Verbal autopsy can consistently measure AIDS mortality:
A validation study in Tanzania and Zimbabwe

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Abstract

Background
Verbal autopsy (VA) is currently the only option for obtaining cause of death information in most populations with a widespread HIV/AIDS epidemic.

Methods
Using a data driven algorithm, we trained a set of criteria for classifying AIDS mortality. We use data from two longitudinal community studies in Tanzania and Zimbabwe, both of which have collected information on the HIV status of the population over a prolonged period of time and maintain a demographic surveillance system that collects information on cause of death through verbal autopsy. We then tested the algorithm in different times (two Phases of the Zimbabwe study) and different places (Tanzania and Zimbabwe).

Results
The trained algorithm, including nine signs and symptoms, performed consistently based on sensitivity and specificity on 15 to 44 year old VA data from Zimbabwe Phase 1 (sen 79%; spec 79%), Phase 2 (sen 83%; spec 75%) and Tanzania (sen 75%; spec 74%). The sensitivity dropped markedly for classifying deaths in 45 to 59 year olds.

Conclusions
Verbal autopsy can consistently measure AIDS mortality with a set of nine criteria. Surveillance should focus on deaths that occur in the 15 to 44 year age group where the method performs reliably. Addition of a handful of questions related to opportunistic infections would enable other widely used verbal autopsy tools to apply this validated methodology in areas where HIV testing and hospital records are unavailable or incomplete.
Verbal autopsy (VA), in which caregivers to the deceased report information on signs, symptoms and circumstances preceding death, is currently the best option for obtaining cause of death information in populations without comprehensive civil registration systems. The World Health Organization (WHO), through the Health Metrics Network is coordinating an effort to develop a common tool for VA, since there is an urgent need to validate currently used questions for different populations, settings and causes of mortality.

There is particular need to develop methods to measure AIDS mortality, which is the leading cause of death among young adults in virtually all countries with generalized HIV epidemics. Improving measurement of AIDS mortality is crucial since the ultimate goal of interventions - including the scale up of antiretroviral therapy - is to reduce AIDS mortality. Monitoring the success of such programmes therefore relies on accurate measurement of AIDS deaths in the community. Hospital records and vital registration of deaths are especially inadequate for estimating the level of AIDS as a cause of mortality because of bias, underreporting and stigma associated with the disease.

Two longitudinal community studies in Tanzania and Zimbabwe provide a unique opportunity to investigate the most sensitive and specific set of questions to ascertain HIV/AIDS-associated mortality. Both studies have collected information on the HIV status of the population over a prolonged period of time and maintain a demographic surveillance system that collects information on cause of death through VA. At the time of the VA studies HIV prevalence was approximately 20% in Zimbabwe cohort and 7% in Tanzania cohort. With data from the Zimbabwe study, we developed a computer algorithm to classify AIDS deaths from VA data validated using serological data from deaths that occurred from 1998-2003. Before the algorithm can be widely used, it must be demonstrated that it performs similarly and predictably in different settings of high HIV associated mortality (validation in place) and can perform well at different Phases of the epidemic when levels of AIDS mortality differ (validation in time).

**Methods**

All participants of both cohorts were followed as part of demographic surveillance and were tested for HIV at each sero-survey. If an individual died between follow-ups an attempt was made to perform VA. An individual’s HIV status at death was assumed to be the same as at his/her most recent test, which was a maximum of three years prior.
The Manicaland Project includes a population-based open cohort study in the rural province of Manicaland in eastern Zimbabwe. The study population were resident in small towns (2) forestry, tea and coffee estates (4) and rural areas (6, including four subsistence farming and two roadside trading centres). A baseline survey took place from 1998 to 2000, with two follow-ups occurring three years and five years later (the inter-survey periods are referred to here as Phase 1 and Phase 2). 8,376 and 7,102 of the households identified in the survey areas at Phase 1 and Phase 2, respectively, were enumerated. Male and female participation rates in the individual cohort study survey were 78% (4,320/5,561) and 80% (5,134/6,419) at Phase 1 and 77% (3,047/3,958) and 80% (3,972/4,936) at Phase 2. VAs were conducted for 94% of all deaths, with 53% of the VA reports obtained from close relatives (spouse 19%, child 7%, parent 16%, sibling 10%). At each follow-up of the study testing for presence of HIV antibody was performed.

The Kisesa HIV cohort is located in Magu District of Mwanza region in North Western Tanzania. The cohort was established in 1994 (when baseline studies were conducted) and data collection is based on a biannual Demographic Surveillance System (DSS) which had conducted 14 Phases by 2002, and sero-surveys repeated approximately every 3 years, with 3 testing surveys completed prior to 2002. The population resident in the DSS area grew from 19,354 in 1994 to 24,403 by 2002. Participation in the DSS is over 98%, with proxy reporting accepted for absent household members. The average participation rate in sero-surveys was 72% in the first 3 surveys. Deaths identified in the DSS are followed up with a verbal autopsy interview between 6 weeks and 6 months later, if a reliable informant can be identified who cared for the deceased during the final illness. Verbal autopsy interviews were completed for 67% (420/629) of the adult male deaths and 64% (424/667) of the adult female deaths recorded in the DSS between 1994 and 2002, 94% of the VA reports were obtained from close relatives (spouse 30%, child 28%, parent 21%, sibling 15%).

The verbal autopsy tool

The study teams identified deaths through the use of checklists of all individuals interviewed at the previous Phase and discussions with village health workers, employers, and surviving household members present at follow-up. Data were collected on the signs, symptoms, and circumstances preceding death using a structured, closed, interviewer-led questionnaire. The verbal autopsy questionnaire was originally developed in Kisesa and contained specific questions related to symptoms of late stage HIV and opportunistic infections and was used in that site from 1994 to 2002. A nearly identical questionnaire was adapted in Manicaland in both Phase 1 and Phase 2. The questionnaires
were administered in local languages (Shona, the predominant local language in Zimbabwe and Swahili, in Tanzania). Interviewers were clinical officers/certified nurses who received special training in how to administer the verbal autopsy questionnaire. VA informants were parents, spouse, other relatives or a neighbour (in rare circumstances when close relatives were not available). The interviews were conducted after the recognised mourning period, in a respectful and unhurried manner. In Kisesa, the interviewer gave a small, culturally appropriate gift (a bar of soap) to the person with whom the interview was conducted, as a token of appreciation of the time devoted to answering the lengthy questionnaire. Ethical approval for the DSS and all related procedures (such as the VA interviews) was granted by the Tanzanian Medical Research Co-ordinating Committee for the Kisesa study and by the Zimbabwe Medical Research Council for the Manicaland Study.

**Validation procedures**

We developed a computer algorithm that creates a set of criteria for classifying AIDS deaths based on VA data. Seventy-five percent of deaths from Manicaland Phase 1 were randomly assigned to a training dataset. From this training dataset, all signs/symptoms with a likelihood ratio >1.92 in univariate analyses were considered as potential identifiers of AIDS death (as defined below). Signs/symptoms were added to a list of criteria one at a time, based on the highest specificity. VA deaths with that sign/symptom were then removed from the dataset, and specificities of the remaining signs/symptoms were recalculated. Sensitivity was plotted against 1-specificity in a receiver operator characteristic (ROC) plot. (The ROC is tool used to select an optimum cut-off for a diagnostics test based on the trade-off of sensitivity and specificity.) These steps were repeated until the (equally-weighted) sensitivity and specificity of the list of symptoms was maximised (i.e. the point closest to the top left hand corner of the ROC plot). Deaths were classified as HIV/AIDS associated if the deceased had one or more of the criteria on the list. The sensitivity and specificity of the list was then tested on the Manicaland Phase 1 test data (the remaining 25% of deaths), all Phase 2 and all Kisesa data. AIDS death in the gold standard was defined as an individual who was (a) HIV positive at baseline survey based on antibody testing, (b) was not reported to have suffered major injury from motor vehicle accident, self-inflicted (suicide), or accidentally (accident) or deliberately inflicted by another person (homicide) in the two weeks prior to death and (c) did not die from direct obstetric causes (death during labor). Preliminary analyses highlighted that HIV prevalence amongst the deceased was markedly lower amongst the relatively older adults, so analyses were stratifies at age 45.

**Results**
There were a total of 376 and 219 deaths in Phases 1 (1998-2003) and 2 (2003-2005), respectively, of the Manicaland study and 197 in Kisesa (1994-2002), amongst 19 to 59 year-olds for which there was a VA and a conclusive HIV test done within three years of the death. A minority of deaths occurred in the 45 to 59 year age group (13%, 17% and 19%) in Manicaland Phase 1, Phase 2 and Kisesa cohorts, respectively (Table 1). In Manicaland, approximately 75% of deaths were caused by AIDS, compared with 51% in Kisesa 15 to 44 year olds, 33% amongst Kisesa 45 to 59 year olds. Herpes zoster, acute respiratory tract infections (ARTI), abscesses and sores, acute diarrhoea and tuberculosis (TB) were all less commonly reported in Kisesa than in Manicaland (Table 2). For deaths under age 45, weight loss, jaundice, tumours, ARTI and TB were less common amongst HIV positive deaths in Kisesa compared with Manicaland.

In applying the previously developed algorithm to Kisesa data, the sensitivity in classifying AIDS deaths was low (67%), mainly because of poor sensitivity (46%) in the 45-59 year age group. Based on this observation, the algorithm was re-trained on Manicaland Phase 1 data, restricted to 15 to 44 year olds. This resulted in a different ordering of symptoms compared with the original algorithm and in the inclusion of a ninth symptom since the addition of diarrhoea gave a slightly higher mean sensitivity and specificity (nine symptoms: 75.1% compared with eight symptoms: 74.7%). Using this new algorithm, a set of nine criteria with a sensitivity of 75.0% and specificity of 75.2% was produced (Figure 1).

The newly trained algorithm performed consistently based on sensitivity and specificity on 15 to 44 year old data from Manicaland Phase 1 test (sen 79%; spec 79%) Manicaland Phase 2 (sen 83%; spec 75%) and Kisesa (sen 75%; spec 74%). Although reasonable specificity was maintained on 45 to 59 year olds, the sensitivity dropped markedly in Manicaland Phase 1 test (sen 73%; spec 73%) Manicaland Phase 2 (sen 68%; spec 80%) and Kisesa (sen 54%; spec = 62%) in this older age group (Figure 2).

The INDEPTH network is an association of health and demographic surveillance systems in African, Asian and Oceania countries (http://www.indepth-network.org/). The network has developed a widely used verbal autopsy questionnaire, though the tool does not collect information on herpes zoster, abscesses or sores, vaginal tumours or oral candidiasis (Table 3).20 We measured the value of using the five signs/symptoms that are available from the INDEPTH questionnaire. In the 15 to 44 year old age group, using only these five signs/symptoms resulted in a sensitivity and specificity of 64% and 82% respectively (Figure 2). The reduction in sensitivity was less than expected, using the same five
criteria in Phase 2 Manicaland data and earlier Kisesa data sensitivity had fallen to 50% and 44% respectively.

**Discussion**

We developed a tool that consistently measures AIDS mortality using verbal autopsy. Through slight modification to our previously proposed criteria, the algorithm performs similarly in Zimbabwe and Tanzania - settings with different HIV prevalence (approximately 20% and 7%, respectively\(^{9,10}\)) and AIDS mortality and different distribution of other causes of death. The algorithm is robust in that it performs consistently when prevalence is above approximately 5%.

This method of measuring AIDS mortality produced reliable estimates only in the 15 to 44 year age group. This is due to increasing levels of other-cause mortality in older ages. In Manicaland, where the proportion of deaths due to HIV in the older age groups remained high,\(^{11}\) the methods worked well. But in Kisesa, where HIV prevalence is lower, AIDS mortality begins to drop off after 35 years of age, especially in women.\(^{6,14,21,22}\) and other causes also increase in the 45 to 59 years age groups. Tuberculosis, in particular, reduces the specificity marginally and the sensitivity markedly\(^{23,24}\) because tuberculosis symptoms overlap substantially with HIV symptoms resulting in miscategorization.

Given the sensitivity and specificity of the method from the training data, we would predict that 88% and 53% of 15 to 44 year old deaths in Manicaland and Kisesa were AIDS deaths, respectively. [The formulæ for this calculation are described in \(^{12}\). This compares with directly measured values of 76% and 51%. The overestimate in Manicaland is a result the algorithm actually performing better in Phase 2 (higher specificity) than it did on the training dataset. To calculate the prevalence of AIDS death, the level of miscategorization is corrected for; however, the level of miscategorization was actually smaller than calculated on the training data. This approach to estimation of AIDS deaths can be applied to other verbal autopsy data where a gold standard is not available, but the accuracy of the prediction will not be known. Therefore further validation of the algorithm is recommended.

The INDEPTH verbal autopsy is a widely used tool which used a shorter symptom list than ours and does not collect information to identify herpes zoster, oral candidiasis, abscesses/sores or vaginal tumours.\(^{23}\) These symptoms were commonly reported in our studies and (excluding vaginal tumours) were prevalent in AIDS deaths with a sensitivity of approximately 20% for zoster and abscesses/sores and 40% for oral candidiasis. We found that the INDEPTH shortlist would perform less well and have higher levels of miscategorization of AIDS deaths.\(^{23}\) The newly released WHO instrument includes
signs and symptoms associated with herpes zoster, abscesses/sores and oral candidiasis. In general, verbal autopsy have only proved accurate enough to assign cause-of-death in very broad categories in adults. However, statistical or algorithmic approaches, such as the method employed here, have been shown to perform adequately for determining prevalence of a specific cause, such as HIV. Unfortunately, causes of death other than HIV could not be validated as neither physician assessment nor diagnostics data were routinely available.

Our analyses show that in areas of generalised epidemics verbal autopsy can consistently measure AIDS mortality. Both studies had HIV prevalence levels exceeding 5%, which is commonly found in eastern and southern Africa. In settings where prevalence is less than 5%, getting AIDS mortality from VA may be difficult, and will require further validation studies. Even in higher prevalence settings analyses should be restricted to age groups where competing causes of mortality, especially other infectious causes, are relatively low. Especially, for the Tanzanian population the verbal autopsy method was much less accurate for deaths over age 45 years. Based on our analyses, we recommend surveillance of deaths in populations with severe HIV epidemics be undertaken in the 15 to 44 year age group. Addition of a handful of questions related to opportunistic infections would enable other widely used verbal autopsy tools (WHO and INDEPTH) to apply this validated methodology in areas where HIV testing and hospital records are unavailable or incomplete.

What this paper adds

What is already known on this subject?
Verbal autopsy is currently the best option for obtaining cause of death information in populations without comprehensive civil registration systems. Verbal autopsy is generally used to assign deaths to broad categories and estimate cause-specific mortality.

What does this study add?
We demonstrate that verbal autopsy can consistently measure AIDS mortality with a simple set of nine criteria. Surveillance should focus on deaths that occur in the 15 to 44 year age group where the method performs reliably. Adding just a handful of questions related to opportunistic infections would enable other widely used verbal autopsy tools to apply this validated methodology to assess AIDS mortality in areas where HIV testing and hospital records are unavailable or incomplete.

Funding
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Author’s contributions

Ben Lopman – drafted manuscript and led data analysis, Adrian Cook– statistical analysis, Jennifer Smith – statistical analysis, Godwin Chawira – VA data collection, Mark Urassa – study co-ordination, Yusufu Kumogola – VA data collection, Raphael Isingo – data management, Chikwe Ihekweazu – physician review of VA, Josephine Ruwende – physician review of VA, Milalu Ndege – demographic surveillance supervision, Simon Gregson – study design and writing of manuscript, Basia Zaba – analysis and writing of manuscript, Ties Boerma – study design

Competing Interest

None declared.
Figure 1. Receiver operator characteristic curve of algorithm on 15 to 44 year old deaths from Manicaland Phase 1

* Recent TB is shown for information but was not included in the final algorithm due poor specificity

Figure 2. Sensitivity and specificity of the trained algorithm. The dashed line represents the performance of the algorithm on the training dataset.

Panels A to D use the full set of nine signs and symptoms. Panels E and F use a smaller set of 5 signs/symptoms available from the current INDEPTH tool.
### Table 1. Prevalence of AIDS mortality in Kisesa and Manicaland verbal autopsy subjects.

<table>
<thead>
<tr>
<th>Age range</th>
<th>Phase 1 Train</th>
<th>Phase 1 Test</th>
<th>Phase 1 Test</th>
<th>Phase 2 Train</th>
<th>Phase 2 Test</th>
<th>Phase 2 Test</th>
<th>Kisesa Test</th>
<th>Kisesa Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>15 to 44</td>
<td>15 to 44</td>
<td>45 to 59</td>
<td>15 to 44</td>
<td>45 to 59</td>
<td>15 to 44</td>
<td>45 to 59</td>
<td>15 to 44</td>
<td>45 to 59</td>
</tr>
<tr>
<td>Total with HIV test and VA (n)</td>
<td>237</td>
<td>88</td>
<td>51</td>
<td>181</td>
<td>38</td>
<td>158</td>
<td>39</td>
<td></td>
</tr>
<tr>
<td>AIDS deaths in gold standard (n (%))</td>
<td>173 (73%)</td>
<td>64 (73%)</td>
<td>40 (78%)</td>
<td>137 (76%)</td>
<td>28 (73%)</td>
<td>81 (51%)</td>
<td>13 (33%)</td>
<td></td>
</tr>
</tbody>
</table>

### Table 2. Sensitivity and specificity of individual signs and symptoms for AIDS deaths in Manicaland and Kisesa cohorts, stratified at age 45.

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Train Manicaland 15-44 years n = 237</th>
<th>Test Manicaland 15-44 years n = 102</th>
<th>Test Manicaland Phase Two 15-44 years n = 180</th>
<th>Test Kisesa 15-44 years n = 158</th>
<th>Test Kisesa 45-45-59 years n = 39</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight loss</td>
<td>Se 9 100 10 99 12 98 0 91 10 96 23 84</td>
<td>Se 9 100 10 99 12 98 0 91 10 96 23 84</td>
<td>Se 9 100 10 99 12 98 0 91 10 96 23 84</td>
<td>Se 9 100 10 99 12 98 0 91 10 96 23 84</td>
<td></td>
</tr>
<tr>
<td>Herpes zoster</td>
<td>12 93 18 95 24 98 19 100 14 97 8 100</td>
<td>12 93 18 95 24 98 19 100 14 97 8 100</td>
<td>12 93 18 95 24 98 19 100 14 97 8 100</td>
<td>12 93 18 95 24 98 19 100 14 97 8 100</td>
<td></td>
</tr>
<tr>
<td>Jaundice</td>
<td>19 93 4 97 4 100 0 100 5 99 8 96</td>
<td>19 93 4 97 4 100 0 100 5 99 8 96</td>
<td>19 93 4 97 4 100 0 100 5 99 8 96</td>
<td>19 93 4 97 4 100 0 100 5 99 8 96</td>
<td></td>
</tr>
<tr>
<td>Vaginal tumours</td>
<td>6 94 6 94 3 100 0 100 0 100 0 96</td>
<td>6 94 6 94 3 100 0 100 0 100 0 96</td>
<td>6 94 6 94 3 100 0 100 0 100 0 96</td>
<td>6 94 6 94 3 100 0 100 0 100 0 96</td>
<td></td>
</tr>
<tr>
<td>Wasting</td>
<td>19 93 19 95 15 95 13 100 16 95 8 100</td>
<td>19 93 19 95 15 95 13 100 16 95 8 100</td>
<td>19 93 19 95 15 95 13 100 16 95 8 100</td>
<td>19 93 19 95 15 95 13 100 16 95 8 100</td>
<td></td>
</tr>
<tr>
<td>ARTI</td>
<td>11 95 10 95 8 95 13 100 5 96 0 88</td>
<td>11 95 10 95 8 95 13 100 5 96 0 88</td>
<td>11 95 10 95 8 95 13 100 5 96 0 88</td>
<td>11 95 10 95 8 95 13 100 5 96 0 88</td>
<td></td>
</tr>
<tr>
<td>Abscesses or sores</td>
<td>24 90 24 92 29 98 32 100 19 96 8 100</td>
<td>24 90 24 92 29 98 32 100 19 96 8 100</td>
<td>24 90 24 92 29 98 32 100 19 96 8 100</td>
<td>24 90 24 92 29 98 32 100 19 96 8 100</td>
<td></td>
</tr>
<tr>
<td>Oral candidiasis</td>
<td>38 86 37 89 45 86 26 91 40 92 15 100</td>
<td>38 86 37 89 45 86 26 91 40 92 15 100</td>
<td>38 86 37 89 45 86 26 91 40 92 15 100</td>
<td>38 86 37 89 45 86 26 91 40 92 15 100</td>
<td></td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>17 95 17 92 29 93 23 100 10 92 8 88</td>
<td>17 95 17 92 29 93 23 100 10 92 8 88</td>
<td>17 95 17 92 29 93 23 100 10 92 8 88</td>
<td>17 95 17 92 29 93 23 100 10 92 8 88</td>
<td></td>
</tr>
<tr>
<td>Recent TB*</td>
<td>27 86 28 88 47 82 32 100 5 99 8 96</td>
<td>27 86 28 88 47 82 32 100 5 99 8 96</td>
<td>27 86 28 88 47 82 32 100 5 99 8 96</td>
<td>27 86 28 88 47 82 32 100 5 99 8 96</td>
<td></td>
</tr>
</tbody>
</table>

Se = Sensitivity; Sp = Specificity

* Recent TB is shown for information but was not included in the final algorithm due poor specificity
Table 3. Signs and symptoms for surveillance of AIDS mortality, and the availability in INDEPTH - another widely used verbal autopsy questionnaire.

<table>
<thead>
<tr>
<th>Sign/Symptom</th>
<th>Definition based on verbal autopsy question</th>
<th>Equivalent in INDEPTH VA questionnaire</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight loss</td>
<td>Moderate or severe weight loss with no other symptoms of malnutrition</td>
<td>Yes</td>
</tr>
<tr>
<td>Herpes zoster</td>
<td>Ever suffered from zoster</td>
<td>Not specifically mentioned (shingles, zoster, herpes) but questions on rash including where rash located (not if it is one-sided), did rash have blisters. No mention of pain during or after rash</td>
</tr>
<tr>
<td>Jaundice</td>
<td>Acute jaundice (yellowing of the whites of the eyes during the disease that lead to death) with fever and/or itching but without history of alcohol abuse</td>
<td>Yes</td>
</tr>
<tr>
<td>Vaginal tumours</td>
<td>Vaginal tumour for at least one month with or without bleeding</td>
<td>No</td>
</tr>
<tr>
<td>Wasting</td>
<td>Moderate or severe weight loss with at least four of the following symptoms: paleness, changing hair colour, oedema of legs, burning sensations of the feet, dry scaly skin</td>
<td>Two out of the five symptoms (but different phrasing): paleness, oedema of ankles</td>
</tr>
<tr>
<td>Acute respiratory tract illness</td>
<td>Trouble breathing, cough lasting 3 to 27 days with fever but not recent TB, weight loss or wasting, as above</td>
<td>Partial</td>
</tr>
<tr>
<td>Abscesses or sores</td>
<td>Had abscesses or sores</td>
<td>No</td>
</tr>
<tr>
<td>Oral candidiasis</td>
<td>Had 2 or 3 of the following: ulcers in the mouth, difficulty swallowing, white patches inside the mouth and tongue</td>
<td>No</td>
</tr>
<tr>
<td>Diarrhoeal disease</td>
<td>Loose stools lasting 3 to 99 days, with or without dehydration</td>
<td>Yes</td>
</tr>
</tbody>
</table>
Reference List


Area under ROC curve = 0.7697
<table>
<thead>
<tr>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
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<tbody>
<tr>
<td><strong>A</strong> 15 to 44 year old deaths</td>
<td><strong>B</strong> 15 to 44 year old deaths</td>
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<td></td>
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<td></td>
<td></td>
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<tr>
<td><strong>C</strong> 45 to 59 year old deaths</td>
<td><strong>D</strong> 45 to 59 year old deaths</td>
</tr>
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<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>E</strong> 15 to 44 year old deaths, using only criteria available from INDEPTH</td>
<td><strong>F</strong> 15 to 44 year old deaths, using only criteria available from INDEPTH</td>
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<td></td>
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