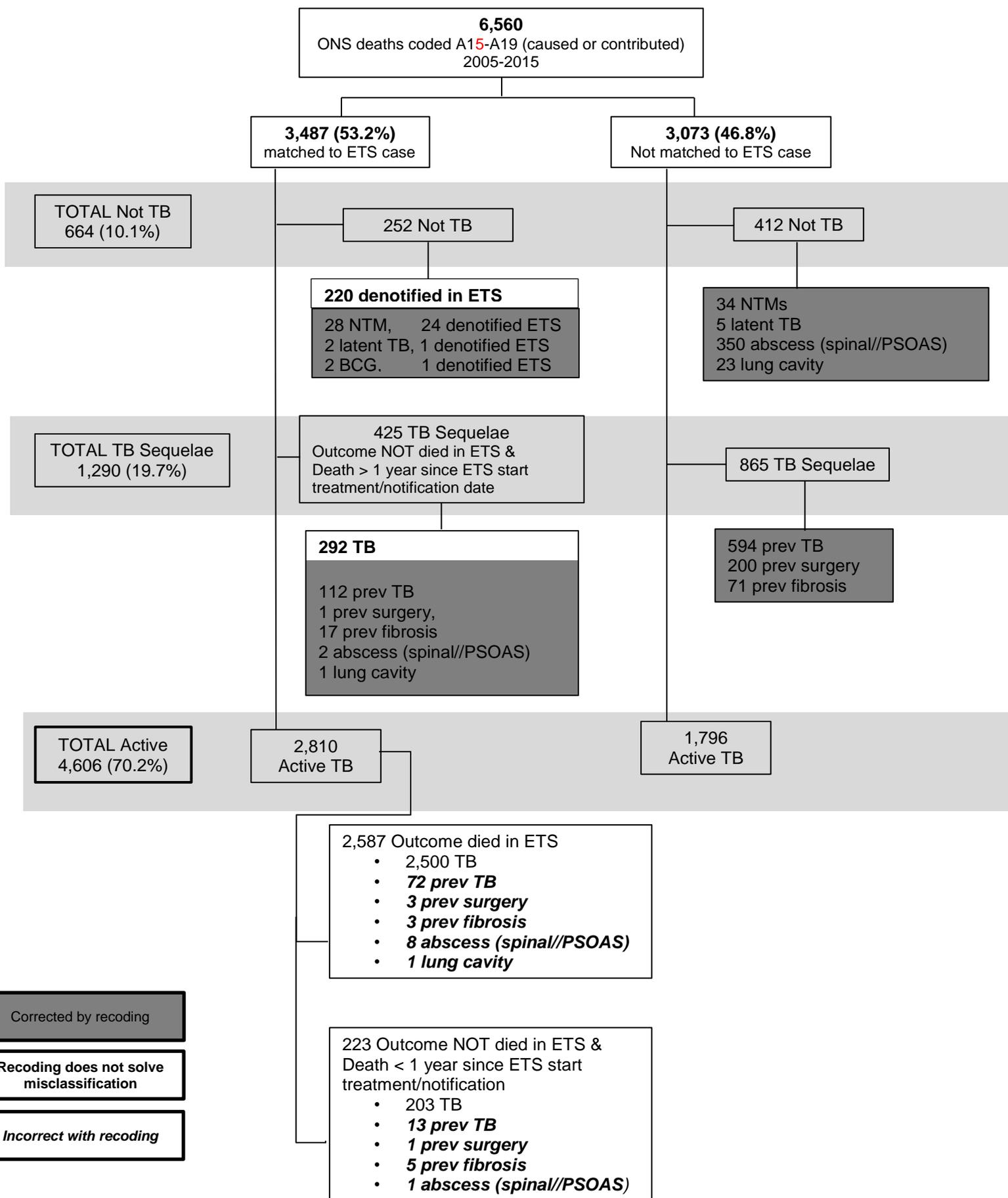
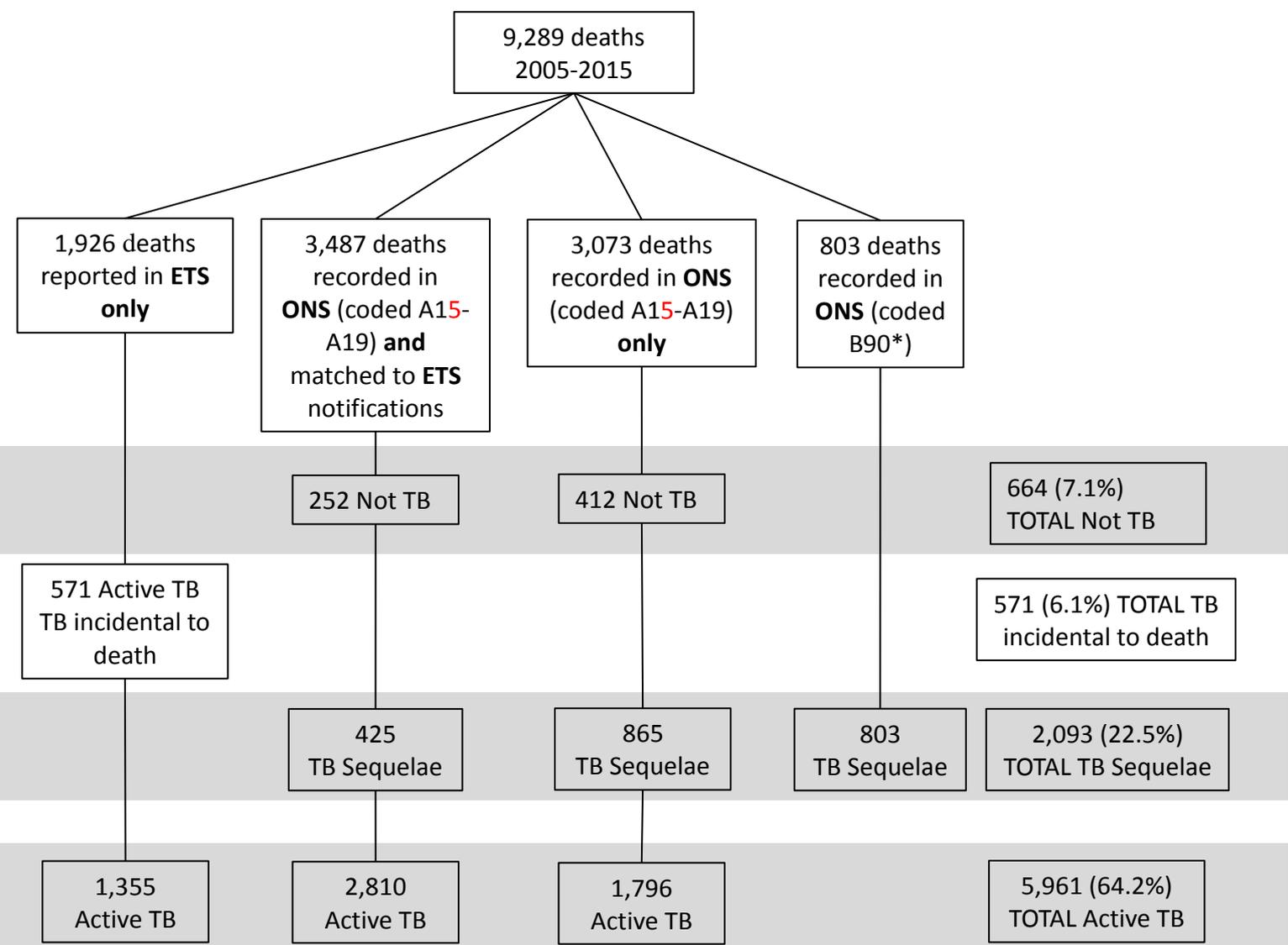
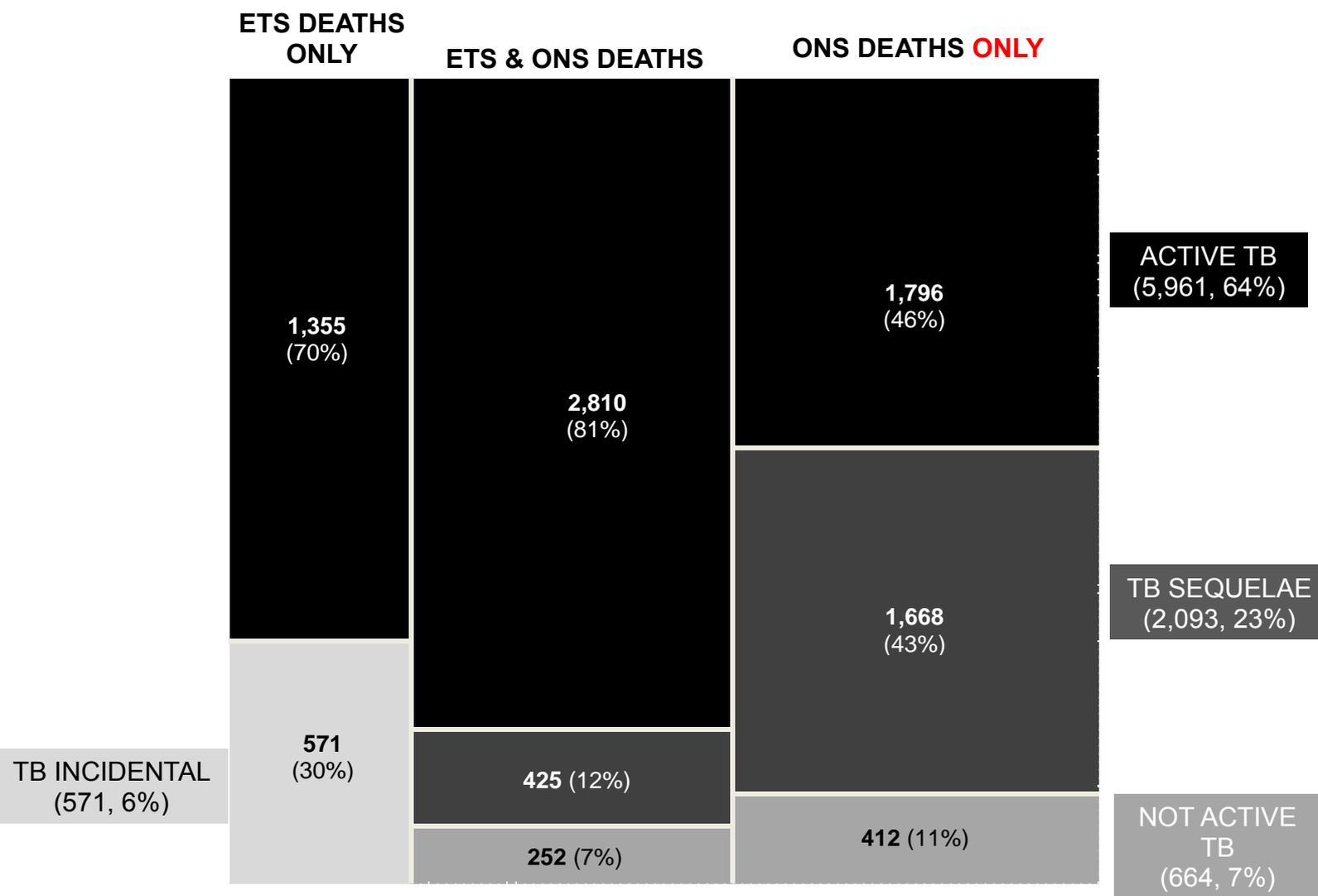


Figure 3: Flow chart of ONS TB deaths coded A15-A19 between 2005 and 2015, stratified by those who have matched or not matched to ETS notifications (cases notified between 2000 and 2015). TB deaths were subsequently classified into not TB, TB sequelae and active TB. Coding changes to the algorithm at ONS could reduce the miscoding of TB deaths as outlined\*.

\*Potential coding changes at ONS; the text on death certificates was able to identify 66.9% (444/664) of those found not to have TB, and 77.4% (998/1,290) of deaths found to be due to TB sequelae and not active disease which could have been coded to B90\* instead of A15-A19 (dark grey). For other deaths (220 Not TB and 292 TB Sequelae- **bold 3**) there was no text present in the death certificate to indicate that they should be coded differently, and thus could not have been coded differently by ONS. A small number of TB deaths have information recorded on the death certificate that would result in them being coded incorrectly with the proposed changes (107 active TB- **bold and italic**).



**Figure 4: Flow chart of all “TB deaths” identified in ETS and ONS between 2005 and 2015, including details of which have matched to ETS notifications (cases notified between 2000 and 2015). TB deaths classified into not TB, TB incidental to death, TB sequelae and active TB.**



**Figure 5: TB deaths between 2005 and 2015, by type and system of capture.** The total area represents TB mortality in England and Wales. All rectangles are proportional to their share of total mortality reported in ETS only (21%), in both ETS and ONS (38%) and ONS only (42%). The proportion of active TB deaths where TB caused or contributed by system was as follows: ETS only (23%), both ETS and ONS (47%) and ONS only (30%). The proportion of deaths by type for each system is presented in the figure within the boxes.

## Appendix 1: Online supplementary material

### Supplementary methods:

It is a statutory requirement to notify all newly diagnosed cases of active TB to ETS within 3 days of making or suspecting the diagnosis. The requirement to notify applies if there are reasonable grounds for suspecting that a patient has died with, but not necessarily from TB (including post-mortem diagnoses) <sup>16</sup>. TB cases can be denotified from the system if duplicate cases are identified, or cases are subsequently found not to have TB (non-tuberculous mycobacteria (NTM) identified, or another alternative diagnosis).

It is a statutory requirement to report all deaths within England and Wales to ONS within 5 days of the death <sup>7</sup>. ICD-10 codes A15 through A19 are used to code for active TB due to *Mycobacterium tuberculosis* or *M.bovis* and does not include congenital TB (ICD-10 P370), pneumoconiosis associated with tuberculosis (J65), silicotuberculosis (J65) or sequelae of TB (ICD-10 B90\*) <sup>9</sup>.

Sequelae of tuberculosis (ICD-10 code B90\*) is defined as including conditions specified as such or as late effects of past tuberculosis disease, and residuals of tuberculosis specified as arrested, cured, healed, inactive, old or quiescent, unless there is evidence of active tuberculosis <sup>17</sup>.

### *Matching datasets*

The ETS dataset included notified TB cases and cases that had subsequently been denotified. Duplicate cases were identified and excluded from the dataset; the most recent episode was kept. For duplicate cases with at least one episode that had been denotified, the most recent episode that was not denotified was kept or the most recent denotified episode was kept where all were denotified. TB cases notified between January 2000 and December 2015 were included as the death may occur several years after the notification and the time between active TB and the death were important in identifying those with active TB and TB sequelae. The data from ETS and ONS (ICD-10 A15-A19 only) were probabilistically matched using personal identifiable information (forename, surname, sex, date of birth, place of birth, date of death, NHS number, post code) contained in both datasets using the matching method previously described <sup>18</sup>.

ONS were flagged for review in Stata by identification of key words written on death certificates in order to identify:

- a) deaths not due to TB: non-tuberculous mycobacteria, latent TB, BCGosis, spinal/sacral/PSOAS/abscess (with no mention of TB) and lung cavity (with no mention of TB).

- b) TB sequelae: previous TB, previously treated TB, surgery due to previous TB, fibrosis due to previous TB

ONS were then classified into groups as follows:

- a) Active TB: ONS not matched to ETS cases and where no text on death certificate suggested it was not active TB and ONS matched to ETS cases where ETS outcome of died was reported (independent of any flag identified by reviewing text on death certificates), and ONS matched to ETS where ETS outcome was not died but the death date was less than a year since the ETS treatment start/notification date (independent of any flag identified by reviewing text on death certificates).
- b) TB Sequelae: ONS not matched to ETS cases and where text on death certificate identified TB Sequelae with no active TB and ONS matched to ETS cases where ETS outcome was not died but where the death was more than a year since the ETS reported start date of treatment/notification.
- c) Not TB: where the case was denotified on ETS or where text on the death certificate indicated the death was not due to active TB

### **Supplementary results**

Potential changes to coding algorithms for assigning ICD-10 codes from text on death certificates could improve accuracy; the text on death certificates was able to identify 66.9% (444/664) of those found not to have TB, and 77.4% (998/1,290) of deaths found to be due to TB sequelae and not active disease which then could have been coded to B90\* instead of A15-A19 (dark grey in **Figure 3**). For other deaths (220 Not TB and 292 TB Sequelae-**bold** in **Figure 3**) there was no text present in the death certificate to indicate that they should be coded differently, and thus could not have been coded differently by ONS. A small number of TB deaths have information recorded on the death certificate that would result in them being coded incorrectly with the proposed changes (107 active TB-**bold and italic** in **Figure 3**).