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The Effect of Misclassification Error on Reported Cause-Specific Mortality Fractions from Verbal Autopsy

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Background. Verbal autopsy (VA) studies are important for measuring cause-specific mortality in areas where medical certification of cause of death is uncommon. This paper explores the effects of misclassification errors on the results of verbal autopsy studies, and recommends ways to take misclassification errors into account in the interpretation of results.
Methods. Mathematical formulae are derived for determining the size and direction of the error in cause-specific mortality estimates based on VA studies caused by misclassification. The levels of sensitivity and specificity found in currently available validation studies for childhood VA are examined.
Results. There can be substantial errors in the estimates of the cause-specific mortality fraction derived from VA studies. The cause-specific mortality fraction itself has an important influence on the size of the error for given levels of sensitivity and specificity, and when the cause-specific mortality fraction is small, the size of the error depends more on specificity than on sensitivity.
Conclusion. Despite its drawbacks VA seems to be the most promising way of establishing cause of death when most deaths take place at home without medical attention. However, more validation studies on standardized instruments are required in order to collect information about sensitivity and specificity and subsequently improve the design of the instrument. At the same time, analysts need to take misclassification errors into consideration in ways outlined in this paper.
Keywords: verbal autopsy, misclassification error, sensitivity, specificity, cause of death

Verbal autopsies (VA) are increasingly being used to monitor the distribution of death by cause in places where medical certification of cause of death is uncommon. They involve interviewing close relatives or caretakers of the deceased and classifying causes of death on the basis of the interview. They are valuable for health managers in establishing baseline data on causes of death in the population and to monitor how well the health services are doing in combating specific diseases, in studies of new interventions aimed at averting deaths from a particular cause, and in epidemiological research into factors associated with mortality from a specific cause.

VA results are not based on clinical or laboratory measures, and are subject to a relatively high degree of misclassification error. To date, very little is known about the size of misclassification error, and misclassification error is rarely taken into account in reports from VA studies. As we will show in this paper: (i) this misclassification can have a profound effect on the reported estimate of the proportion of deaths due to a specific cause (the cause-specific mortality fraction); and (ii) it is possible to estimate the size and direction of some of these errors, and correct for them.

In a companion paper in this issue Maude and Ross[1] focus on sample sizes required for population-based surveys aimed at estimating changes in cause-specific mortality over time. However, this paper focuses on estimating the fraction of deaths due to a single cause. First, there is a discussion of the ways in which misclassification error arises and its effects on the estimated cause-specific mortality fraction. Second, conditions are derived under which VA results are overestimates or underestimates of the true cause-specific mortality fraction. Third, levels of sensitivity and specificity found so far in child VA validation studies are reviewed in terms of their potential for producing accurate estimates. Fourth, there is discussion on the judicious choice of diagnostic criteria, including a table presenting the expected size and direction of errors from VA studies for different levels of sensitivity, specificity, and for different cause-specific mortality fractions.

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TABLE 1 *Hypothetical examples illustrating the effects of changes in the cause-specific rates, sensitivity and specificity on the VA estimates of a cause-specific mortality fraction*

Row	Sensitivity	Specificity	True cause-specific mortality fraction	Estimated cause-specific mortality fraction	Estimated cause-specific morality fraction minus true cause-specific mortality fraction
1	0.70	0.90	0.300	0.280	–0.020
2	0.70	0.90	0.100	0.160	+0.060
3	0.70	0.90	0.250	0.250	0.000
4	0.70	0.80	0.250	0.325	+0.075
5	0.60	0.90	0.250	0.225	–0.025
6	0.80	0.90	0.250	0.275	+0.025

Fifth, conclusions are drawn about how misclassification affects VA results. Steps to improve the accuracy of the results are indicated.

Misclassification errors arise in two ways. For example, when estimating mortality caused by diarrhoea in children, error occurs if (i) a child who did not die from diarrhoea is classified as a diarrhoeal death, or if (ii) a child who did die from diarrhoea is classified as a non-diarrhoeal death. These two types of measurement error give rise to the well-known concepts of sensitivity and specificity. The sensitivity of a VA for a particular cause of death such as diarrhoea is the proportion of the deceased whose cause of death is correctly identified as diarrhoea out of all those who truly died from diarrhoea, while the specificity is the proportion whose cause of death is identified as not diarrhoea among those who truly did not die from diarrhoea.

Misclassification affects the accuracy of the VA estimate whenever it creates an imbalance between the number of false positives and the number of false negatives. When there is an excess of false positives over false negatives, the estimate of the cause-specific mortality fraction based on VA is an overestimate. Conversely, when there is an excess of false negatives over false positives, it is an underestimate. When the number of false positives equals the number of false negatives, the errors are counterbalancing and therefore they do not affect the VA estimate. Thus, the fact that there is misclassification, in and of itself, does not necessarily imply that the resulting VA estimate of the cause-specific mortality fraction will be inaccurate.

This paper does not address a separate but important problem in estimating cause-specific mortality fractions which arises when only one cause of death is coded. Using such a coding scheme, inaccurately measuring one cause of death necessarily implies inaccurately measuring other causes of death, and therefore it is necessary to look at misclassification of several causes of death at a time. This problem does not arise when multiple causes of death are allowed.

The Effect of the Cause-Specific Mortality Fraction on the Accuracy of VA Estimates

The effect of misclassification on observed estimates of mortality from a specific cause depends upon two factors: (i) the sensitivity and specificity of the VA instrument; (ii) the true proportion of deaths from that cause (the cause-specific mortality fraction). Table 1 presents hypothetical examples (discussed below) to illustrate how each of these two factors affects the accuracy of VA estimates.

The first three rows of Table 1 show how the cause-specific mortality fraction affects the accuracy of VA estimates. In these first three rows, a sensitivity of 0.70, and a specificity of 0.90 are assumed, but the cause-specific mortality fraction is different in each row. In the first row, 30% of the deaths were caused by A. In this example, the VA estimates that 28% of deaths were caused by A, a two percentage point underestimate. In the second row 10% of deaths were caused by A. This resulted in a six percentage point overestimate of deaths caused by A (16%–10%). In the third row 25% of the deaths were caused by A which is a correct estimate. In this case the misclassification errors are counterbalancing.

These three examples illustrate that sensitivity and specificity alone, while very important, are not sufficient to determine the accuracy of VA results. In fact, the same VA instrument can sometimes overestimate and sometimes underestimate deaths due to a specific cause, depending on the underlying proportion of deaths due to that cause in the population in which the VA is being used.

The Effect of Sensitivity and Specificity on the Accuracy of VA Estimates

Rows 3–6 of Table 1 present four hypothetical examples, each with a true cause-specific mortality fraction of 0.25. As discussed above, row 3 illustrates a situation in which a correct VA estimate was achieved. The remaining rows 4–6 present hypothetical examples in which either the sensitivity or specificity differs from the example summarized in row 3. In row 4 where the specificity is less than row 3, the VA results in a substantial overestimate (32.5% versus 25%). In row 5 where the sensitivity is less than in row 3, the VA results in an underestimate.

These two examples correspond to intuitive expectations that decreases in sensitivity or specificity imply decreases in accuracy. This is not always the case, as shown by comparing rows 3 and 6 in Table 1. Decreasing the sensitivity of the VA instrument from 0.80 (row 6) to 0.70 (row 3) results in a more accurate estimate of the cause-specific mortality fraction (an overestimate for row 6 versus a correct estimate for row 3).

The preceding examples illustrate the dependency of the VA estimate on the cause-specific mortality fraction, sensitivity and specificity. They also illustrate the necessity of understanding more about those situations in which VA results are overestimates or underestimates, especially since decreasing sensitivity and/or specificity does not necessarily decrease accuracy. When VA are used for measuring cause-specific mortality fractions, there is usually no way of knowing the true cause-specific mortality fraction. Therefore, it is necessary to examine the relationship between the estimated cause-specific mortality fraction (rather than the true cause-specific mortality fraction), and the sensitivity and specificity of the instrument.

CONDITIONS UNDER WHICH VA RESULTS UNDERESTIMATE, CORRECTLY ESTIMATE OR OVERESTIMATE CAUSE-SPECIFIC MORTALITY

In this section an equation is derived for the difference between the true proportion of deaths from a specific cause and the VA estimate. It is based on the basic definitions of sensitivity and specificity. For clarity the definition of terms used in this document are presented in Table 2.

From Table 2 it is clear that equations (1) and (2) hold:

$$(\text{sensitivity}) \times (N_t) + (1 - \text{specificity}) \times (N_f) = a + b \quad (1)$$

TABLE 2 *Hypothetical table showing the numbers of deaths truly attributable to cause A by the numbers of deaths attributed to cause A by a VA*

Cause of death based on VA	True cause of death		
	Cause A	Not cause A	Total
Cause A	a	b	a + b
Not cause A	c	d	c + d
Total	N_t	N_f	N

Sensitivity = a/(a + c)
Specificity = d/(b + d)
Cause-specific mortality fraction based on VA = (a + b)/N.
True cause-specific mortality fraction = N_t/N.

$$(1 - \text{sensitivity}) \times (N_t) + (\text{specificity}) \times (N_f) = c + d \quad (2)$$

Solving these equations for N_t

$$N_t = \frac{(1 - \text{specificity}) \times (c + d) - (\text{specificity}) \times (a + b)}{1 - \text{sensitivity} - \text{specificity}} \quad (3)$$

(This equation is undefined if sensitivity + specificity = 1.)

The difference 'diff' between the true proportion of deaths from a specific cause, N_t/N, and the VA estimate of the proportion of deaths from that cause, (a + b)/N, can be algebraically derived from equation (3) and represented as follows:

$$\text{diff} = \frac{N_t - (a + b)}{N} = \frac{[(c + d) \times (1 - \text{specificity})] - [(a + b) \times (1 - \text{sensitivity})]}{N \times (1 - \text{specificity} - \text{sensitivity})} \quad (4)$$

The smaller $|\text{diff}|$ is, the more accurate the estimate, and the larger $|\text{diff}|$ is, the less accurate the estimate. Equation (4) yields an important observation about the relationship between sensitivity, specificity and the accuracy of the VA estimate, namely that the accuracy of the VA estimate is usually much more dependent on the specificity of the VA instrument than the sensitivity. This is because the cause-specific mortality fractions are generally small, and consequently a + b is generally much smaller than c + d. Unless the specificity is high, and therefore (1 – specificity) is relatively small, the first addend in the numerator [(c + d) × (1 – specificity)]

is likely to be much larger than the second addend $[(a + b) \times (1 - \text{sensitivity})]$.

This has important implications for the design (and validity testing) of VA instruments which are intended mainly for use in estimating cause-specific mortality fractions. In general, these instruments should be designed to maximize specificity even if this means sacrificing some sensitivity. This compromise is particularly important for diseases in which the cause-specific mortality fraction is expected to be relatively small.

Equation (4) can also show whether or not a given VA result is likely to be an underestimate, an overestimate, or a correct estimate of the true cause-specific mortality fraction. By definition, when diff > 0, the VA instrument underestimates cause-specific mortality; when diff = 0, the VA correctly estimates cause-specific mortality and when diff < 0 the VA overestimates cause-specific mortality. Substituting these values in equation (4) and assuming that sensitivity + specificity >1, yields the following relationships:

$$\text{The VA is an underestimate if } \frac{a + b}{N} > \frac{1 - \text{specificity}}{2 - \text{specificity} - \text{sensitivity}}$$

$$\text{The VA is a correct estimate if } \frac{a + b}{N} = \frac{1 - \text{specificity}}{2 - \text{specificity} - \text{sensitivity}}$$

$$\text{The VA is an overestimate if } \frac{a + b}{N} < \frac{1 - \text{specificity}}{2 - \text{specificity} - \text{sensitivity}}$$

Using the above inequalities, it is possible to judge the direction of error of a VA estimate for given levels of sensitivity and specificity by comparing the VA estimate of cause-specific mortality fraction to the ratio (1 – specificity)/(2 – specificity – sensitivity).

A REVIEW OF LEVELS OF SENSITIVITY AND SPECIFICITY FROM VALIDATION STUDIES

To date relatively few VA validation studies have been done; therefore, available information on sensitivity and specificity for specific causes of death is scanty at best.[2] Efforts are currently under way to increase the availability of such information. A joint WHO/UNICEF consultation in December 1992 recommended that a 'best judgement' VA questionnaire for infants and children be developed and tested for validity in a number of sites carefully chosen for their geographical and epidemiological diversity.[3] A questionnaire has been developed and is currently undergoing validation for settings in Bangladesh, Uganda, and Nicaragua. An adult VA instrument is currently being tested for validity in Tanzania, Ghana and Ethiopia. Despite the lack of precise estimates for sensitivity and specificity, it is worth investigating whether or not the information gathered so far on sensitivity and specificity for childhood VA can shed light on the precision of VA estimates. This seems sensible, since ignoring misclassification errors assumes that the VA has perfect sensitivity and specificity, an assumption which we know is incorrect, and sometimes grossly misleading.

Table 3 presents the sensitivity and specificity values found for common causes of childhood deaths reported by several VA validation studies. Despite the use of different questionnaires and methodologies, some patterns emerge. Some causes of childhood death, such as neonatal tetanus, measles, and accidents, have relatively high rates of sensitivity and specificity, while others such as acute respiratory infections (ARI), malaria and diarrhoea have lower levels of sensitivity and/or specificity.

For most studies and for most major childhood causes of death, there is at least one set of diagnostic criteria that results in a specificity of at least 0.85, and often higher. ARI is an important exception. Except for one study in Kenya (in which the sensitivity (0.28) was extremely low), no other study achieved a specificity for ARI greater than 0.82. Given the need for high levels of specificity discussed in the previous section, formulating a more highly specific set of diagnostic criteria for ARI is essential. In the meantime, reported estimates of mortality from ARI based on VA should be treated with considerable caution.

CHOOSING AMONG DIAGNOSTIC CRITERIA

For most causes of death, there are considerable differences in specificity and sensitivity depending on the diagnostic criteria used. The stricter the criteria, the higher the specificity and the lower the sensitivity. For example, in Table 3, sensitivity and specificity corresponding to two different diagnostic criteria for measles are presented for a study in Namibia. For the first criterion (age at least 120 days plus rash), sensitivity and specificity are 0.71 and 0.85 respectively. When a second criterion (fever for $\geqslant$3 days) was added, some measles cases that met the first criteria failed to meet the second criteria, and sensitivity fell to 0.67. Similarly, some non-measles cases that met the first criteria failed to meet the second criteria, causing specificity to rise to 0.90.

Table 4 (which is based on equation (4) above) presents values of diff for various levels of sensitivity, specificity and different cause-specific mortality fractions.

TABLE 3 *Sensitivity and specificity of verbal autopsies for detecting major causes of childhood death based on available validation studies*

Cause of death	Country	Source*	Sensitivity	Specificity	Comments
Neonatal tetanus	Philippines	1	94–100	–	
	Kenya	2	90	79	
	Bangladesh	5	97	98	
Measles	Philippines	1	98	90	Age ⩾120 days, rash and fever ⩾3 days
	Philippines	1	98	93	Age ⩾120 days, fever ⩾3 days, rash anywhere except only on extremities
	Philippines	1	83	99	Age ⩾120 days, fever ⩾3 days, rash anywhere except only on extremities, plus rash progression
	Kenya	2	90	96	
	Namibia	3	71	85	Age ⩾120 days, rash
	Namibia	3	67	90	Age ⩾120 days, rash, fever ⩾3 days
Diarrhoea	Kenya	2	36	96	
	Philippines	1	60	85	⩾6 liquid stools per day
	Philippines	1	78	79	Frequent loose or liquid stools
	Namibia	3	56	90	⩾6 liquid stools per day
	Namibia	3	89	61	Loose or liquid stools
	India	4	90	78	Gastro-enteritis
	Bangladesh	5	77	97	⩾6 liquid stools
AIR	Philippines	1	66	60	Cough and dyspnoea ⩾1 day
	Philippines	1	59	77	Cough ⩾4 days and dyspnoea ⩾1 day
	Kenya	2	28	91	
	Namibia	3	72	64	Cough with dyspnoea or tachypnoea
	India	4	56	81	
	Bangladesh	5	58	82	Cough or difficult breathing or fast breathing
Malaria	Kenya	2	46	89	Diagnosis based on medical records included all malaria parasitemia
	Namibia	3	45	87	Fever and convulsions or loss of consciousness (for all malaria parasitemia)
	Namibia	3	72	85	Fever and convulsions or loss of consciousness (for cerebral malaria only)
Malnutrition	Kenya	2	89	96	
	Namibia	3	73	76	
	India	4	71	100	
Accidents	Kenya	2	78	100	
	India	4	100	100	Accidents and major congenital problems
Sepsis	Kenya	2	61	81	Neonates

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NB: This Table is adapted from Table 1 of reference 1.

This table can be helpful when evaluating the feasibility of using a VA study in a particular setting, since it allows the reader to see how the accuracy of the VA estimate varies with different assumptions about sensitivity, specificity and the cause-specific mortality fraction.

This table can also be used in selecting the diagnostic criteria most likely to result in an accurate estimate. For example, as shown in Table 3 for the Philippines validation study, sensitivity and specificity associated with diarrhoea were 0.60 and 0.85 respectively for the strictest criterion (⩾6 liquid stools per day) and close to

TABLE 4 *Differences between the verbal autopsy estimate of and the true cause-specific mortality fraction for different levels of specificity and sensitivity and for different cause-specific mortality fractions*

Sensitivity	True cause-specific mortality fraction	Specificity						
		0.60	0.70	0.80	0.85	0.90	0.95	0.99
0.60	0.01	+0.392	+0.293	+0.194	+0.145	+0.095	+0.046	+0.006
	0.05	+0.360	+0.265	+0.170	+0.123	+0.075	+0.028	–0.010
	0.10	+0.320	+0.230	+0.140	+0.095	+0.050	+0.005	–0.031
	0.20	+0.240	+0.160	+0.080	+0.040	+0.000	–0.040	–0.072
	0.30	+0.160	+0.090	+0.020	–0.015	–0.050	–0.085	–0.113
	0.40	+0.080	+0.020	–0.040	–0.070	–0.100	–0.130	–0.154
0.70	0.01	+0.393	+0.294	+0.195	+0.146	+0.096	+0.047	+0.007
	0.05	+0.365	+0.270	+0.175	+0.128	+0.080	+0.033	–0.005
	0.10	+0.330	+0.240	+0.150	+0.105	+0.060	+0.015	–0.021
	0.20	+0.260	+0.180	+0.100	+0.060	+0.020	–0.020	–0.052
	0.30	+0.190	+0.120	+0.050	+0.015	–0.020	–0.055	–0.083
	0.40	+0.120	+0.060	0.000	–0.030	–0.060	–0.090	–0.114
0.80	0.01	+0.394	+0.295	+0.196	+0.147	+0.097	+0.048	+0.008
	0.05	+0.370	+0.275	+0.180	+0.133	+0.085	+0.038	–0.001
	0.10	+0.340	+0.255	+0.160	+0.115	+0.070	+0.025	–0.011
	0.20	+0.280	+0.200	+0.120	+0.080	+0.040	+0.000	–0.032
	0.30	+0.220	+0.150	+0.080	+0.045	+0.010	–0.025	–0.053
	0.40	+0.160	+0.100	+0.040	+0.010	–0.020	–0.050	–0.074
0.90	0.01	+0.395	+0.296	+0.197	+0.148	+0.098	+0.049	+0.009
	0.05	+0.375	+0.280	+0.185	+0.138	+0.090	+0.043	+0.005
	0.10	+0.350	+0.260	+0.170	+0.125	+0.080	+0.035	–0.001
	0.20	+0.300	+0.220	+0.140	+0.100	+0.060	+0.020	–0.012
	0.30	+0.250	+0.180	+0.110	+0.075	+0.040	+0.005	–0.023
	0.40	+0.200	+0.140	+0.080	+0.050	+0.020	–0.010	–0.034
0.99	0.01	+0.396	+0.297	+0.198	+0.148	+0.099	+0.049	+0.010
	0.05	+0.380	+0.285	+0.190	+0.142	+0.095	+0.047	+0.009
	0.10	+0.359	+0.269	+0.179	+0.134	+0.089	+0.044	+0.008
	0.20	+0.318	+0.238	+0.158	+0.118	+0.078	+0.038	+0.006
	0.30	+0.277	+0.207	+0.137	+0.102	+0.067	+0.032	+0.004
	0.40	+0.236	+0.176	+0.116	+0.086	+0.056	+0.026	+0.002

0.80 and 0.80 respectively for the more inclusive criterion, (frequent loose or liquid stools); furthermore, according to the research literature, diarrhoeal disease frequently accounts for 10–30% of all childhood deaths. In this case, the strictest criterion ($\geqslant$6 liquid stools per day) would result in a difference between the VA estimate and the true cause-specific mortality fraction of 9.5% if the cause-specific mortality fraction was 10%, while the more inclusive criterion would result in a difference of 16%. If the cause-specific mortality fraction were 30%, the difference would be –1.5% for the strictest criterion and 8% for the more inclusive criterion. In both cases, the stricter criterion would result in the more accurate estimate.

Table 4 also illustrates just how dependent the accuracy of the VA estimates is on the cause-specific mortality fraction, and clearly indicates that use of a VA questionnaire to measure change in cause-specific patterns, without taking into consideration how this change itself affects accuracy would be misleading. For example, suppose cause-specific mortality went from 0.30 to 0.10 over a 10-year period. If the sensitivity and specificity of a VA instrument were both 0.90, the initial VA estimate of the cause-specific mortality fraction would be 0.34, while the estimate 10 years later would be 0.18. This would result in an estimated decrease of 48% instead of a real decrease of 67%.

CONCLUSIONS

This paper has been concerned with misclassification of cause of death by VA and its implication for the design and interpretation of VA instruments. The first section demonstrated that misclassification errors can be

substantial and that they depend not only on sensitivity and specificity, but also on the cause-specific mortality fraction.

The inequalities present conditions under which VA overestimate or underestimate the true cause-specific mortality fraction, and equation (4) presents a formula for calculating the difference between a VA estimate and the true cause-specific mortality fraction. Both of these equations require information about the specificity and sensitivity of the VA instrument. Based on the discussions in this paper, it is easy to see that specificity is more important than sensitivity in determining the accuracy of the VA instrument, especially when the cause-specific mortality fraction is low, say below 0.10.

To date, unfortunately, there is little information on the sensitivity or specificity of many of the VA instruments currently in use. The few available validation studies have used different instruments and validation procedures. Nonetheless, for most important causes of childhood death, there is at least one diagnostic formulation which leads to a specificity of at least 0.85 (an exception is ARI which will require more research to get up to that level).

Despite its deficiencies, VA seems to be the most promising way of establishing cause of death when most deaths take place at home without medical attention. In order to improve the accuracy of estimates of VA, more validation studies using standardized instruments and study designs are required, in order to provide opportunities to collect information about its sensitivity and specificity and subsequently to improve the design of the instrument. At the same time, analysts should take into consideration how misclassification errors affect the accuracy of reported cause-specific mortality rates in the ways outlined in this paper.

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