InSilicoVA - An Algorithm for Automated COD Classification using Verbal Autopsy Data

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Overview

Preliminaries

Motivation: global burden of disease and cause of death

Verbal autopsy
- VA algorithms and InterVA
- InSilicoVA
- VA Algorithm Validation Study
- Software, and users

Beyond InSilicoVA

Acknowledgements

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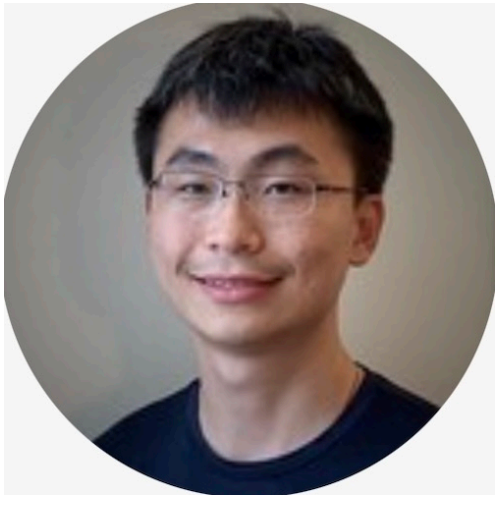
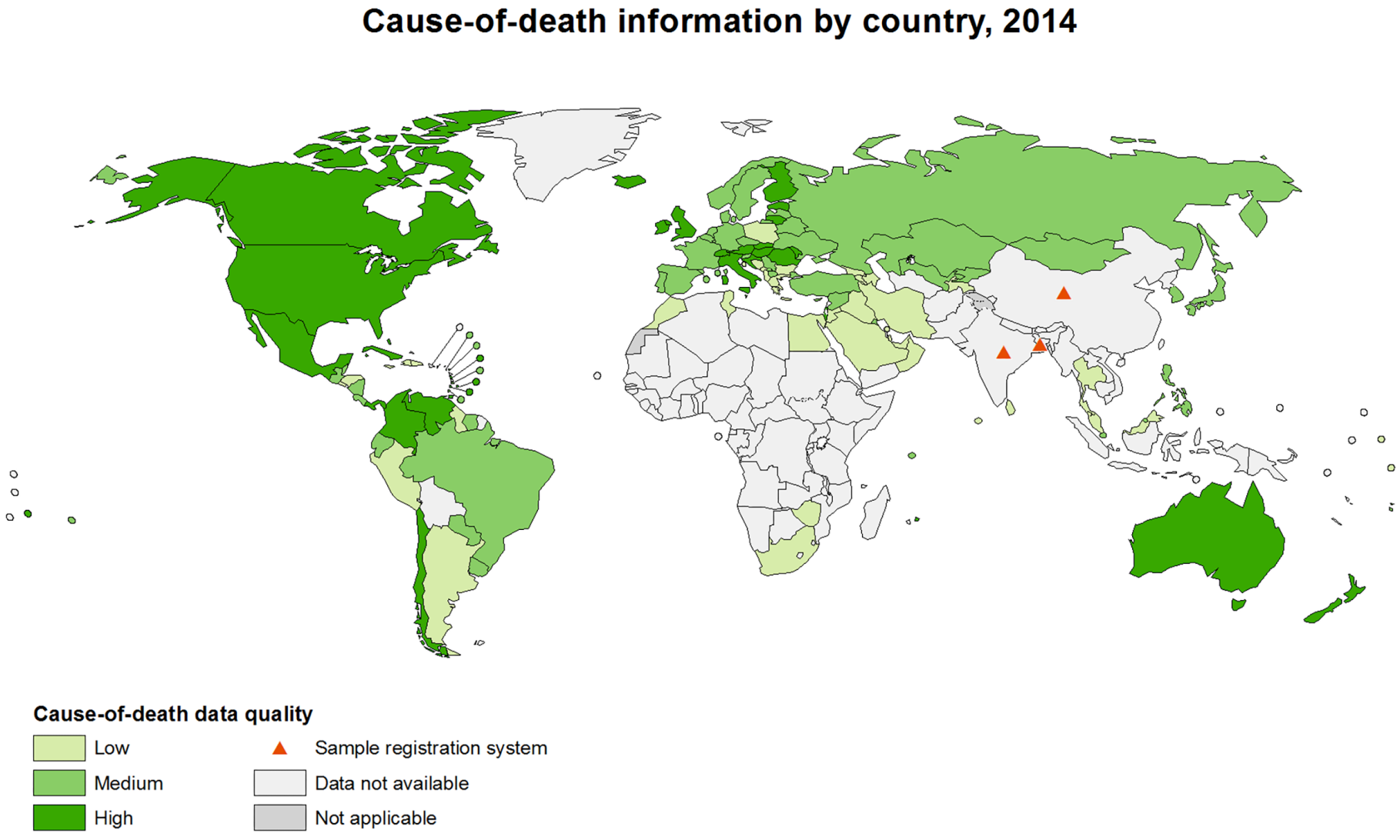


Richard Li

Tyler McCormick

Global COD information (Nichols et al. [43])



Burden of disease and cause of death determination

Burden of disease - BOD

- BOD is the distribution of deaths by cause
- BOD is fundamental population health metric
- Little *empirical knowledge* of the BOD for Africa and other resource-constrained settings

COD determination

- Registering and establishing a cause for all deaths are important population health priorities
- Traditional methods for COD determination are not feasible in resource-constrained settings
- The only realistic alternative is verbal autopsy - VA

Verbal autopsy – **VA**

Aim: Assign a cause to a death with VA – classify the death using an abbreviated VA cause list

Data:

1. Data from VA interview with knowledgeable caregiver of decedent
   - quantitative questions on signs, symptoms, diagnoses, durations, etc.
   - respondent's free-form narrative account of period leading up to death
2. Symptom-cause information (**SCI**) that describes the relationships between VA signs/symptoms and causes included in the VA cause list

Classification:

1. Physicians review VA data and assign causes: PCVA
2. Automated statistical/computational algorithms assign causes using VA data *and* SCI: CCVA

VA is an imperfect and frustrating approach

Advantages

- FEASIBLE compared to traditional COD determination: autopsy, medical review, etc.
- Comparatively cheap
- Comparatively tractable – logistics, skills, etc.
- With computer coding:
  - does not require advanced skills
  - produces reproducible cause assignments in a timely fashion
  - no physician opportunity costs
- Capable of providing highly useful COD and BOD information for public health assessment and planning

Disadvantages

- Much less accurate compared to traditional COD determination: autopsy, medical review, etc.
- Abbreviated cause list that does not easily mesh with full ICD cause lists, large catch-all causes
- Inherently low-information with many potential sources of error and bias: **classification is difficult**

Why I work on VA

- VA is a challenging approach that often produces underwhelming – but still useful – results
- Computer-coded VA is the only feasible solution for large-scale COD determination in resource-constrained settings without functioning vital statistics systems
- The remainder of this talk will be a technical discussion of the **InSilicoVA** automated cause coding algorithm for VA data developed by myself, **Richard Li**, and **Tyler McCormick**

VA Algorithms

VA cause-coding algorithms have three separable components

1. The VA data themselves
2. SCI that describes the relationship between VA symptoms and VA causes
3. The logic of the algorithm itself – mathematical, computational, statistical

The performance of each algorithm depends on both its logic and the SCI it uses

SCI can be swapped in/out and updated

This means that the performance of an algorithm can evolve and be adapted to a particular population

We will focus on algorithm logic and come back to SCI

Foundation for InSilicoVA: InterVA's origin, usage, and future

InSilicoVA originates with and fixes many weaknesses of InterVA, so we start with a discussion of InterVA

- InterVA (for 'Interpret VA') was developed by Peter Byass and his colleagues over many years, e.g. [8, 7, 17, 19, 10, 49, 21, 6, 9]
- InterVA is widely used and has been validated in a variety of ways – many substantive publications have relied on InterVA, e.g. [4, 44, 17, 3, 49, 11, 20, 21, 40, 12, 24, 50, 2, 37, 18, 46, 45, 6, 52, 48, 31, 47, 1, 41, 29, 16, 32, 5, 22, 42, 39]
- The last version is InterVA-5 [9]
- Peter Byass passed away during the pandemic; the openVA Team maintains openVA software that implements InterVA-5 but does not intend to produce any new updates

InterVA

InterVA is a computational algorithm designed

1. To distribute a single death across a number of causes with more weight on causes that are more consistent with the signs/symptoms associated with the death
2. Generate a population-level distribution of causes by summing up the fractions of a death associated with each cause across all individuals in the population

InterVA details 1

Notation

- J deaths: y_j
- N causes of death: c_n
- Death y_j with cause c_n: y_{jn}
- K sign/symptoms: $s_k \in \{0, 1\}$
- Vector of signs/symptoms for an individual death: $\vec{S}_j$
- Cause-specific mortality fractions (CSMF): f_n

InterVA details 2

Data

- For each death y_j, the VA interview produces a binary-valued vector of signs/symptoms

$$\vec{S}_j = \{s_{j1}, s_{j2}, \ldots s_{jK}\}$$

- Symptom-cause information in the form of 'probbase': a $K \times N$ matrix of conditional probabilities

$$\begin{bmatrix} \Pr(s_1|c_1) & \Pr(s_1|c_2) & \cdots & \Pr(s_1|c_N) \\ \Pr(s_2|c_1) & \Pr(s_2|c_2) & \cdots & \Pr(s_2|c_N) \\ \vdots & \vdots & \ddots & \vdots \\ \Pr(s_K|c_1) & \Pr(s_K|c_2) & \cdots & \Pr(s_K|c_N) \end{bmatrix}$$

InterVA details 3

Using Bayes' Rule we can derive an expression for what we want: the probability of a death with cause c_n, given that a specific set of symptoms were present or not present

$$\Pr(y_{jn}, \vec{S}_j) = \Pr(y_{jn}|\vec{S}_j)\Pr(\vec{S}_j) = \Pr(\vec{S}_j|y_{jn})\Pr(y_{jn})$$

$$\Pr(y_{jn}|\vec{S}_j) = \frac{\Pr(\vec{S}_j|y_{jn})\Pr(y_{jn})}{\Pr(\vec{S}_j)} \tag{1}$$

InterVA details 4

Assuming signs/symptoms are independent given cause, the probability of a specific sign/symptom vector is the product of the applicable probbase $\Pr(s_k|c_n)$ values when a sign/symptom exists and their complements when the sign/symptoms do not exist, so equation 1 can be expanded,

$$\Pr(y_{jn}|\vec{S}_j) = \frac{\Pr(y_{jn}) \prod_{k=1}^{K} \Pr(s_k|c_n)^{s_{jk}} [1 - \Pr(s_k|c_n)]^{(1-s_{jk})}}{\sum_{n'=1}^{N} \left(\Pr(y_{jn'}) \prod_{k=1}^{K} \Pr(s_k|c_{n'})^{s_{jk}} [1 - \Pr(s_k|c_{n'})]^{(1-s_{jk})} \right)}$$

Note

- Uses both presence and absence of symptom
- **NOT** how InterVA works!

InterVA details 5

To get InterVA

- keep pieces in blue that correspond to the presence of a sign/symptom
- drop pieces in red that correspond to absence of a sign/symptom

$$\Pr(y_{jn}|\vec{S}_j) = \frac{\Pr(y_{jn}) \prod_{k=1}^{K} \Pr(s_k|c_n)^{s_{jk}} [1 - \Pr(s_k|c_n)]^{(1-s_{jk})}}{\sum_{n'=1}^{N} \left(\Pr(y_{jn'}) \prod_{k=1}^{K} \Pr(s_k|c_{n'})^{s_{jk}} [1 - \Pr(s_k|c_{n'})]^{(1-s_{jk})} \right)}$$

Although not explained explicitly in the literature, it appears that the absent-symptom factors were dropped because most VA data available at the time did not have information on missing symptoms

InterVA details 6

With these deletions, InterVA calculates something different

$$\frac{\Pr(y_{jn}) \prod_{k=1}^{K} \Pr(s_k|c_n)^{s_{jk}}}{\sum_{n'=1}^{N} \left(\Pr(y_{jn'}) \prod_{k=1}^{K} \Pr(s_k|c_{n'})^{s_{jk}} \right)} = \Pr(y_{jn}|\vec{S}'_j)$$

where $\vec{S}'_j$ is a vector that contains *the subset of the elements of* $\vec{S}_j$ *whose values are all equal to 1*

In general

$$\Pr(y_{jn}|\vec{S}_j) \neq \Pr(y_{jn}|\vec{S}'_j)$$

except in the unique case when $\vec{S}_j$ and $\vec{S}'_j$ have the same number of elements and all the elements of both are equal to 1; in general not true

InterVA details 7

- We refer to the InterVA result quantities $\Pr(y_{jn}|\vec{S}'_j)$ as 'cause-specific propensities'
- InterVA reports the three causes with the largest propensities that exceed 0.4
- If there are no propensities with magnitudes larger then 0.4, the cause is reported as 'indeterminate'
- 0.4 is an arbitrary threshold for which we cannot find any justification
- InterVA calculates CSMFs by summing cause-specific propensities across all deaths for each cause:

$$f_n = \sum_{j=1}^{J} \Pr(y_{jn}|\vec{S}'_j)$$

InterVA: Implications

InterVA

- Does not compute the probability $\Pr(y_{jn}|\vec{S}_j)$ – **not** a probabilistic algorithm
- Computes probable cause conditional *only* on symptoms that were present, the propensity $\Pr(y_{jn}|\vec{S}'_j)$
  - **Critically**, this is fundamentally a different quantity for each death and therefore **not comparable** across deaths
  - Does not differentiate between observed absence of a sign/symptom and unobserved or missing
  - Sensitive to noise in data and obscures data issues related to symptoms that do not exist
- CSMFs are deterministic rescaling of individual-level cause determination
- Lots of other issues we don't have time for ...

InSilicoVA Setup

InSilicoVA (for on-chip/computational VA) is a statistical-computational algorithm that

1. At the individual level identifies a distribution of probabilities associated with each cause
2. At the population level identifies a distribution of counts of deaths for each cause
3. Links the two so that they are consistent with each other
4. Through these distributions quantifies uncertainty at both levels, again so that each is consistent with the other
5. Utilizes information from all deaths to help classify each death
6. Is comparatively robust to noise in data [15]

Uncertainty: if we are not sure about the cause for a death at the individual level, then in a proportionate way, we cannot be sure about that death's contribution to the cause-specific mortality fractions at the population level

InSilicoVA algorithm in words

Imagine a joint distribution of CSMF vectors and cause-specific probabilities for each death

Repeat the following steps many times, and for each loop, record the CSMFs and cause-specific probabilities for each death

1. For each death, use the current CSMFs (anything to start), knowledge of VA sign/symptom-cause relationships (SCI), and the VA data to calculate the probability of each cause
2. Again for each death, using those cause-specific probabilities, draw a cause from a multinomial distribution
3. Sum the deaths assigned to each cause to create a set of cause-specific death counts
4. Using the cause-specific death counts, draw a new set of CSMFs from a Dirichlet distribution

This procedure has two random steps that introduce uncertainty at the individual and population levels, and the cause-assignment step keeps the two levels linked together so that they are consistent with each other

The CSMFs aggregate information from all deaths and pass it along to each individual death in the next step

InSilicoVA algorithm – equations 1

Notation for InSilicoVA, similar to InterVA

- J deaths: y_j
- N causes of death: c_n
- Deaths, each with 1 assigned cause: $y_{jn} \in \{0, 1\}$; $\forall j : \sum_n y_{jn} = 1$ and $\sum_j \sum_n y_{jn} = J$
- $J \times N$ matrix of cause assignments for each death: $\mathbf{Y}$
- K sign/symptoms: $s_k \in \{0, 1\}$
- Vector of signs/symptoms for individual j: $\vec{S}_j$; elements s_{jk}
- For individual j, probability of cause n: ℓ_{jn}
- $J \times N$ matrix of cause-specific probabilities for each death: $\mathbf{L}$
- Cause-specific death count (CSDC): m_n
- Cause-specific mortality fraction (CSMF): f_n
- Vector of CSMFs: $\vec{F}$; $\sum_n f_n = 1$

InSilicoVA algorithm – equations 2

Following is a *minimal description* of InSilicoVA that illustrates the main ideas only – the full, published model has lots of refinements and nuances, see [38]

Data

- For each death y_j, VA interview produces a binary-valued vector of signs/symptoms

$$\vec{S}_j = \{s_{j1}, s_{j2}, \ldots s_{jk}\}$$

- Symptom-cause information as a $K \times N$ matrix of conditional probabilities $\Pr(s_k|c_n)$ – the same as InterVA

InSilicoVA algorithm – equations 3

Sketch of the model/algorithm

- We are interested in the joint distribution $(\vec{F}, \mathbf{L})$ – both unknown quantities
- So, we introduce a data augmentation procedure and use simulated cause assignments to stitch the two together
- Model CSMFs $\vec{F}$ conditional on cause assignments $\mathbf{Y}$

$$\vec{F}|\mathbf{Y} \sim \text{Dirichlet}(\vec{\alpha} + \vec{M}) \tag{2}$$

where the elements of $\vec{M}$ are

$$m_n = \sum_{j=1}^{J} y_{jn}$$

This ties the CSMFs $\vec{F}$ to the cause assignments y_{jn}

InSilicoVA algorithm – equations 4

- Model cause-assignments y_{jn} conditional on CSMFs $\vec{F}$ and the **data** – signs/symptoms $\vec{S}_j$

$$y_{jn}|\vec{S}_j, \vec{F} \sim \text{Multinomial}(1, \vec{L}_j) \tag{3}$$

The n components of $\vec{L}_j$ are

$$\begin{aligned} \ell_{jn} &= \Pr(y_{jn}|\vec{S}_j, \vec{F}) \\ &= \frac{\Pr(\vec{S}_j|y_{jn}, \vec{F}) \Pr(y_{jn}|\vec{F})}{\Pr(\vec{S}_j|\vec{F})} \end{aligned}$$

Assume signs/symptoms are independent given cause and therefore independent of $\vec{F}$

$$\ell_{jn} \propto \Pr(\vec{S}_j|y_{jn}) \Pr(y_{jn}|\vec{F})$$

InSilicoVA algorithm – equations 5

- The cause-specific mortality fraction for cause n f_n is $\Pr(y_{jn}|\vec{F})$ and again, assuming signs/symptoms are independent given cause,

$$\Pr(\vec{S}_j|y_{jn}) = \prod_{k=1}^{K} \Pr(s_k|c_n)^{s_{jk}} \left[1 - \Pr(s_k|c_n)\right]^{(1-s_{jk})}$$

So,

$$\ell_{jn} \propto f_n \prod_{k=1}^{K} \Pr(s_k|c_n)^{s_{jk}} \left[1 - \Pr(s_k|c_n)\right]^{(1-s_{jk})}$$

This ties the cause assignments y_{jn} to the CSMFs $\vec{F}$

InSilicoVA algorithm – computation

Computation

- Take sample from joint distribution $(\vec{F}, \mathbf{L})$ using a Gibbs sampler
- The model defines the conditional distributions we need
- Initialize the CSMF vector to a reasonable set of values and execute the following 2 steps many times
  1. Use equation 3 to draw a cause for each death
  2. Use those cause assignments in equation 2 to draw a new CSMF vector
- After both $\vec{F}$ and $\mathbf{L}$ have settled into a stationary distribution, record the values of both in a (large) number of steps
- This set of values approximates the joint distribution $(\vec{F}, \mathbf{L})$
- Summarize the margins of the sample as necessary to produce desired outputs, usually distributions and a measure of their central tendencies for
  - elements of $\vec{F}$
  - for each death, the cause-specific elements of $\vec{\ell}_j$

InSilicoVA summary

InSilicoVA advances and advantages

- Provides mutually consistent estimates of individual-level probabilities of dying and population-level CSMFs
- Both are reported as distributions so there is a metric of uncertainty for both
- Builds on InterVA and utilizes the same SCI – *immediately usable*
- Provides information on all causes for all deaths, no 'indeterminate' cause - wide, flat distributions instead
- Uses information from all deaths to strengthen each individual death classification – equation 2 incorporates information from all deaths into the CSMF that then informs the cause assignments for each death
- Compared to InterVA, much more robust to noise in data (reporting errors) [15]
- Computationally feasible – barely, we are developing faster versions of the software using C/C++

InSilicoVA main publication [38]

JOURNAL OF THE AMERICAN STATISTICAL ASSOCIATION
2016, VOL. 111, NO. 515, 1036–1049, Applications and Case Studies
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Probabilistic Cause-of-Death Assignment Using Verbal Autopsies

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ABSTRACT

In regions without complete-coverage civil registration and vital statistics systems there is uncertainty about even the most basic demographic indicators. In such regions, the majority of deaths occur outside hospitals and are not recorded. Worldwide, fewer than one-third of deaths are assigned a cause, with the least information available from the most impoverished nations. In populations like this, verbal autopsy (VA) is a commonly used tool to assess cause of death and estimate cause-specific mortality rates and the distribution of deaths by cause. VA uses an interview with caregivers of the decedent to elicit data describing the signs and symptoms leading up to the death. This article develops a new statistical tool known as *InSilicoVA* to classify cause of death using information acquired through VA. InSilicoVA shares uncertainty between cause of death assignments for specific individuals and the distribution of deaths by cause across the population. Using side-by-side comparisons with both observed and simulated data, we demonstrate that InSilicoVA has distinct advantages compared to currently available methods. Supplementary materials for this article are available online.

ARTICLE HISTORY
Received November 2014
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KEYWORDS
Bayesian methods; cause of death; Demography; Verbal autopsy; Vital records

Miscellaneous observations of work on InSilicoVA

- We replicated work on InterVA and Tariff 1.0/2.0 algorithms and implemented both in openVA
- Replication is **very** hard – literature is woefully incomplete in terms of describing methods
- Both algorithms were available as proprietary implementations with no source code – this made it even harder/impossible to really understand what was going on
- **Lots** of not-described data pre-processing, automated data cleaning, etc.
- We conduct ourselves in the opposite way, hence the **openVA Team**
- As a result of our activities, all VA algorithms are now available as open source software
- We are thoroughly committed to a transparent, open source approach to creating, disseminating, and supporting methods
- We are working on several new approaches, but none are mature yet, see [34, 30, 33, 36]

South Africa VA validation study

We recently validated InSilicoVA, InterVA, and Tariff 2.0 using a high quality VA study in South Africa

South Africa Medical Research Council conducted the South African National Cause-of-Death Validation study [26]

A component of the study created a national sample of deaths with verbal autopsy

- Fieldwork 2017 – 2019
- 2016 WHO Standard VA
- 5,387 respondents consented and VA completed
- Multiple physician cause coding
- Underlying cause determined by Iris [25]
- 4,535 VA deaths received an valid underlying cause
- HIV is a major cause of death: 22.8% of deaths

VA algorithm validation using South Africa VA validation study

Working with the South African team, the openVA Team

- Applied openVA algorithms InterVA-5, InSilicoVA, and IHME algorithm Tariff 2.0 to the validation deaths
- Compared causes assigned by algorithms to reference causes identified by physicians and Iris
- Calculated a variety of comparison metrics
- Published in December, 2023 [23]

Algorithm comparison 1

Algorithm	Individual-Level Agreement: Overall Agreement Top Cause (95% CI)	Overall Agreement Top 3 Causes (95% CI)	Kappa Top cause (95% CI)	Chance Corrected Concordance Top Cause	Population-Level: CSMF Accuracy	Spearman Rank correlation (95% CI)
Total Sample N = 4,534						
InterVA-5	48.2 (46.7 – 49.7)	70.9 (69.6 – 72.2)	0.43 (0.42 – 0.44)	0.39	0.81	0.64 (0.62 – 0.65)
InSilicoVA	51.6 (50.2 – 53.1)	73.8 (72.5 -75.1)	0.47 (0.46 – 0.48)	0.42	0.84	0.68 (0.67 – 0.70)
Tariff 2.0	51.2 (49.8 – 52.7)	*	0.46 (0.45 – 0.47)	0.38	0.82	0.66 (0.65 – 0.68)
Neonate (0-27 days) N = 82						
InterVA-5	78.5 (67.5 – 86.4)	78.0 (67.5 – 86.4)	-0.05 (-0.14 – 0.04)	0.13	0.90	0.02 (-0.02 – 0.24)
InSilicoVA	79.3 (68.9 – 87.4)	79.3 (68.9 – 87.4)	-0.04 (-0.14 – 0.05)	0.13	0.84	0.02 (-0.02 – 0.24)
Tariff 2.0	47.6 (36.4 – 58.9)	*	0.01 (-0.04 – 0.06)	0.06	0.83	-0.06 (-0.27 – 0.16)
Child (28 days – 11 years) N = 165						
InterVA-5	36.4 (29.0 – 44.2)	50.3 (42.4 – 58.2)	0.32 (0.28 – 0.36)	0.32	0.66	0.43 (0.30 – 0.55)
InSilicoVA	40.6 (33.0 – 48.5)	56.4 (48.4 – 64.1)	0.36 (0.32 – 0.40)	0.40	0.64	0.65 (0.55 – 0.73)
Tariff 2.0	28.5 (21.7 – 36.0)	*	0.24 (0.20 – 0.28)	0.20	0.66	0.50 (0.37 – 0.60)

InSilicoVA rankings in performance comparisons

Population Group	N	First	Second	Third
Total Sample	4,534	6	0	0
Neonate (0-27 days)	82	4	2	0
Child (28 days – 11 years)	165	5	0	1
Adult (12 – 49 years)	1,812	2	4	0
Elder (50+ years)	2,475	4	2	0
Male	2,400	3	3	0
Female	2,134	6	0	0
Died in Health Facility	2,591	4	2	0
Died Out of Health Facility	1,943	6	0	0
Total		40	13	1

Looks good. But, examination of results reveals that none of the algorithms performed exceptionally well and the magnitude of InSilicoVA's lead is often small

Still work to do

South Africa VA validation study [23]

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RESEARCH ARTICLE

OPEN ACCESS Check for updates

Agreement between cause of death assignment by computer-coded verbal autopsy methods and physician coding of verbal autopsy interviews in South Africa

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ABSTRACT

Background: The South African national cause of death validation (NCODV 2017/18) project collected a national sample of verbal autopsies (VA) with cause of death (COD) assignment by physician-coded VA (PCVA) and computer-coded VA (CCVA).

Objective: The performance of three CCVA algorithms (InterVA-5, InSilicoVA and Tariff 2.0) in assigning a COD was compared with PCVA (reference standard).

Methods: Seven performance metrics assessed individual and population level agreement of COD assignment by age, sex and place of death subgroups. Positive predictive value (PPV), sensitivity, overall agreement, kappa, and chance corrected concordance (CCC) assessed individual level agreement. Cause-specific mortality fraction (CSMF) accuracy and Spearman's rank correlation assessed population level agreement.

Results: A total of 5386 VA records were analysed. PCVA and CCVAs all identified HIV/AIDS as the leading COD. CCVA PPV and sensitivity, based on confidence intervals, were comparable except for HIV/AIDS, TB, maternal, diabetes mellitus, other cancers, and some injuries. CCVAs performed well for identifying perinatal deaths, road traffic accidents, suicide and homicide but poorly for pneumonia, other infectious diseases and renal failure. Overall agreement between CCVAs and PCVA for the top single cause (48.2–51.6) indicated comparable weak agreement between methods. Overall agreement, for the top three causes showed moderate agreement for InterVA (70.9) and InSilicoVA (73.8). Agreement based on kappa (–0.05–0.49)and CCC (0.06–0.43) was weak to none for all algorithms and groups. CCVAs had moderate to strong agreement for CSMF accuracy, with InterVA-5 highest for neonates (0.90), Tariff 2.0 highest for adults (0.89) and males (0.84), and InSilicoVA highest for females (0.88), elders (0.83) and out-of-facility deaths (0.85). Rank correlation indicated moderate agreement for adults (0.75–0.79).

Conclusions: Whilst CCVAs identified HIV/AIDS as the leading COD, consistent with PCVA, there is scope for improving the algorithms for use in South Africa.

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Physician-coded; computer-coded; verbal autopsy; agreement

openVA Suite

The openVA Team has developed and supports a range of software for VA, including InSilicoVA

- openVA: https://cran.r-project.org/package=openVA
- InSilicoVA: https://cran.r-project.org/package=InSilicoVA
- interVA5: https://cran.r-project.org/package=InterVA5
- interVA4: https://cran.r-project.org/package=InterVA4
- Tariff 1: https://cran.r-project.org/package=Tariff
- CrossVA: https://cran.r-project.org/package=CrossVA
- pyCrossVA: https://pypi.org/project/pycrossva/0.92/
- openVA Pipeline: https://pypi.org/project/openva-pipeline/
- Python openVA – in final testing, release planned mid 2024
- Others: https://github.com/verbal-autopsy-software
- User-oriented description and tutorial – **The openVA Toolkit for Verbal Autopsies** [35]

The openVA Suite is the reference implementation of VA algorithms that support WHO VA standards and is used by a wide variety of researchers and CRVS organizations globally – MOH of Tanzania has just published study endorsing InSilicoVA and openVA

openVA Toolkit [35]

The R Journal

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The openVA Toolkit for Verbal Autopsies

Abstract:

Verbal autopsy (VA) is a survey-based tool widely used to infer cause of death (COD) in regions without complete-coverage civil registration and vital statistics systems. In such settings, many deaths happen outside of medical facilities and are not officially documented by a medical professional. VA surveys, consisting of signs and symptoms reported by a person close to the decedent, are used to infer the COD for an individual, and to estimate and monitor the COD distribution in the population. Several classification algorithms have been developed and widely used to assign causes of death using VA data. However, the incompatibility between different idiosyncratic model implementations and required data structure makes it difficult to systematically apply and compare different methods. The openVA package provides the first standardized framework for analyzing VA data that is compatible with all openly available methods and data structure. It provides an open-source, R implementation of several most widely used VA methods. It supports different data input and output formats, and customizable information about the associations between causes and symptoms. The paper discusses the relevant algorithms, their implementations in R packages under the openVA suite, and demonstrates the pipeline of model fitting, summary, comparison, and visualization in the R environment.

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Preliminaries

Motivation: global burden of disease and cause of death

Verbal autopsy
- VA algorithms and InterVA
- InSilicoVA
- VA Algorithm Validation Study
- Software, and users

Beyond InSilicoVA

Issues that InSilicoVA doesn't solve

Limitations of InSilicoVA

- Assumes conditional independence of symptoms – lots of information lost
- Does not utilize free text account part of VA data – physicians place great weight on this, more information lost
- Does not recognize or account for different epidemiological domains

Additional challenge: SCI is not sufficiently informative

- Current SCI – $\Pr(s|c)$ – is inadequate, out of date, static, and related to limited epidemiological settings
- Two options to create SCI: elicite from physicians or calculate from reference deaths
- Physicians are comparatively easy and cheap but provide less nuance and essentially no information on dependence among symptoms
- Reference deaths are very hard to accumulate in sufficient numbers but potentially provide much more information, e.g. dependence among symptoms and domain-specific information

The key role of SCI

- We have demonstrated that with current algorithm logics, the SCI is at least, and often more, important than the algorithm logic in explaining the differences in algorithm performance [14]
- We have also shown that SCI dramatically affects algorithm performance and that, as expected, SCI is domain-specific [14, 38]
- Consequently, improving SCI is arguably more important than improving algorithm logic
- Two options for better SCI
  - Improved physician-elicited $\Pr(s|c)$, or
  - Large collection of reference deaths with VA and independent reference cause to infer/estimate/calculate new, more informative SCI

WHO 2022 VA and 'probbase' update – update to physician-elicited SCI

- The WHO VA Reference Group and Data for Health partners created an streamlined and strengthened, post-CV19 update to the WHO Standard VA
- The 2022 VA is much shorter, smoother, and has CV19 as a new cause
- This requires a big update to the algorithms and completely new SCI – the $\Pr(s|c)$ in the probbase
- Supported by the Data for Health Initiative through the CDC Foundation, I am currently leading a team of about 70 people, mostly physicians, to create a new physician-based SCI for the 2022 standard VA
- The openVA algorithm code has been updated and is ready to go
- Anticipate testing the new 2022-compatible algorithms in late 2024

Reference Death Archive

The openVA Team with many partners is currently creating a global reference death archive for VA

- Reference deaths from many sites around the world, many with reference deaths informed by pathology through minimally-invasive tissue sample (MITS – autopsy-light)
  - Cover wide variety of epidemiological domains and develop/test domain-adaptive algorithms
  - Updated through time
  - Include enough deaths to estimate dependencies among symptoms and include those in new algorithms
- Hosted at WHO in Geneva, globally available
- Many reference deaths from mortality surveillance units in Brazil who are conducting traditional autopsy and WHO 2022 VA
- Supported by Bill and Melinda Gates Foundation; right now mired in bureaucratic setup activities around the world!

Interview

- We have demonstrated that reporting error can dramatically reduce algorithm performance [15], InSilicoVA is more robust to this
- For this reason, the quality and consistency of the VA interview is critical
- Clarissa Surek-Clark – sociolinguist/translator/interpreter, Nicole Angotti – sociologist/demographer, and soon Brian Houle – sociologist/demographer are conducting qualitative studies of the VA interview, language usage, and translation/interpretation issues aiming to
  - improve the interview experience for respondent and interviewer – *whole topic for a different talk*
  - standardize the interview design and conduct of interviews
  - standardize the way languages are handled, processed, etc.
  - develop a standard protocol for narrative account elicitation
- The hope is to greatly improve the conduct of the interviews and the quality and consistency of the VA data they produce
- A key goal is to greatly improve the free-text narrative account so that it is respondent-friendly and maximally useful for machine-based text processing

Incorporating free-form text from account

Physicians place great weight on the narrative account when assigning causes to VA deaths

- InSilicoVA does not use any part of the account
- We are exploring various ways of producing consistent, useful information from the accounts using off-the-shelf NLP methods – not going very well
- Attempts have been made to classify VA deaths based solely on automated text processing of accounts – doesn't work well yet, many studies exaggerate performance by truncating/aggregating the cause list, e.g. [28, 51, 27]
- This effort is combined with work on the interview to ensure that elicitation of text-based accounts is both maximally meaningful and consistent with the needs of automated text processing methods
- Various approaches to incorporating text into algorithms are being considered; anticipate significant improvement in algorithm performance when text-based information is available

openVA Team

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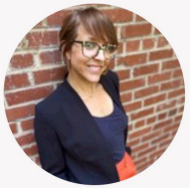
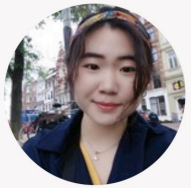


Nicole Angotti



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Algorithm comparison 1

Algorithm	Individual-Level Agreement: Overall Agreement Top Cause (95% CI)	Overall Agreement Top 3 Causes (95% CI)	Kappa Top cause (95% CI)	Chance Corrected Concordance Top Cause	Population-Level: CSMF Accuracy	Spearman Rank correlation (95% CI)
Total Sample N = 4,534						
InterVA-5	48.2 (46.7 – 49.7)	70.9 (69.6 – 72.2)	0.43 (0.42 – 0.44)	0.39	0.81	0.64 (0.62 – 0.65)
InSilicoVA	51.6 (50.2 – 53.1)	73.8 (72.5 -75.1)	0.47 (0.46 – 0.48)	0.42	0.84	0.68 (0.67 – 0.70)
Tariff 2.0	51.2 (49.8 – 52.7)	*	0.46 (0.45 – 0.47)	0.38	0.82	0.66 (0.65 – 0.68)
Neonate (0-27 days) N = 82						
InterVA-5	78.5 (67.5 – 86.4)	78.0 (67.5 – 86.4)	-0.05 (-0.14 – 0.04)	0.13	0.90	0.02 (-0.02 – 0.24)
InSilicoVA	79.3 (68.9 – 87.4)	79.3 (68.9 – 87.4)	-0.04 (-0.14 – 0.05)	0.13	0.84	0.02 (-0.02 – 0.24)
Tariff 2.0	47.6 (36.4 – 58.9)	*	0.01 (-0.04 – 0.06)	0.06	0.83	-0.06 (-0.27 – 0.16)
Child (28 days – 11 years) N = 165						
InterVA-5	36.4 (29.0 – 44.2)	50.3 (42.4 – 58.2)	0.32 (0.28 – 0.36)	0.32	0.66	0.43 (0.30 – 0.55)
InSilicoVA	40.6 (33.0 – 48.5)	56.4 (48.4 – 64.1)	0.36 (0.32 – 0.40)	0.40	0.64	0.65 (0.55 – 0.73)
Tariff 2.0	28.5 (21.7 – 36.0)	*	0.24 (0.20 – 0.28)	0.20	0.66	0.50 (0.37 – 0.60)

Algorithm comparison 2

Algorithm	Individual-Level Agreement: Overall Agreement Top Cause (95% CI)	Overall Agreement Top 3 Causes (95% CI)	Kappa Top cause (95% CI)	Chance Corrected Concordance Top Cause	Population-Level: CSMF Accuracy	Spearman Rank correlation (95% CI)
Adult (12 – 49 years) N = 1,812						
InterVA-5	58.3 (56.0 – 60.6)	77.2 (75.1 – 79.1)	0.49 (0.47 – 0.51)	0.34	0.80	0.75 (0.73 – 0.77)
InSilicoVA	62.3 (60.0 – 64.5)	79.7 (77.8 – 81.5)	0.54 (0.52 – 0.56)	0.37	0.84	0.79 (0.77 – 0.81)
Tariff 2.0	65.4 (63.2 – 67.6)	*	0.56 (0.55 – 0.58)	0.38	0.89	0.75 (0.73 – 0.75)
Elder (50+ years) N =2,475						
InterVA-5	40.6 (38.7 – 42.6)	67.5 (65.6 – 69.4)	0.35 (0.34 – 0.36)	0.34	0.80	0.47 (0.44 – 0.50)
InSilicoVA	43.7 (41.7 – 45.7)	70.4 (68.6 – 72.2)	0.38 (0.37 – 0.40)	0.37	0.83	0.51 (0.48 – 0.54)
Tariff 2.0	42.5 (40.5 – 44.5)	*	0.38 (0.37 – 0.39)	0.39	0.76	0.55 (0.52 – 0.58)
Male N = 2,400						
InterVA-5	47.7 (45.7 – 49.7)	71.1 (69.3 – 72.9)	0.43 (0.41 – 0.44)	0.39	0.76	0.68 (0.66 – 0.70)
InSilicoVA	52.0 (50.0 – 54.0)	74.1 (72.3 – 75.9)	0.47 (0.46 – 0.48)	0.43	0.80	0.73 (0.71 – 0.73)
Tariff 2.0	55.3 (53.2 – 57.3)	*	0.50 (0.49 – 0.52)	0.39	0.84	0.71 (0.69 – 0.73)

Algorithm comparison 3

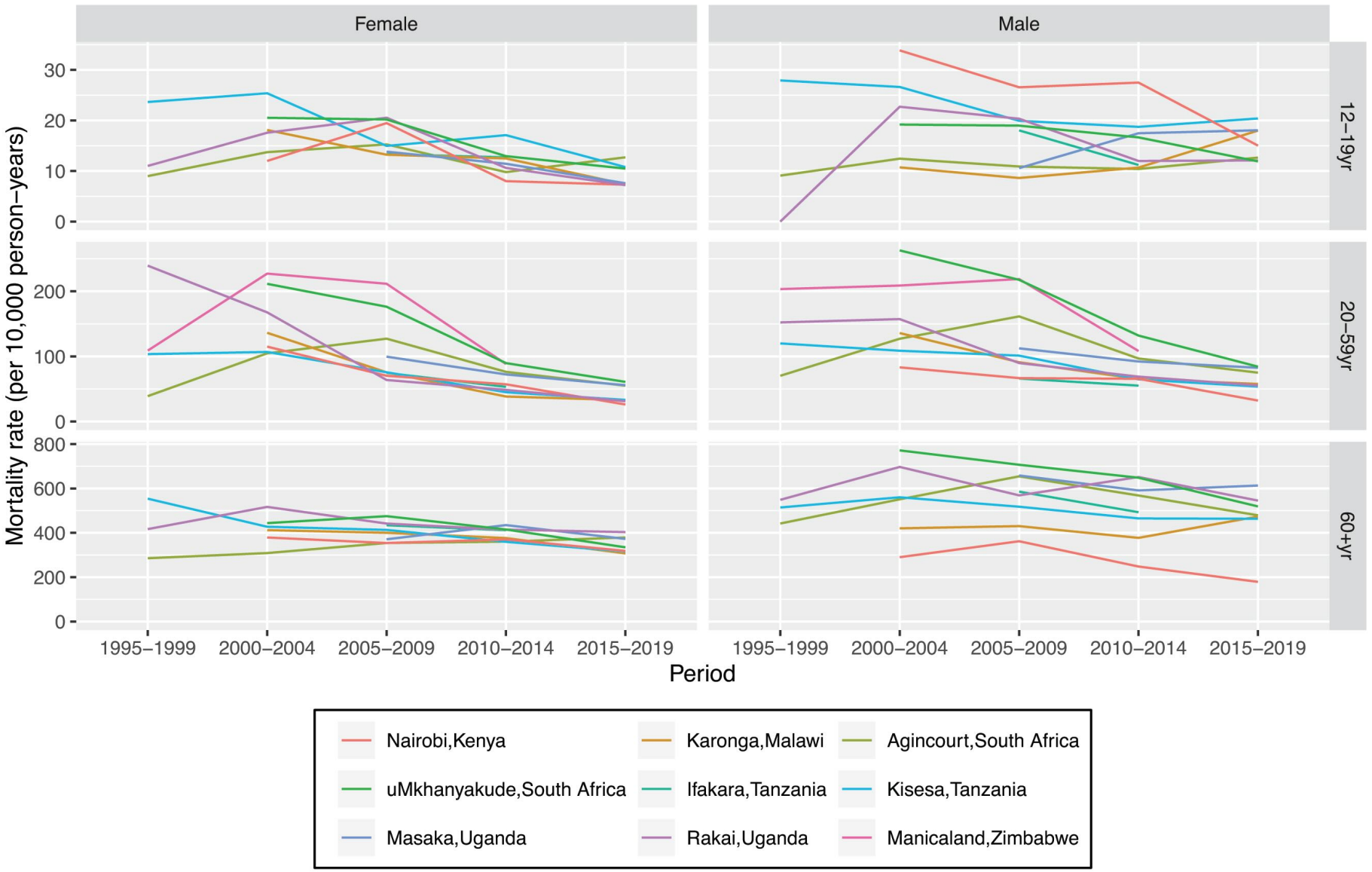
Algorithm	Individual-Level Agreement: Overall Agreement Top Cause (95% CI)	Overall Agreement Top 3 Causes (95% CI)	Kappa Top cause (95% CI)	Chance Corrected Concordance Top Cause	Population-Level: CSMF Accuracy	Spearman Rank correlation (95% CI)
Female N =2,134						
InterVA-5	48.8 (46.6 – 50.9)	70.7 (68.7 – 72.6)	0.43 (0.41 – 0.44)	0.38	0.87	0.57 (0.54 – 0.60)
InSilicoVA	51.2 (49.1 – 53.4)	73.4 (71.5 – 75.2)	0.46 (0.44 – 0.47)	0.40	0.88	0.61 (0.59 – 0.64)
Tariff 2.0	46.7 (44.6 – 48.9)	*	0.41 (0.40 – 0.43)	0.34	0.79	0.60 (0.57 – 0.63)
Died in Health Facility N = 2,591						
InterVA-5	47.4 (45.4 – 49.3)	71.2 (69.4 – 72.9)	0.41 (0.40 – 0.42)	0.38	0.80	0.57 (0.54 – 0.59)
InSilicoVA	50.6 (48.7 – 52.6)	73.5 (71.8 – 75.2)	0.45 (0.43 – 0.46)	0.43	0.82	0.63 (0.60 – 0.65)
Tariff 2.0	51.6 (49.7 – 53.5)	*	0.45 (0.44 – 0.46)	0.36	0.82	0.65 (0.63 – 0.67)
Died Out of Health Facility N = 1,943						
InterVA-5	49.3 (47.1 – 51.6)	70.6 (68.5 – 72.6)	0.45 (0.44 – 0.46)	0.39	0.82	0.71 (0.69 – 0.73)
InSilicoVA	53.0 (50.7 – 55.2)	74.1 (72.1 – 76.0)	0.49 (0.48 – 0.50)	0.41	0.85	0.74 (0.72 – 0.76)
Tariff 2.0	50.7 (48.5 – 53.0)	*	0.47 (0.46 – 0.48)	0.40	0.81	0.66 (0.64 – 0.69)

ALPHA Network HDSS cause-specific mortality study

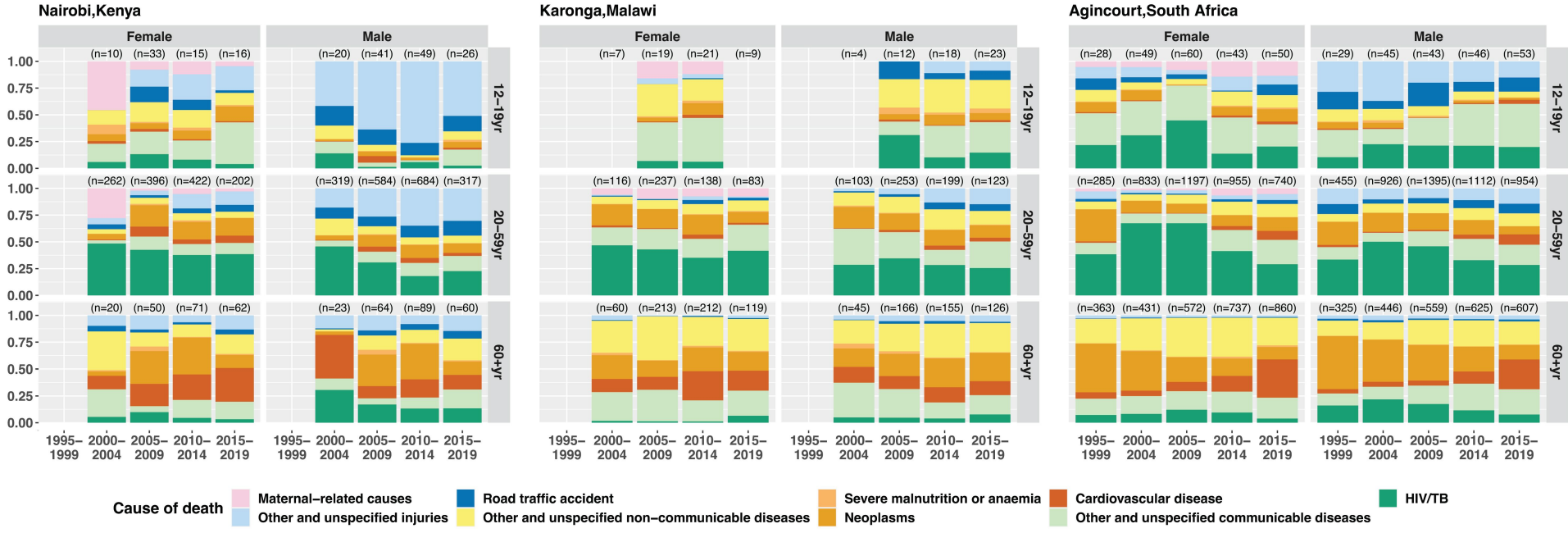
Work with Clara Calvert, Yue Chu, Milly Marston and ALPHA Network HDSS sites [13]

- Harmonized all exposure, death, and VA data from 9 health and demographic surveillance system sites (HDSS) in East and Southern Africa – *all are high HIV prevalence populations*
- Apply InSilicoVA to ascertain cause of death from VA
- Calculate trends in all-cause and cause-specific mortality
- Just published in Lancet Global Health

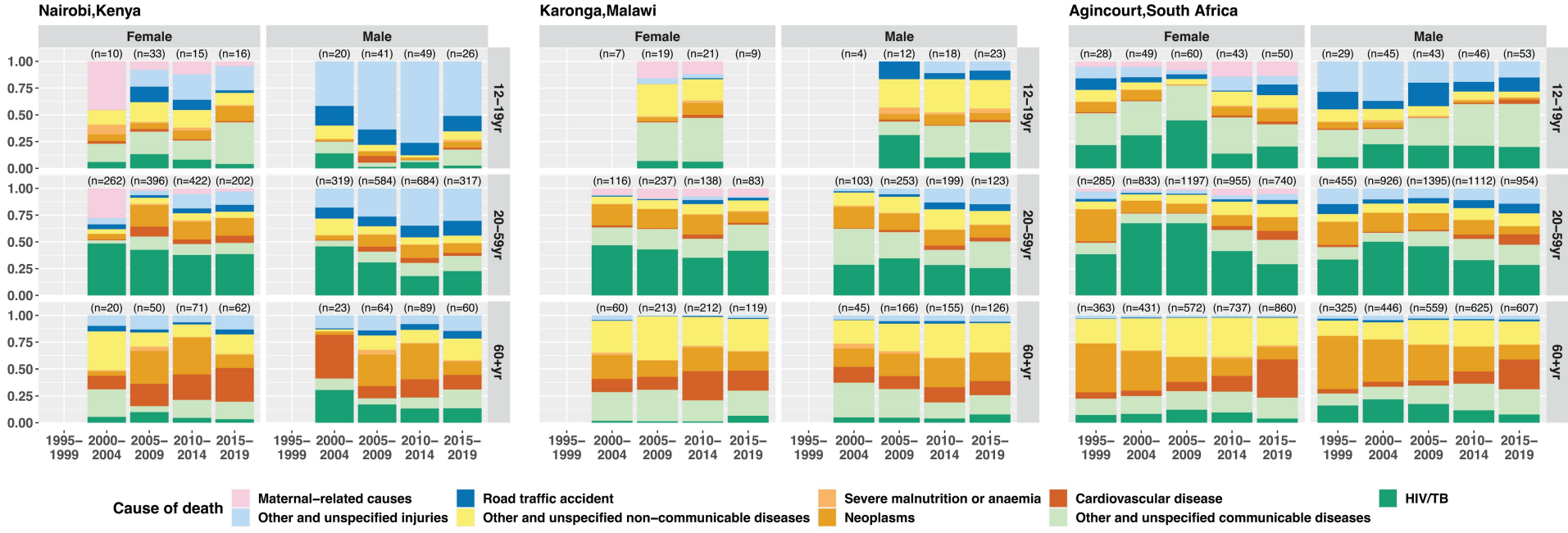
ALPHA Network all-cause mortality trends



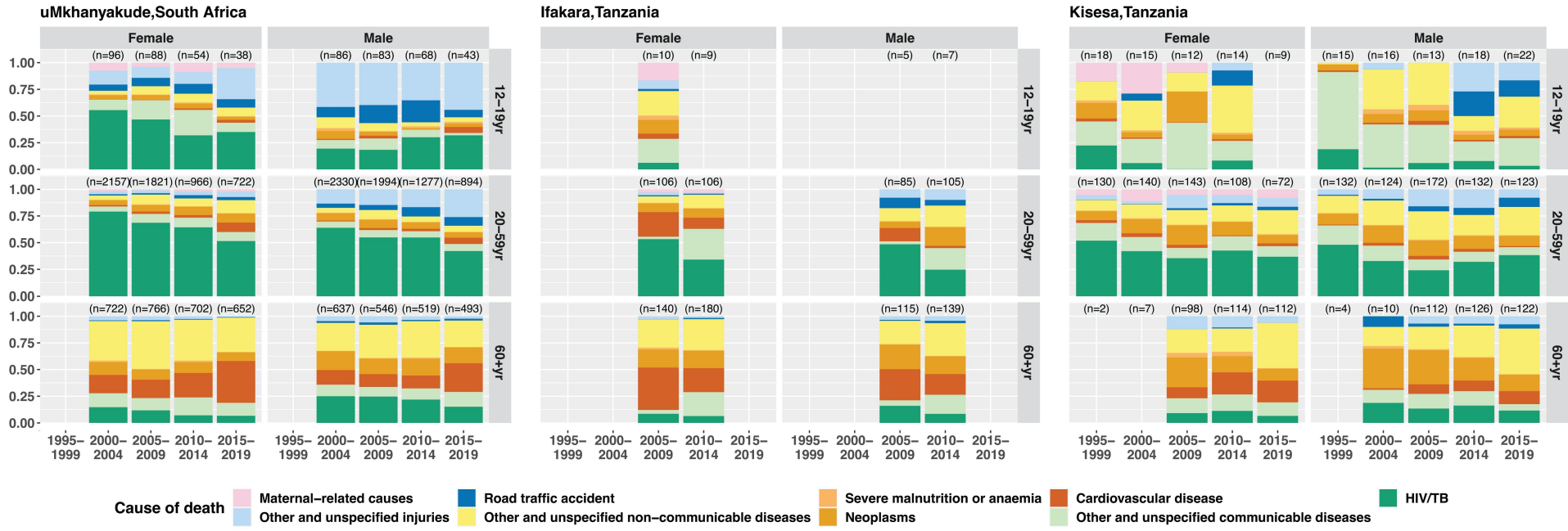
ALPHA Network cause-specific mortality fractions 1



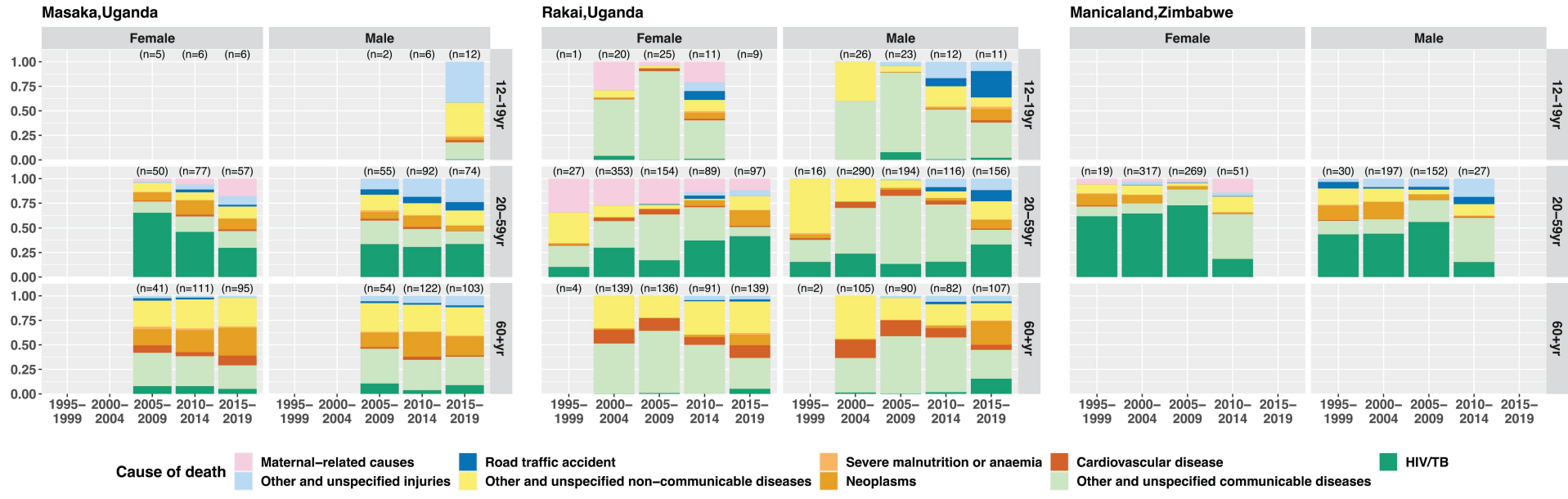
ALPHA Network cause-specific mortality fractions 1



ALPHA Network cause-specific mortality fractions 2

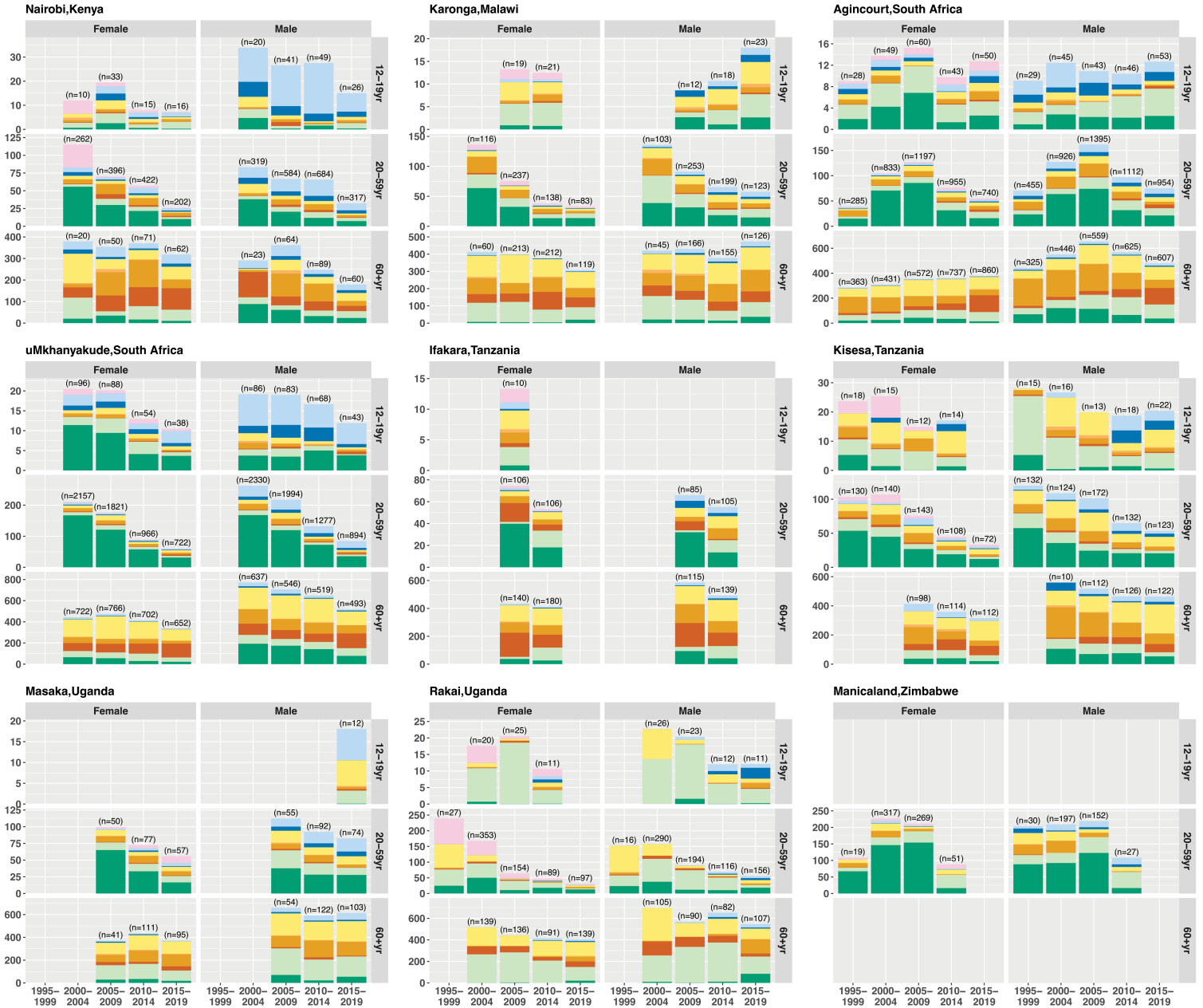


ALPHA Network cause-specific mortality fractions 3



ALPHA Network CSMFs

ALPHA Network cause-specific mortality rates



ALPHA Network cause-specific mortality publication [13]

Temporal changes in cause of death among adolescents and adults in six countries in eastern and southern Africa in 1995–2019: a multi-country surveillance study of verbal autopsy data

Yue Chu, Milly Marston, Albert Dube, Charles Festo, Eveline Geubbels, Simon Gregson, Kobus Herbst, Chodziwadziwa Kabudula, Kathleen Kahn, Tom Lutalo, Louisa Moorhouse, Robert Newton, Constance Nyamukapa, Ronald Makanga, Emma Slaymaker, Mark Urassa, Abdhalah Ziraba, Clara Calvert, Samuel J Clark**

Summary

Background The absence of high-quality comprehensive civil registration and vital statistics systems across many settings in Africa has led to little empirical data on causes of death in the region. We aimed to use verbal autopsy data to provide comparative, population-based estimates of cause-specific mortality among adolescents and adults in eastern and southern Africa.

Methods In this surveillance study, we harmonised verbal autopsy and residency data from nine health and demographic surveillance system (HDSS) sites in Kenya, Malawi, Tanzania, South Africa, Uganda, and Zimbabwe, each with variable coverage from Jan 1, 1995, to Dec 31, 2019. We included all deaths to adolescents and adults aged 12 or over that were residents of the study sites and had a verbal autopsy conducted. InSilicoVA, a probabilistic model, was used to assign cause of death on the basis of the signs and symptoms reported in the verbal autopsy. Levels and trends in all-cause and cause-specific mortality rates and cause-specific mortality fractions were calculated, stratified by HDSS site, sex, age, and calendar periods.

Findings 52 484 deaths and 5 157 802 person-years were reported among 1 071 913 individuals across the nine sites during the study period. 47 961 (91·4%) deaths had a verbal autopsy, of which 46 570 (97·1%) were assigned a cause of death. All-cause mortality generally decreased across the HDSS sites during this period, particularly for adults aged 20–59 years. In many of the HDSS sites, these decreases were driven by reductions in HIV and tuberculosis-related deaths. In 2010–14, the top causes of death were: road traffic accidents, HIV or tuberculosis, and meningitis or sepsis in adolescents (12–19 years); HIV or tuberculosis in adults aged 20–59 years; and neoplasms and cardiovascular disease in adults aged 60 years and older. There was greater between-HDSS and between-sex variation in causes of death for adolescents compared with adults.

Interpretation This study shows progress in reducing mortality across eastern and southern Africa but also highlights age, sex, within-HDSS, and between-HDSS differences in causes of adolescent and adult deaths. These findings highlight the importance of detailed local data to inform health needs to ensure continued improvements in survival.

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See **Comment** page e1217

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