Performance of InSilicoVA for assigning causes of death to verbal autopsies: multisite validation study using clincial diagnositic gold standards

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# Abstract

**Background:**

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# Background

Reliable population-level causes-of-death estimates are critically important for designing effective public health policies.[ref] Verbal autopsy is a key component of enhancing health information systems in many countries which do not have complete civil registration and vital statistics systems.[ref] Verbal autopsy consists of a structured interview with family members of the deceased with the purpose of gathering enough information to infer the likely cause of death.[ref] In some countries where 60 to 80 percent of death occur without medical attendance, verbal autopsy provides the only usable information for generating population-level estimates with reasonable and representative coverage.[ref] Computer algorithms which can assign a cause of death greatly increase the feasibility of integrating VA into CRVS systems. Computer coding of verbal autopsy (CCVA) allows systems to be scalable, consistent, and sustainable.[ref]

Numerous algorithms for predicting the cause of death from verbal autopsies have been developed over the last decade.[refs] We previously developed a framework for validating the predictive accuracy of different methods.[ref] This validation procedure allows for direct comparison of methods using the same standard set of criteria. It provides a way of determining how well an algorithm will perform in different populations when the true distribution of causes of death is not known. This is crucial for generalizing results to new study populations and accurately capturing unknown changes in cause of death composition in the same population across time. We have used this procedure to determine the accuracy of a wide range of previously developed methods.[ref horserace]

Recently a new algorithm for CCVA called *InSilicoVA* was developed and published.[ref JASA paper on insilico] This method builds off previous research with the InterVA algorithm. InSilicoVA advances research in CCVA in a number of key ways. Of particular interest, the algorithm quantifies uncertainty in the individual-level predictions and uses this information to better predict the cause distribution at the population-level. This aligns well with the current focus of using VA to estimate the distribution of causes of death for populations. The authors use a number of ways to determine the performance and of their algorithm, including the method we proposed. However, the authors only validated the results for adult deaths and not child or neonate deaths. Additionally, for technology which has long lasting effects on health systems, we believe that independent validation of results is essential. Policy makers in countries are working to incorporate verbal autopsy into routine surveillance and vital statistics. Today’s choices about which technology to use, may be harder reverse later.

In this study we independently validate the performance of the InSilicoVA algorithm for all ages using the same Population Health Metric Research Consortium (PHMRC) gold standard database used in the original study. We conduct the validation procedure developed in Murray et al. and assess performance both at the individual-level, using chance-corrected concordance (CCC), and at the population-level, using chance-corrected cause-specific mortality fraction (CCCSMF) accuracy. We found the performance of InSilicoVA lower than reported in the original study, especially for children.

# Methods

## Algorithm

InSilicoVA is a Bayesian method, like InterVA (Byass, Huong, and Van Minh 2003) and the Symptom Pattern Method (Murray et al. 2007). The algorithm is documented in detail elsewhere and key points are summarized here (McCormick et al. 2016). InSilicoVA seeks to improve on InterVA in three key ways. First, the model uses information about symptoms which are not endorsed to estimate probabilities for each cause which are comparable across observations. This allows the model to estimate the uncertainty of each prediction. Second, the individual-level and population-levels are estimated simultaneously in a manner which allows the model to leverage the information about the uncertainty in individual-level predictions to produce more accurate population-level predictions. Third, the model provides a mechanism for incorporating additional information, such as physician labeled cause of death. The model is estimated using Markov-Chain Monte-Carlo (MCMC) simulations. To produce usable results the algorithm must run a sufficient number of samples to ensure convergence.

The authors have released their algorithm as an R package, with computationally intensive Markov chain Monte Carlo calculation implemented in Java through R’s rJava package. The algorithm utilizes a matrix of condition probabilities between each cause and each symptom. These propensities, which the authors call the *probbase*, capture the user’s initial estimate of the relative likelihood of a symptom being endorsed for a given cause of death. They can be derived from data or from expert judgement. The R package allows the user to input their own probbase file and also provides a default probbase based on the InterVA project. Open-source source code for the R implementation of InSilicoVA is available online free of charge.

## Data

We used the Population Health Metrics Research Consortium (PHMRC) gold standard database (“Population Health Metrics Research Consortium Gold Standard Verbal Autopsy Data 2005-2011” 2013) to validate the InSilicoVA algorithm. This dataset contains verbal autopsies matched to cause of death diagnoses from medical autopsies. A complete description of this dataset is available elsewhere and is summarized here (Murray, Lopez, et al. 2011). Cases included in the dataset were initially identified from deaths in hospitals where strict, pre-determined diagnostic criteria, were satisfied. This ensured that true cause of death was known with as much certainty as deaths included in well informed vital registration systems. For cases which met the gold standard diagnostic criteria, blinded verbal autopsy were collected using an enhanced version of the WHO verbal autopsy instrument.

The database contains 12,530 records from six sites in four different countries. Data were collected in Andhra Pradesh, India; Bohol, Philippines; Dar es Salaam, Tanzania; Mexico City, Mexico; Pemba Island, Tanzania; and Uttar Pradesh, India between 2007 and 2010. The database includes deaths from 7,841 adults, 2,064 children, 1,620 neonates and 1,005 stillbirths. The recommended target list of gold standard diagnosis includes 34 adult causes, 21 child causes and 6 neonate causes (including stillbirth). The number of records in each cause category is presented in Table XXX.

## Validation Framework

All statistics which can assess the performance of a classifier at the population level are affected by the composition of cause distribution in the study population (Murray, Lozano, et al. 2011). If a classifier is biased and predicts one cause a high proportion of the time regardless of the predictors, it may appear to high predictive accuracy if used in a population which coincidentally has a high rate of the cause for which the classifier is biased towards. However, it is extremely likely the classifier will perform very poorly in most other populations. For this reason, it is essential to test the predictive performance of a classification method on multiple datasets which have different cause compositions. In this study we follow the recommendations of Murray et al. for validating verbal autopsy classification methods (Murray, Lozano, et al. 2011). For methods which require training, the validation dataset is divided into 500 train-test sets. For each set, any given record appears in either the train set or the test set, but not both. The test is then resampled to an uninformative Dirichlet distribution. This ensures that the cause composition of the train and test sets are completely uncorrelated.

When assessing the performance of an algorithm for predicting cause of death from verbal autopsy data it is useful to look at how well it performs at both the individual level and the population level. To assess performance at the individual level we use the median chance correct concordance (CCC) across causes (Murray, Lozano, et al. 2011). To assess performance at the population level we use chance corrected cause-specific mortality fraction accuracy (CCCSMF).[ref] Chance correct concordance is calculated as … Values range between -1.0 and 1.0 where 1.0 indicates perfect ability to detect a cause, 0.0 indicates random guessing, and -1.0 indicates no ability to detect a cause. The key benefit of chance corrected concordance is that it is not affect by the cause distribution in the study population. This allows for comparison across different studies without needing to know or control for the true cause distribution. Cause-specific mortality fraction (CSMF) accuracy is calculated as … This statistic can be corrected for chance as shown by Flaxman et al (Flaxman et al. 2015). Chance-corrected CMSF is calculated as … Similarly to CCC, CCCSMF ranges from negative to 1.0 with 0.0 indicating completely random guessing.

## InSilicoVA Validation

The InSilicoVA R package allows for a range of customizations to the inputs used to predict the cause of death. We validate the algorithm using three different configurations of inputs to assess its usability and performance. These configurations are: 1) using the built-in default training data, 2) training the algorithm with inputs which resemble the defaults, and 3) training the algorithm with inputs which do not resemble the defaults. For each of these configuration we test all age groups both with and without health care experience questions.

The default configuration assumes the input data matches the InterVA4 format with 245 symptoms. It uses the conditional probabilities used in InterVA as a baseline and predicts one of 60 causes. With the default configuration no ancillary training data is required. To validate the default configuration, we mapped the PHMRC database to the InterVA format, and then used InSilicoVA to predict the cause of death. We then mapped the predicted WHO causes to the PHMRC gold-standard cause list. These mapped predictions were compared to the gold-standard cause listed in the PHMRC database and were used to calculate performance. Since the algorithm was not trained empirically, we used the entire validation dataset to test the predictive performance. It is still important to test the algorithm on different datasets with different cause compositions. We tested the default configuration on 500 test datasets, each with a cause composition drawn from an uninformative Dirichlet distribution and samples drawn with replacement from the complete dataset. The 46 adult causes present in the original PHMRC dataset mapped to 36, the 21 child causes were mapped to 20, and the 6 neonate causes were mapped to 7. Of the 245 symptom predictors used by InSilicoVA, the PHMRC dataset contained data for 124 adult symptoms, 69 child symptoms and 62 neonate symptoms.

Next we assessed how InSilicoVA performed with training data which matched it expected inputs. For this assessment, the PHRMC database was mapped to the InterVA format and the gold standard causes were mapped to the WHO causes. For each of the 500 test-train splits, we used the train split to calculated the empirical probability of an InterVA symptom being endorsed conditional on the WHO cause. This conditional probabilities matrix was used as the input probbase and the algorithm predicited WHO causes for the data in the test split after it been resampled to an uninformative Dirichlet cause distribution.

Finally, we assessed how the algorithm performed with training data of a different format than the standard inputs. For this assessment, the PHMRC database was mapped to the set of symptoms used by the Tariff 2.0 algorithm. Data were mapped to 171 adult symptoms, 86 child symptoms, and 110 neonate symptoms. For each of the 500 test-train splits, we used the train split to calculate the empirical probability of a Tariff 2.0 symptom being endorsed conditional on the original PHMRC gold standard cause. The InSilicoVA algorithm used this conditional probabilities matrix to predict PHMRC causes for data in the test split after it had been resampled to an uninformative Dirichlet cause distribution. Of the three assessment, this configuration should be the most favorable towards InSilicoVA since it avoids any possible discrepancies in between definitions of the PHMRC causes and the WHO causes and it provides more symptom predictors for the algorithm to use.

The R packages has 10 hyperparameters which allow users to tune the estimation procedure. Except where specifically mentioned, we used the default value provided by the InSilicoVA packages. Training was accomplished using the extract.prob function provided by the InSilicoVA package.

# Acknowledgements

# Competing Interests

The authors declare that they have no competing interests.

# Author’s contributions

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