Title: Verbal autopsy-assigned causes of death among adults being investigated for tuberculosis in South Africa

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Running head: verbal autopsy assigned causes of death

Abstract

Background: Adults being investigated for tuberculosis (TB) in South Africa experience high mortality, yet causes of death (CoD) are not well defined. We determined CoD in this population using verbal autopsy (VA), and compared HIV- and TB-associated CoD using physician-certified verbal autopsy (PCVA) and InterVA-4 software.

Methods: Cross-sectional study. All contactable consenting caregivers of participants who died during a trial comparing Xpert MTB/RIF to smear microscopy were interviewed using the World Health Organization VA tool. CoD were assigned using PCVA and InterVA-4. Kappa statistic(K) and concordance correlation coefficient (CCC) were calculated for comparison.

Results: Among 231 deaths, relatives of 137 deceased were interviewed. Of the 137 deceased (76[55.4%] males, median age 41 years [interquartile range 33-50]). PCVA assigned 70(51.1%) TB immediate CoD (44[62.8%] pulmonary TB; 26[37.1%] extra-pulmonary TB); 21(15.3%) HIV/AIDS-related; and 46(33.5%) other CoD. InterVA-4 assigned 48 (35.0%) TB deaths; 49(35.7%) HIV/AIDS-related deaths; and 40(29.1%) other CoD. Agreement between PCVA and InterVA-4 CoD was slight at individual level (K =0.20; 95% confidence interval [CI] 0.10-0.30) and poor at population level (CCC 0.67; 95% CI 0.38 - 0.99).

Conclusion: TB and HIV are leading CoD among adults being investigated for TB. PCVA and InterVA agreement at individual level was slight and poor at population level. VA methodology needs further development where TB and HIV are common.

Introduction

Tuberculosis (TB) is a leading cause of death (CoD) in South Africa[1] and is a public health priority, with an estimated 380,000[2] cases in 2013, among whom 62% were also living with human immunodeficiency Virus (HIV).[3] The World Health Organization (WHO) has set global targets to reduce TB mortality by 75% in 2025 compared to 2015 figures as a baseline.[2] To track the reduction in TB mortality, accurate data on numbers of TB deaths are needed. CoD is most accurately assigned using pathological autopsy.[4] However, pathological autopsies are logistically difficult and rarely performed. In areas where not all deaths occur in health facilities and CoD are not determined, poor vital statistics, as well as the need to better understand the distribution of CoD at population level, have led to verbal autopsy (VA) being used to estimate CoD. This involves interviewing caregivers about the signs, symptoms, medical history, and circumstances surrounding the individual's death.[5] VA interview data can be interpreted to estimate CoD using methods such as physician-certified verbal autopsy (PCVA) and computer-coded verbal autopsy (CCVA), with PCVA being the most widely used method. CCVA uses software that employs algorithms and probabilistic methods (including InterVA-4), while the PCVA method involves at least two physicians examining each record and attempting to reach a consensus on CoD using codes from the 10th version of the International Classification of Diseases (ICD-10).[6,7]

The XTEND trial, a pragmatic cluster-randomised trial embedded in the South African national roll-out of Xpert MTB/RIF, compared mortality over six months among adults investigated for TB using Xpert MTB/RIF vs. smear microscopy as the initial diagnostic test.[8] XTEND found high mortality in adults being investigated for TB, with no difference in mortality at six months between the study arms.[8] The cohort of XTEND participants who died, presented a unique opportunity to evaluate VA methodologies in a cohort with high TB/HIV prevalence. The aim of this paper was to: use VA to assign CoD, among adults being investigated for TB with a particular interest in TB, and to compare CoD assigned by PCVA to that assigned by a CCVA method (InterVA-4).

Methods

XTEND study

The parent XTEND trial is described in detail elsewhere.[8] Between June and November 2012, a representative sample of 4656 consenting participants who were ≥18 years, planning to live in the study catchment area for more than 8 months, identified by clinic staff as needing investigation for TB and providing sputum for TB testing were enrolled into the study. At enrolment, participants provided contact details and those of close relatives or friends. Vital status was ascertained by contacting participants, their next of kin or friends by telephone and, if necessary, conducting home visits. Vital status of participants was further ascertained by reviewing the Department of Home Affairs vital statistics register.

Verbal autopsy

All XTEND participants who died during the study were eligible for the VA sub-study, including some who died more than six months post-enrolment and hence did not contribute to the XTEND primary outcome. Demographic details and past medical history of deceased participants were extracted from the XTEND database, but were not available to staff doing VA interviews nor to physicians assigning CoD. The XTEND database also included case note reviews where TB treatment start dates and antiretroviral treatment(ART) start dates were obtained. Caregivers, defined as a relative or friend closely associated with the participant at time of death, were invited to participate by telephonic contact, or if unsuccessful, home visit. Lay counsellors, trained in administering the standardized 2012 WHO VA tool and in grief counselling, administered the questionnaire. The tool comprised of closed questions with 'yes', 'no', or 'don't know' responses and a narrative section. The caregiver recounted the events leading up to the participant's death, detailing information about the deceased's signs, symptoms, medical history, and circumstances preceding death in the narrative section.[5] Time from enrolment to death was defined as period from enrolment to date of death. Time from enrolment to TB treatment initiation was the period from enrolment to date of TB treatment initiation and time from enrolment to ART initiation was the period from enrolment to date of ART initiation.

Interpretation of verbal autopsies using PCVA

PCVA involved two physicians independently assigning immediate and underlying CoD using ICD-10 guidelines, based on VA data, including the caregiver's narrative for each decedent. Where different immediate or underlying CoD were assigned by the physicians, a consensus meeting was held; if no consensus was reached, the case was referred to a third independent physician. If still no consensus was reached, the case was classified "indeterminate". Physicians were aware that all decedents were participants in the XTEND trial and had been investigated for TB. For individual CoD analysis, the following ICD-10 codes were considered to be HIV-related deaths: B20 (HIV resulting in infectious and parasitic diseases), B21 (HIV disease resulting in malignant neoplasms), B22 (HIV disease resulting in other specified diseases), B23 (other conditions associated with HIV), and B24 (unspecified HIV disease). ICD-10 codes A15 (respiratory tuberculosis, bacteriologically and histologically confirmed) and A16 (respiratory tuberculosis, not confirmed bacteriologically or histologically) were categorized as pulmonary TB (PTB) while A17 (TB of nervous system), A18 (TB of other organs), and A19 (miliary TB) as extra-pulmonary TB (EPTB). [9] Individual CoD assigned by PCVA were processed further using mortality medical data system (MMDS) software, which generates underlying CoD from multiple CoD.[10] The output generated by MMDS was categorised into WHO 2012 VA causes of death groups; cause specific mortality fractions (CSMFs) were calculated by dividing the number of deaths assigned to a group by the total number of deaths. [5,10]

Interpretation of verbal autopsies using InterVA-4

InterVA version 4.03 RC1 (InterVA-4, www.interva.net) is software that uses Bayesian probabilistic theory to assign CoD. The software generates up to three probable CoD for each case based on a pre-determined algorithm with the CoD assigned the highest likelihood being referred to as the most probable CoD .[11, 12,13] VA data were imported into InterVA-4, set at high HIV and low malaria prevalence for our study setting. InterVA-4 assigns only PTB as a TB-related cause of death, classifying all EPTB as "other unspecified infectious diseases". Specificity of InterVA-4 in assigning HIV-related CoD has previously been reported to be 90.1% (95% confidence interval [CI] 88.7-91.4%)[14] . The probable CoD generated for each individual were further processed to generate population CSMFs.

Comparing InterVA-4 and PCVA

The two methods assign a wide range of CoD but for this study we concentrated on HIV/AIDS- and TB-related deaths. At individual level, we focused on the most probable CoD assigned by InterVA-4,

compared with underlying CoD generated by MMDS for PCVA. For TB deaths, we compared PTB deaths assigned by PCVA and by InterVA-4. For HIV deaths, ICD-10 codes (B20-24) assigned by physicians were grouped together and compared with HIV/AIDS related deaths assigned by InterVA-4. For individual CoD assigned, the level of agreement between the two methods was estimated using Cohen's kappa (K) statistic with a 95% CI. K=1 would indicate perfect agreement, and K=0 would indicate agreement no better than chance.[15] Cause specific mortality fractions generated by the two methods were compared using Lin's concordance correlation coefficient (CCC) which ranges from -1 to +1 with +1 being perfect agreement and 0 showing no agreement.[16] All analyses were done using Stata (version 13, Stata Corp LP, College Station, Texas).

Results

231 XTEND participants died between 08 June 2012 and 31 June 2013. From 1 August to 29 November 2013, 231 interviews were attempted with caregivers. Of these 138 (60.0%)were completed; 68 (29.4%) caregivers could not be traced and 25 (10.8%) refused to be interviewed. Interviews were conducted within median time of 11 months (interquartile range [IQR] 8-12 months) after deaths had occurred. One interview was excluded due to a missing narrative section leaving 137 for analysis. Among the 137 decedents, 76 (55.4%) were male and the median age was 41 years (IQR 33-50). Ninety-seven (70.8%) had self-reported being HIV-positive with median self-reported CD4 count 118 (IQR 52-290) cells/μL. Baseline characteristics of those who were included were similar to those who were not included except for number of TB symptoms reported at enrolment (Table 1). Furthermore there was no difference in time from enrolment to death between the two groups. A total of 41 participants were started on TB treatment and 28 (20.4%) had a VA done. Median time from enrolment to TB treatment was 11 days (IQR 7-33) in those with a VA versus 15 days (IQR 5-30) in those without a VA; this was not different between the two groups. A total of 162 participants self-reported being HIV positive in the study and 61(37.6%) had evidence of being initiated on ART. Of the 61, 35 (57.4%) started ART after enrolment into XTEND. Median time from enrolment to ART treatment initiation was not different between the groups (Table 1).

PCVA-assigned CoD

PCVA assigned immediate and underlying CoD for 134 (98.0%) VAs; three (2.2%) VAs were indeterminate (Table 2). Of the 134 with a CoD, 95 (70.9%) were assigned without requiring a consensus meeting and 39 (28.5%) after a consensus meeting. Among the 137 decedents, the most common

immediate CoD assigned was TB (70 decedents [51.1%]). Of these 70 TB deaths, 44 (62.8%) were attributed to PTB, of which 8 (18.2%) were classified as bacteriologically confirmed as reported on VA. EPTB was assigned as CoD in 26/70 (37.1%) TB deaths. Of these, 11 (42.3%) were TB of the nervous system, 10 (38.4%) miliary TB and five (19.2%) TB of other organs. 57/70 (81.4%) of those assigned an immediate TB CoD were assigned an underlying HIV CoD by the physicians. HIV/AIDS-related immediate CoD were assigned in 21 (15.3%) decedents; gastrointestinal diseases in seven (5.1%) decedents; pneumonia in five (3.6 %); cardiac disease and respiratory ailments in four (3.0%) each; renal failure and malignant neoplasm in three (2.0%) each; while liver disease and intentional self-harm were in two (1.5%) each (Table 2). Cause specific mortality fractions were calculated after PCVA CoD were processed by MMDS software: HIV/AIDS-related deaths accounted for 66.4% of PCVA deaths; PTB for 9.5%; cardiac disease for 2.9%; and malignant neoplasms, gastrointestinal diseases and accident/self harm for 2.2% each (Table 3).

InterVA-assigned CoD

InterVA-4 assigned CoD to 136 (99.2%) decedents; one (0.7%) was classified as indeterminate. 48/137 (35.0%) individuals were assigned a most probable CoD of PTB, 49 (35.7%) an HIV/AIDS-related CoD, and 14 (10.2.%) a malignancy-related CoD. Only one decedent was assigned an “other unspecified infectious diseases” CoD by InterVA-4 (Table 2). InterVA-4 assigned 16 decedents with more than one CoD, 13 were assigned two CoD and three were assigned three CoD. Of the 16 with more than one CoD, three (18.7%) had HIV as a less probable CoD and four (25.0%) had TB as less probable CoD. Only one decedent with a most probable CoD of PTB had HIV assigned as a less probable CoD and also one with HIV as a most probable CoD had PTB assigned as a less probable CoD. InterVA-4 CSMFs were calculated using all assigned CoD: PTB accounted for 33.2% of deaths; HIV/AIDS for 32.8%; malignant neoplasms for 9.6%; and respiratory ailments for 4.9% (Table 3).

Comparing InterVA-4 and PCVA CoD

A direct comparison of the single underlying CoD assigned by MMDS for PCVA and the most probable CoD assigned by InterVA-4 showed agreement in 65/137 (47.4%) decedents with kappa statistic 0.20 (95% CI 0.10-0.30); representing slight agreement (Table 4). Comparison of CSMFs assigned by PCVA and InterVA showed a CCC of 0.67 (95% CI 0.38 - 0.97), which was poor (Table 3).

Discussion

The XTEND study is the largest cohort to date of adults being investigated for TB. In this sub-study, we used VA to investigate CoD, which showed that about half (51% based on PCVA and 35% based on InterVA-4) the deaths were attributed to TB. These findings might be surprising as these were people accessing health care who had investigation for TB initiated and who had submitted at least one sputum specimen for smear microscopy or Xpert MTB/RIF. Though one might hope that people who had TB investigations initiated should not die of TB, some patients may already been very sick at the time TB investigation was initiated, as illustrated by the 18.9% with BMI<18.5 and the 64.2% reporting three or four TB symptoms. If these CoD data are correct, it suggests that persons are presenting for care too late, or that the current health system is failing to identify and treat persons who have TB, or both. It could also be that the health system is too slow to diagnose TB, resulting in delays in TB treatment initiation. This latter possibility was suggested by data from the XTEND trial which showed median time to starting TB treatment of seven days[8] which is a little longer than the Department of Health recommended two-to-five days [17]. HIV-related disease was the second most common CoD, consistent with absence of ART at enrolment being a risk factor for death among XTEND participants.[8]

Adults being investigated for TB have been far less studied than those starting TB treatment, and where CoD data exist, they are generally from hospitals rather than primary health care clinics. The high proportion of deaths attributable to TB was similar to studies using pathological autopsy to assign CoD. An autopsy study in South Africa among hospitalised HIV-positive adults either on ART or eligible for ART, showed that 66% died of TB, while only 27% were on TB treatment at time of death and 33% had never been treated for TB prior to death.[18] In Zambia, a study amongst hospitalised adults, mostly HIV-positive (81%), reported that 62% of deaths were attributed to TB and 26% were never treated for TB prior to death.[19] A recent systematic review among HIV-positive adults and children reported that TB was a primary cause of death in 91.4% (95% CI 85.5-97) of those diagnosed at autopsy.[20] Another study in South Africa seeking to understand CoD among ART initiators dying in hospital using VA and hospital case reviews also reported similar findings where mortality attributable to TB was 44.3%.[21]

Our study compared PCVA and InterVA-4 methods of assigning CoD at individual and population level. The majority of studies comparing these methodologies have been done in community settings in health and demographic surveillance system (HDSS) sites where VAs are done for all persons who die. In our study, when comparing immediate and most probable CoD, PCVA assigned more deaths to TB than InterVA-4. This could be because InterVA-4 can only assign PTB as a TB related death and assigns EPTB to

other infectious diseases, while PCVA allows deaths to be assigned as either PTB or EPTB, so EPTB deaths are not misclassified. PCVA and InterVA-4 models have been compared in other populations and have shown fair to moderate agreement.[22, 23, 24] A study conducted in an HDSS in Kenya, collecting data on CoD over a six-year period amongst children <5 years and adults aged ≥18 years, showed that PCVA assigned 9.9% of deaths to PTB and 34% to HIV/AIDS while InterVA assigned 31% to PTB and 16% to HIV/AIDS (K=0.27, 95% CI 0.25-0.30).[22] In Ethiopia, data on CoD collected over a 2 year period from adults aged ≥14 years in an HDSS showed that PCVA assigned 23% to PTB and InterVA-3 assigned 36% deaths to PTB (K=0.5, 95% CI 0.4-0.6).[23] When comparing CSMF assigned by PCVA and InterVA, InterVA assigned more TB than PCVA. This is largely because ICD-10 coding rules require that assignment of single CoD in individuals with immediate CoD of TB and underlying CoD of HIV be classified as an HIV/AIDS related death.[9] This resulted in 57(81%) of immediate TB deaths assigned at individual level being classified as HIV/AIDS-related deaths after processing by the MMDS software. A recent study done in Asia and Africa comparing VA CoD as assigned by PCVA and InterVA-4 also reported a CCC of 0.83 (95% CI 0.75-0.91) between the methods and this was higher than the 0.67 found in our study.[25]

PCVA assigned more immediate PTB CoD in our study compared to HDSS studies, most likely because our study included people with symptoms suggestive of TB who were identified by clinic staff as needing TB investigation. It is also possible that, because the physicians who interpreted the VAs knew that all study participants were being investigated for TB, this could have biased them to choose TB as a CoD.

A major strength of our study is that our study population was a large systematic sample of adults being investigated for TB in a real-world setting. Our results can be generalised to adults being investigated for TB in similar settings and also to people with TB symptoms severe enough to need investigation. We also managed to perform the majority of VA interviews within one year of death which made it easier for respondents to recall exact events leading to a participant's death. A study limitation is that we could not conduct a VA for everyone who died, and could thus have missed other causes of death which has implications on the profile of causes reported in this population. A higher proportion of decedents who had VA done had started TB treatment compared to those who died but did not have a VA done. Those who were on TB treatment would have been easier to contact because they were already in care, therefore overestimating TB as a CoD in the study.

Our findings show that when interpreting verbal autopsy data using either PCVA or InterVA-4 for adults being investigated for TB, TB is a leading CoD. These results also suggest that the current TB diagnostic pathway is inadequate as people with TB disease may still be missed or commenced on treatment too

late. Thirdly, the fact that HIV was identified as the second most common CoD points to the importance of integrated TB and HIV care and linkage into care for both diseases. The health service through implementation science research needs to find ways to facilitate access to TB and HIV care for persons who need to navigate both services. We recommend that adults being investigated for TB need to be aware of their HIV status, as data from XTEND also showed that people were more likely to die if they were HIV positive and not on ART or if their HIV status was unknown [8]. Intensified TB screening also needs to be improved as the sensitivity of the current screening tool is suboptimal and a diagnostic test for TB with high sensitivity and specificity that could be used in primary health care settings is a priority . We also recommend that current CCVA methods should be improved so they include EPTB. Research has shown that 88% of HIV-positive individuals with autopsy evidence of TB have disseminated disease [20]; if VA methods do not classify EPTB as TB, a large number of TB deaths will be missed.

Authors contribution: The study was designed by ADG, KM, GJC, SC, KK and VC. NM,KM,SC,VC, ADG and ASK were responsible for data collection. NM and ASK were responsible for the analysis. NM drafted the first draft and all other authors provided guidance on revision of the manuscript. All authors read and approved the final manuscript. NM is the guarantor of the paper.

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Ethical approval: The study was approved by the ethics committees of the University of Witwatersrand and the London School of Hygiene & Tropical Medicine. All respondents gave written informed consent, or witnessed verbal consent if unable to read and write.

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355 Table 1: Characteristics of deceased participants who had verbal autopsy vs those who did not

Variables	Verbal autopsy done N=137	Verbal autopsy not done N=94	P value
Characteristics at baseline			
Gender, n (%)			
Male	76 (55.4)	57 (60.6)	0.43
Age, years (median, interquartile range)	41 (33-50)	37 (31- 48)	0.14
Country of origin, n (%)*			
South Africa	128 (93.4)	84 (89.4)	
Non-South African	9 (6.5)	9 (9.6)	0.39
Self-reported HIV status at enrolment, n (%)*			
Positive	97 (70.8)	65 (69.1)	
Negative	15 (10.9)	11 (11.7)	
Unknown	25 (18.2)	17 (18.1)	0.98
Self-reported CD4 count (median, interquartile range)*	118 (52-290)	199 (103-253)	0.17
Number of TB symptoms reported at enrolment, n (%)*			
0	0 (0)	2 (2.1)	
1	15 (10.9)	4 (4.3)	
2	34 (24.8)	16 (17.0)	
3	38 (27.7)	36 (38.3)	
4	50 (36.5)	35 (37.2)	0.05
Body mass index (kg/m2)*			
<18.5	26 (18.9)	22 (23.4)	
18.5-24.9	74 (54.0)	56 (59.5)	
25-29.9	20 (14.6)	8 (8.5)	
30+	17 (12.4)	7 (7.4)	0.27
HIV and TB treatment initiation, death			
Time from enrolment to death, days (median, interquartile range)#	64 (31-115)	57 (28-113)	0.65
Number started on TB treatment, n (%)			
Overall 41(17.7%)	28 (20.4)	13 (13.8)	0.19

Time from enrolment to TB treatment initiation, days (median, interquartile range)	11 (7-33)	15 (5-30)	0.94
Number started on ART after enrolment, n=35 (%)	23 (65.7)	12 (34.2)	0.50
Time from enrolment to ART initiation, days (median, interquartile range)	25 (9-48)	15 (8-40)	0.30

*Data missing for 1 participant in the group without a verbal autopsy
data missing for 12 participants

361 Table 2: Immediate cause of death assigned by physician-certified verbal autopsy compared with 'most
362 probable' cause of death assigned by InterVA-4 (n=137)

Cause of death	Physician-certified verbal autopsy N (%)	InterVA-4 N (%)
Pulmonary tuberculosis	44 (32.1)	48 (35.0)
Not bacteriologically-confirmed	*36 (26.0)*	NA
Bacteriologically-confirmed	*8 (6.0)*	NA
Extrapulmonary tuberculosis	26 (19.0)	NA
Tuberculosis of nervous system	*11 (8.0)*	NA
Miliary tuberculosis	*10 (7.0)*	NA
TB of other organs	*5 (4.0)*	NA
HIV/AIDS-related deaths	21 (15.3)	49 (35.7)
Gastrointestinal diseases	7 (5.1)	4 (3.0)
Pneumonia	5 (3.6)	4 (3.0)
Cardiac disease/ failure	4 (3.0)	5 (3.6)
Respiratory ailments	4 (3.0)	2 (1.5)
Renal failure	3 (2.0)	1 (0.7)
Malignant neoplasm	3 (2.0)	14 (10.2)
Liver diseases	2 (1.5)	1 (0.7)
Intentional self-harm/poisoning	2 (1.5)	1 (0.7)
Meningitis	1 (0.7)	0 (0.0)
Indeterminate/unspecified	4(3.0)	1 (0.7)
Other	11 (8.0)	7 (5.1)
Total	137	137

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369 Table 3: Comparison of cause specific mortality fractions as assigned by physician certified verbal
370 autopsy and MMDS and InterVA-4

Cause of death	PCVA CSMF %	InterVA-4 CSMF %
HIV/AIDS related death	66.4	32.8
Pulmonary tuberculosis	9.5	33.2
Cardiac diseases	2.9	2.9
Malignant neoplasm	2.2	9.6
Gastrointestinal diseases	2.2	0.5
Accident/self-harm	2.2	0.7
Diabetes Mellitus	1.5	1.0
Respiratory ailments	1.5	4.9
Liver diseases	1.5	1.0
Other diseases	8.0	6.2
Unknown cause of death	2.2	7.4
Total	100	100

371 Concordance correlation coefficient: 0.67 (95% CI 0.38 - 0.97)

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Table 4: Agreement between 'most probable' cause of death assigned by InterVA-4 and single underlying cause of death assigned by physician-certified verbal autopsy and MMDS for 137 deceased XTEND participants

		Physician-certified verbal autopsy			
		TB	HIV	Other	Total
InterVA-4	TB	10	32	6	48
	HIV	1	38	10	49
	Other	2	21	17	40
	Total	13	91	33	137

Cohen's kappa: 0.20; 95% CI (0.10 - 0.30)