Counting deaths, accounting for lives

Novel applications of standardised verbal autopsy methods for augmented health systems

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"*What gets measured gets done*".

~Anonymous

To my family…and to a great person, my Aunt Zakia Alshakhs

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ABSTRACT

Half of the world's deaths and their causes are never recorded by virtue of the under-resourced civil registration and vital statistics (CRVS) systems which limits capacity of health systems to respond to population needs. Verbal autopsy (VA) has emerged as a pragmatic approach for determining causes of death using standard interviews including signs, symptoms and circumstances of death, conducted with the bereaved family. With aims to investigate relevant challenges of VA methods and further proposes integrated novel approach to advance the VA applications, this work maintained close collaboration with communities in the Agincourt Health and socio-Demographic Surveillance System (HDSS) in rural South Africa using over 20-years of VA records.

Agreement between VA and respondent-reported causes of death was used to assess local perception of causes of death whereas recall period, from death to VA interview, was adopted to explore the impact of operational and cultural practices within HDSSs on the overall VA assessment. This thesis also examined the latest InterVA-5 model with integrated novel system to incorporate relevant Circumstances Of Mortality CATegories (COMCAT) to the existing VA medical processing of causes of death. Communities in South Africa provided a much less consistent and complete picture of causes of death and, recall period of up to one year did not have any consequential effects on the VA assessment. The demonstration of COMCAT using the integrated InterVA-5 model gave plausible and potentially useful findings, consistent with what might be expected in that population shedding the light on the compatibility of InterVA-5 model which handled VA data from various standards reasonably well. VA is the most expedient method to use in resource-poor settings for tracking patterns of causes of death over time and space. The automated InterVA-5 integrated with the COMCAT can serve as a standardised and comprehensive tool for monitoring universal health coverage.

Keywords: Verbal autopsy, cause of death, vital registration, health system, surveillance, World Health Organization

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SAMMANFATTNING PÅ SVENSKA

Hälften av världens alla dödsfall registreras aldrig på grund av otillräckliga resurser och system för befolkningsstatistik, och andelen där dödsorsak registreras är ännu lägre. Detta gör det svårt för många länders hälsovårdssystem att anpassa sig efter befolkningens behov. Då det i många fall saknas resurser för att medicinskt fastställa dödsorsak, har en alternativ metod kallad 'verbal autopsy' (verbal obduktion, VA) utvecklas. Denna metod bygger på standardiserade intervjuer med anhöriga till den döda, där tecken, symtom och omständigheterna kring dödsfallet undersöks. Målet med avhandlingen är att undersöka de största utmaningarna och problemen med VA, och att utveckla nya metoder för att förbättra tillämpningen av VA. Arbetet har utförts i nära samarbete med samhällen på den Sydafrikanska landsbygden som ingår i upptagningsområdet för Agincourt Health and socio-Demographic Surveillance System, ett övervakningssystem som samlar in hälsodata och sociodemografisk data och har över 20 år av VA-data tillgängligt.

För att utvärdera den lokala befolkningens uppfattning om dödsorsaker jämfördes dödsorsak fastställd från VA med dödsorsaken som rapporterats av respondenterna. Undersökningen visade samstämmigheten var relativ låg och varierade beroende på dödsorsak; dödsfall med icke-medicinska orsaker som olyckor och mord visade en högre samstämmighet, medan de med medicinska orsaker visade en lägre. En slutsats som kan dras av undersökningen är att den rapporterade dödsorsaken är bristfällig och att det finns behov av standardiserade metoder som VA. Avhandlingen studerade även hur resultaten av VA påverkas av tiden som förflyter mellan att dödsfallet inträffar och VA-intervjun utförs. Resultaten visade att så länge intervjun utfördes inom ett år efter dödsfallet så var påverkan liten. Denna kunskap är av största vikt när VA ska optimeras för tillämpning inom system för övervakning av hälsodata. Slutligen vidareutvecklades en av de mest populära VA-modellerna, InterVA-4, i avhandlingen. Ett av huvudsyftena med den nya modellen, InterVA-5, var möjligheten att utnyttja data som samlats in enligt det nya VA-instrumentet WHO-2016. En annan viktig del var att utveckla och integrera ett system för att klassificera omständigheterna runt dödsfall. Systemet gavs namnet Circumstances Of Mortality CATegories (COMCAT), och visades ge rimliga och potentiellt användbara resultat. Då InterVA-5 även kan hantera data från instrumenten WHO-2012 och Tariff-2, undersöktes en datamängd som innehöll frågor från samtliga instrumenten. Resultatet var en hyfsad god samstämmighet, och således kan InterVA-5 harmonisera tolkningen av resultat från data insamlade med olika instrument.

LIST OF PAPERS

This thesis is based on the following studies, referred to in the text by their Roman numerals.

I. Hussain-Alkhateeb L, Fottrell E, Petzold M, Kahn K and Byass P. Local perceptions of causes of death in rural South Africa: a comparison of perceived and verbal autopsy causes of death. Global Health Action. 2015; 8: 28302.

II. Hussain-Alkhateeb L, Petzold M, Tollman S, Kahn K and Byass P. Effects of recall time on cause-of-death findings using verbal autopsy: empirical evidence from rural South Africa. Emerg Themes Epidemiology. 2016;13:10.

III. Hussain-Alkhateeb L, D' Ambruoso L, Tollman S, Kahn K, Van Der Merwe M, Twine R, Schiöler L, Petzold M and Byass P. Enhancing mortality data: adding Circumstances Of Mortality CATegories (COMCAT) to deaths investigated by verbal autopsy. Lancet Global Health (Submitted).

IV. Byass P, Hussain-Alkhateeb L, D' Ambruoso L, Tollman S, Kahn K, Schiöler L and Petzold M. An integrated approach to processing WHO-2016 verbal autopsy data: the InterVA-5 model (Manuscript).

CONTENTS

ABBREVIATIONS

AIDS	Auto-Immune Deficiency Syndrome
CCC	Concordance Correlation Coefficient
CI	Confidence Interval
COMCAT	Circumstances Of Mortality CATegories
CRVS	Civil Registration and Vital Statistics
CSMF	Cause-Specific Mortality Fraction
CSV	Comma-Separated Values
CVD	Cardio-Vascular Diseases
GIS	Geographic Information System
HDSS	Health and socio-Demographic Surveillance System
HDI	Human Development Index
HIV	Human Immunodeficiency Virus
HSDU	Health Service Department Unit
ICD-10	International Classifications of Diseases-10th revision
INDEPTH	International Network of field sites with continuous Demographic Evaluation of Populations and Their Health
InterVA	Interpretation of Verbal Autopsy
LMIC	Low-Middle Income Country
MDG	Millennium Development Goals
MRC	Medical Research Council
NCD	Non-Communicable Diseases
OR	Odds Ratio
PAR	Participatory Action Research
PCVA	Physician-Certified Verbal Autopsy
PHC	Primary Health Care
PHMRC	Population Health Metrics Research Consortium
PWH	People living With HIV
RRCoD	Respondent-Reported Cause of Death
SA	Social Autopsy
SDG	Sustainable Development Goals
SES	Socio-Economic Status
SF-VA	Short-Form Verbal Autopsy
TB	Tuberculosis
UHC	Universal Health Coverage
UN	United Nations
UNSD	United Nations Statistical Division
VA	Verbal Autopsy
VACoD	Verbal Autopsy-derived Cause of Death
VASA	Verbal Autopsy Social Autopsy
WHO	World Health Organization

1 INTRODUCTION

"Mortality is very brief but immeasurably important."

Joseph B. Wirthlin

1.1 Vital data: a brief history of development

Only 500 years ago, the science of vital statistics was born, typically depicted by the "Black Death" in London - the pneumonia plague mortality. John Graunt (1620-1674), acknowledged as the father of medical statistics for his *Natural and Political Observations upon the Bills of Mortality*, based his findings and interpretations on the plague mortality reports that had been collected by the Company of Parish Clerks in London starting in 1592 and continuing intermittently until 1858 - possibly the earliest known reference of this kind of activities. Although this has taken almost an entire century since its prime collection, which commenced strictly at the outbreak of a plague, John Graunt was pioneer in effectively directing the public attention to the invaluable public health implications deduced from using affordable statistics on deaths (1, 2). By mid-nineteenth century, this systematic practice was formally put under the authority of the Corporation of London which later extended registrations to other parishes including information on causes of death, as defined by death searchers at the time. Although presumably based on the Bills of Mortality, the reliability of mortality data was arguably dubious and several questions were raised including that whether mortality data was collected and compiled by death counts on plague or simply constructed? Hence, reviewing the criticism of accuracy of the Bills of Mortality could probably provide insight on the personal's statistical expertise and views of handling vital data at that time. Nonetheless, this criticism could likely be misguided, such as that by the excessive and unfair criticisms of female searchers who reported mortality data at the time (3). The Swedish recognition of vital statistics including information on causes of death was initiated by the Registrar-General in 1749, much earlier than other European countries. This was originally triggered by the increased maternal mortality which had a rate of 900 per 100,000 live births during that period. It was until 1858 when the collection process was taken over by the Swedish Central Bureau of Statistics and continues until today (4, 5). Efforts to systematically collect and document mortality data have affectedly followed from these initiatives in some parts of Europe and the US, mainly linked to common endemic episodes of different

illnesses (6). Hence, the concept of data reporting and its reliability is documented in history and continues as a recognized global issue until today.

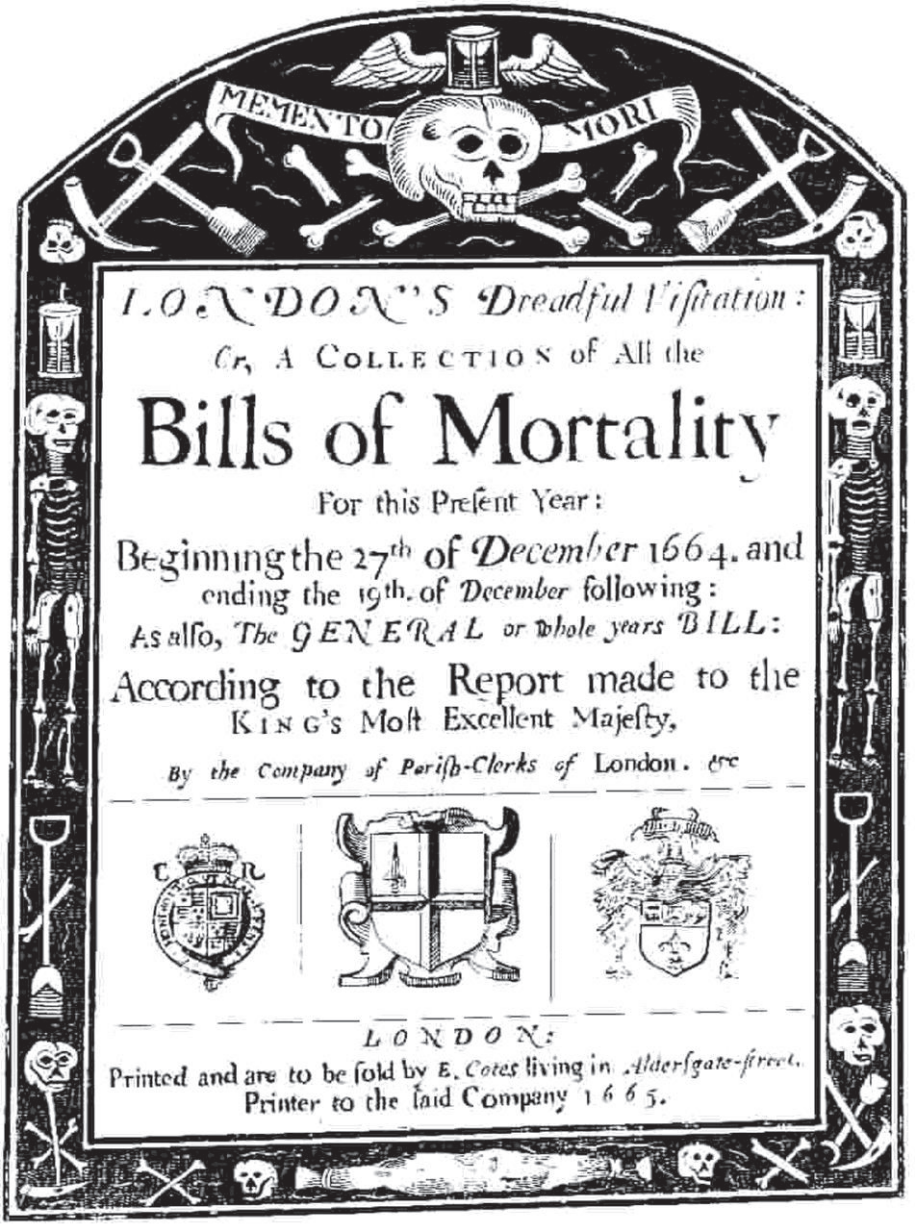

Figure 1. The Bills of Mortality, documenting the impact of Plague on London during the sixteenth century. Public domain image reproduced from the Pinterest, https://www.pinterest.se/pin/565483296942316341/

1.2 Historical reasoning for failing vital data registration

During the 19th century, Miasma was the prevailing assumption among medical doctors and public health attendants particularly in the city slums of England, France, Germany, Scandinavia and the United States, and further extended to India and China (7). It generally entailed poisonous vapour filled with substances from decomposed subjects which caused the illness. Nevertheless, Dr. John Snow's founding work between 1849 and 1854 on the sources of cholera, and advancements of other pioneers such as Jakob Henle and his *Manual of Rational Pathology* in 1846, Louis Pasteur's demonstration of a living organism as the agent in an epidemic in 1865 and Roberts Koch's discovery of the mycobacterium as "the cause" of tuberculosis (TB) in 1882 were all seen as the symbolic figures of grounding the new era of public health perspective on the prevention of disease. The new model of disease that followed from their contributions, namely the *germ theory* which carried the view of specific causes, eventually led to the reinforcement of laboratory perspective of the disease-specific model. This has resulted in the development of vaccine to prevent disease transmission (immunization), antibiotics to cure and the science of laboratory-based for precise diagnosis but more importantly, to the retirement of the miasma. Albeit accurate conclusions deduced from germ theorists in their causal attributions for many communicable diseases, this narrow focus on controls of infectious agents has impeded the progress of the population epidemiology and the social dynamics of diseases. This has further resulted in declines of previous efforts in advancing with the design and performance of field surveys, analyses of large sets of data and more importantly, the establishment of national statistical systems for vital data which was disregarded in many places and continues until today (8).

1.3 From individual to population health perspective

Among other transitional diseases that have emerged in modern time (9), the human immunodeficiency virus (HIV) epidemic was the most dominant and cross-national form of illness during the later period of the 20th century and of highest impact on local health systems (10, 11). Epidemiological contributions lacked key understandings of the epidemic of this chronic illness to be able to propose appropriate controls. Although its immediate risk behaviours and determinants are known, the public health arena remained susceptible to

overturn the HIV epidemic or translate its risk behaviours into protection program. This reflects on how some health problems which are driven by societal forces are difficult to be explained merely by some health paradigms. This has nonetheless directed the public health community to view health and risk behaviours from a population-level research rather than the individually-focused studies (8, 12).

The individual's decision about his or her engagement in a particular risk behaviour usually follows the individual's own choice which could likely deviate from the population's view. Typically, the individual's interest in health risk is personally-driven rather than viewed as a population gain. In this sense, personal gain is commonly reached when both absolute and relative risks are quite high, and when these conditions present, individual's behaviours often change. For example, the majority of heart attack survivors quit smoking within one year following the event. Nonetheless, individuals tend to include human perceptions of time value and cost throughout their decision making process rather than appropriately weighing their associated risk behaviour which may eventually influence the health equation (13). This has consequently driven regional epidemiologists and public health researchers to focus their data collection practices to be more continuous and systematic measurements in defined populations, while also taking considerations for differences that exists at individual levels. Hopefully, and certainly ideally, the long-term goal should be towards accounting the health for every individual at global level (14).

1.4 Global dilemma of cause of death data

The period dating from late 1970s was marked by rapid increase in interconnectedness in the international institutional framework, a concept that defines globalization (15). During this phase, there is a significant interaction between acts of globalization and some key determinants of population health such as demographic changes; which is characterized by population aging and growth and influenced by improvements of economic and quality of life, environmental changes; like the epidemic infectious diseases and, the emerging epidemic of non-communicable diseases (NCDs). Globalization, which is characterized by cross-border migrations of economy, cultures, believes, ethnic groups and diseases, has imposed additional challenges to face public health practitioners and health policy makers. Moreover, global health today is featuring a widespread challenge by the "multiple burden" of disease, including the resource-constrained settings like the Sub-Saharan Africa and

South East Asia. Those nations that are still battling the old and new forms of infectious diseases are now forced to deal with the emerging epidemics of the NCDs such as cardio-vascular diseases (CVDs), diabetes and cancer as well as maternal and child health and, violence and injuries (16). Although the majority of the NCDs are preventable, and in theory most of infectious disease epidemics (15), cause of death data providing reliable information about their determinants and risk factors is simply unavailable. Aggravatingly, scarcity of causes of death data is reported to inextricably correlate with poverty, limiting their ways into the global literature. In fact, poor cause of death data from impoverished settings, both in terms of quality or quantity, leads to that either no results from these settings reaches the literature, or that substandard research publications for health planning are produced (17). The process of vital registration of mortality data and their causes, defined by the continuous, permanent and universal recording of data on births and deaths of a population (18), marks a direct example to illustrate the current dilemma of health data.

1.5 Successful failure of causes of death registration: where and why?

Vital data, characterized by births and deaths, as well as the causes of death information, mark crucial contributions to the public health action. Although appropriate focus of national health services should well be steered towards the care of the living, reliable cause of death data constitute important sources for public health planning (19). But such data on cause of death are generally scarce — despite rapidly expanding global information systems. Dubbed 'the single most critical development failure of the past 30 years', half of all deaths worldwide are thought to pass without notification of medical causes, three-quarters of which occur in sub-Saharan Africa and South East Asia (20-22), with central sub-Sahar Africa having the most limited evidence base with only little causes of death information (23).

The intermittent progress towards complete civil registration systems cannot be regarded as direct neglect by international bodies. The United Nations Statistical Office issued the *Principles for a Vital Statistics System* in 1953 followed by the Health Metrics Network, directly under the World Health Organization (WHO), to guide and serve as two sources for health information at country, region and global levels (24). However, one conceivable explanation for the lack of vital registration might be that routine surveillance to capture cause of death records is an unaffordable luxury in these recourse-

poor settings which are inevitably associated with under-resourced health systems. Arguably, however, the needs for such information to aid the management and prioritizations of health services are even more crucial when resources are limited (5). In general, deficiency in death registration is inevitably linked to weakness in birth registration. In such settings, where births are simply passed undocumented, deaths are less likely to be reported and registered. Typically in any data-reporting system, the informant and the data collector are the two main actors to ensure adequately-functioning system. However, in terms of reporting deaths, a number of factors may influence this registration mechanism. Cultural values and peoples' perceptions of their actual cause of death are commonly associated with reluctance to disclose these events. In some settings like South East Asia for instance, infants are not perceived to be fully human until their first birthday whereas in sub-Saharan Africa, stigma and shame are strongly linked to certain cause of death such as HIV/ AIDS (auto-immune deficiency syndrome) (25, 26). Hence, people in some specific settings are less likely to report new born deaths or those are thought to die from HIV-related causes. Traditional beliefs that relate to soul or spirit are also considered relevant factors to influence how people may perceive these causes of mortality thus, the reporting of deaths (27). Nevertheless, the lack of death reports can further advance into operational and managerial consequences within the health system which can have negative public health implications.

1.6 Towards systematic reporting of causes of death data

The extent of specific details mortality patterns provide for effective health planning can range from local to global levels, and presenting a detailed breakdown of cause of death categories is crucial for monitoring health. Regional epidemiologists and health service researchers may find proportions of causes-specific mortality very useful for understanding the risk factors of particular mortality in one population which is necessary for effective interventional programs. In this sense, the ability to capture all deaths in one population can formulate a solid ground (denominator) to reliably quantifying these cause-specific mortality which, in theory, mimics the routine civil registration and vital statistics (CRVS) systems that exists in the industrialised world.

Surprisingly, systematic measurements of mortality are fairly recent acts, albeit their overriding role in several national and global health estimates. Globally,

they were introduced in the Millennium Development goals (MDGs) and the Human Development Index (HDI) as relatively useful component for effective planning and implementations of a population's health (28). Out of eight MDGs, two were specifically mortality-related; the reduction of child mortality and improvement of maternal health (29). Although the MDGs goals were assessed between the years 2000-2015, the concluding message that characterised the era of the MDGs was growing calls for consistent data and reliable statistics to assist health planning, at national and international levels (30). Drawing on the more recent United Nations (UN) Sustainable Development Goals (SDGs), there are new goals to achieve universal improvement in CRVS reporting by 2020 and involving direct indicators to ensure that, 60% of deaths are continuously notified, 80% of deaths in hospitals have official cause of death certification and 50% of deaths at home or in communities have probable cause of death determined in real time (31).

Unlike some countries with long-standing and successful implementations of routine CRVS as in Scandinavia (5), settings that are most likely unable to achieve complete coverage of vital data in the near future, a circumscribed population can be a feasible alternative for securing reasonably detailed, consistent and quality community-based data. This concept is typically applied via Health and socio-Demographic Surveillance Systems (HDSS) which is able to provide the needed population denominator for deriving health measures (32).

1.7 Surveillance

Information gathered and interpreted from the weekly "Bills of Mortality" in London were considered one of the earliest examples of public health surveillance, a term that nowadays refers to *the ongoing systematic collection, analysis, interpretation and dissemination of health data (33)*. Graunt's interpretations of records from the "Bills of Mortality" were the first to estimate "case counts" of specific cause of death at population level providing meaningful information on diseases patterns and quantity. In recent years the concept of surveillance has extended further to imply a close follow up to evaluate the effectiveness of interventional and health care programs such as the effect of vaccination program on the disease. Although surveillance and monitoring are often used interchangeably, surveillance is distinct which is unlike the monitoring of usually a group of people, surveillance concerns an entire populations (6).

Surveillance activities involve collections of demographic and vital data such as births, deaths and in- and out-migrations that can facilitate detailed descriptions and more nuanced understandings of transitional patterns and variation across settings and time. Under this act, prospective data are robust sources for details necessary for informed planning and policy, addressing the health burdens and inequities currently in lower- and middle-income countries (LMICs) (34). Although in principle the concept of CRVS is present and functioning in many industrialised countries, substantial lack of national identification system and inconsistent operational and technical practices of the CRVS at national level raise significant concerns about the quality of the derived CRVS data (31, 35, 36). At present, more than 60% of the world's population are outside any kind of systematic health surveillance which limits public health and research activities in the most resource-constrained communities (5). The increasing regional and global appraisals of mortality trends are critical to our comparative understanding (23). Nonetheless, a weakness is the lack of national and sub-national outcome data to inform health systems development – particularly given dynamic demographic, epidemiological, and social change (34). In fact, despite a globalization-dominant world, there is still no universal and systematic individual registration of vital events at global level, particularly ignoring the mortality and causes of death information (14).

Whilst the goal of universal and accurate vital registration systems remains, in the mid-term at least other interim solutions are needed to provide the data required (37). A major step forward, at a reasonable cost, consists of providing complete coverage of all the vital events occurring in a defined population and follow these events over an extended period. HDSS is a shining example that can provide vital information through routine update rounds within an initially censored population in a described geographical area, including documenting cause of death reliably using verbal autopsy (VA). VAs are standard interviews to elicit specific information about signs, symptoms and circumstances of death through family members or caregivers of a recently deceased person and is commonly applied in places without systematic medical certifications (38, 39). In HDSSs, updating and verifying existing data or recording new events such as pregnancy outcomes, in- and out-migrations and other socio-economic features as well as birth and death events are carried out via regular update rounds. These rounds may be annual, or more frequent (40). This concept was introduced at sites such as that at Matlab which has been carrying out continuous population surveillance in rural Bangladesh since early 1960s (41). As a result of a workshop held in Dar es Salaam, Tanzania, in 1998, INDEPTH (International Network of field sites with continuous Demographic Evaluation of Populations and Their Health in developing countries), was formulated to build capacity at sentinel demographic sites through technical training,

scientific engagement and the establishment of cross-site research groups (40). Today, the INDEPTH comprises 49 HDSSs that monitor the lives of nearly 4 million individuals across 20 countries and is distributed at both rural and urban locations, often in underserved settings (42). The INDEPTH is currently revising its strategy to engage along other SDGs, crucial goals that relate to poverty, gender equality and hunger, as well as genomic data and blood biomarkers (43). In doing so, it is committed to tracking SDGs by mapping and publishing baseline metrics for each target and regularly publicizing progress. INDEPTH has therefore the potential to increase its relevance in a transitional global health environment and further assist local, national and international health policies while it is currently expanding the scope and timeliness of its vital data (42).

Figure 2. The INDEPTH Network of 49 HDSS, monitoring around 4 million individuals across 20 countries, 2017. Reproduced from the INDEPTH (44)

1.8 Verbal autopsy standard: a brief history of development

Until today, in large part of the world, physician certifications of death are traditionally practiced, usually as a compulsory routine performed in connection with the local healthcare provider. In other part of the world, however, deaths may not even be counted (17). In response to the global deficit of mortality data, mainly in settings where there is no adequate CRVS, VA has emerged in recent decades as a pragmatic alternative to determine likely cause-specific mortality fractions (CSMFs). Pioneer projects in Asia and Africa during early 1960s used systematic interviews, with bereaved relatives or caregiver of the deceased, performed by trained physicians to investigate possible cause of death. It is the Narangwal project in India that primarily labelled this method 'verbal autopsy' which continued to spread and develop into a standardised tool and shifting to lay-reporting of health information instead of relying on the medically-trained doctors, as suggested by the WHO during the 1970 (45, 46). Hence, it is now uncommon for physicians to actually conduct VA interviews themselves rather than trained fieldworkers. Nonetheless, until fairly recently VA materials were presented to local physicians for interpreting the VA data to derive a probable cause of death; physician-certified verbal autopsy, PCVA (47). This typically involved two independent physicians to review the VA data and where no consensus was reached, a third physician was invited. If all three physicians disagreed about a probable cause of death, the cause was usually listed as 'indeterminate'. However, to consider time, cost and consistency of the PCVA, computerized methods that are cheap, consistent and proven robust alternatives to derive probable causes, are now in widespread use (48).

Being mainly research driven, the VA technique had been used in different settings with little coordination or concerns to ensure comparability of datasets between countries and over time. This has resulted in disagreement on how VA should be presented during interviews in terms of questionnaires format and data analysis and reporting (49). Efforts by the INDEPTH and an expertise panel from the WHO have outlined key characteristics of a convenient VA data-collection instrument which includes both open- and close-ended sections (50). VA closed sections use filter questions on signs, symptoms and circumstances at and around death, providing information on indicators that were absent or present prior death. On the other hand, open-ended questions usually helps record verbatim details of disease indicators and this information can be useful if closed questions fail to capture all information or in rare conditions like causes by neonatal deaths. (49). Following a two decades of proliferation interest and research development around the VA process,

including aspects related to data-collection, questionnaires' content, cause of death assignment and coding as well as the validation of the VA tool, demands for standardisation led to the 2007 publication of the WHO VA standards. The standard included VA questionnaires structured into three age groups; under four weeks, four weeks to 14 years and 15 years and above. VA questionnaires using the older age group instrument also comprise of items for assessing pregnancy-related and childbirth cause of death. The standardised VA used cause of death certification and coding resources consistent with the international classifications of diseases - 10th revision (ICD-10) (51). Additionally, the VA interview instrument include a question seeking the respondent's opinion on the cause of death of the deceased – providing a source for local perception of cause of death, (52), which also forms the basis items used in paper I.

Nonetheless, growing interest in strengthening countries' CRVS systems, which consequently let to demands for a simplified VA instrument and aligned with local information technology applications, triggered the modification of the 2007 WHO VA instrument based on existing evidences. International entities and local governments have recognised the essence of designing VA for use in routine CRVS to enhance the national cause-specific mortality data while employing a new instrument that can eliminate unreported causes and includes more focused and useful questions. This has led to the revision of the 2007 WHO VA materials and the formation of the 2012 WHO VA instrument which utilised 192 cause of death related questions (indicators) suitable for use in local interviews at lower costs and amenable to software analysis for automated ascertainment of cause of death (53). Following continuous research and compiled evidence from the validated and most extensively used VA procedures, consensus was reached to form the 2014 WHO VA (54). During these revision attempts, questions were added or edited to facilitate the use of publicly available analytical resources for assigning causes of death. Further experience from the field in using 2012 WHO VA instrument and the interim 2014 WHO VA tools, as well as cognitive testing, added more inputs in the refinement of the older instrument to form the 2016 WHO VA instrument. The currently-applied 2016 WHO VA instrument allows for responses with a simple "yes" and "no" answer, multiple choices and very few free text fields to capture some information that may be used in reviews but not to analyse in the software (55). However, the number of questions has slightly increased in the 2016 version compared to the 2012 instrument because some questions were added and some complex questions were split into two to make sure they ask only one question at a time. The skip pattern (a process that navigate the various combinations of age-, sex-, maternal- and perinatal-specific indicators within a single, comprehensive instrument) has been edited

based on evidence from field testing of the older VA instrument. All age groups, including maternal and perinatal deaths as well as deaths caused by trauma have been considered in the new instrument. This development can further introduce more consistency and cross-comparability of VA-derived cause of death data to use in routine CRVS. The 2016 WHO VA instrument may additionally serve data collections using paper-based questionnaires. However, for the purpose of using automated analytical software for the cause of death assignment and for the comparison of the responses across VA studies, all data should be entered into a digitalised database (56).

The method has been applied in over 45 countries and WHO publishes standard VA interview protocols for cross national monitoring and analysis (51, 53, 54, 56). When conducted in large household surveys, VAs produce information on cause of death representative of populations. During the past two decades, there has been extensive experience in the use of VA in research environments (45, 47-49, 57). Consequently, VA has significantly advanced into more rigorous questionnaire designs — ultimately reducing time and cost of VA interviews — and integrated into other technologies shifting from a paper-based to mobile tablet-VA tool (58, 59). Though VA is linked to an ongoing ethical debate by the VA community given its sensitive nature — having to recall emotional memories about death (60) — respondents and fieldworkers are in general favour of pursuing VA application with tendency towards sharing the derived cause of death with relatives of the deceased. This is based on the common view that, such information are likely to benefit individuals and their community with increased potential to saving lives (61). Furthermore, due to the emotional stress VA may cause to some bereaved relatives, or the requirement of understanding specific medical terms during VA interviews, special counselling techniques and standardised training across various sites for the VA interviewers is important but which is currently lacking and thus, there is a demand for a universal protocol (49, 62).

Table 1. Distribution of VA standard questions by age group and segment/ depth section of the questionnaire. The 'entry level' questions will always be asked. The levels refer to the skip questions. Questions for CVRS are a set recommended by the United Nations Statistical Division (UNSD) and these are not necessary be in all settings. The questions asking for content of a medical certificate of cause of death may provide helpful information in certain settings and in case such a certificate has been issued (56).

Segment/ depth	Neonatal	Child	Adult (incl. maternal)
Personal	19	21	20
Entry level	15	17	16
Level 2	4	4	4
CRVS	13	18	18
Entry level	2	2	3
Level 2	11	16	15
Cause of death	122	161	184
Entry level	38	86	66
Level 2	65	72	96
Level 3	19	3	22
Context	23	23	19
Entry level	7	12	10
Level 2	10	10	8
Level 3	6	1	1
Death Certificate	12	12	12
Entry level	1	1	1
Level 2	1	1	1
Level 3	10	10	10
Grand total	**189**	**235**	**253**
Entry level	63	118	96

1.9 Interpreting VA data: using InterVA model

In recent years increasing attention has been paid to automated-processing of VA data for determining the cause of death. Unlike the PCVA, computerised methods are fast, cheap and reproducible over time and space and likely to speed up the VA interview process by obviating the need for transcribing lengthy narratives (63). There are three families of automated VA models of

relevance to the WHO VA standard currently used for the interpretation of VA data to derive probable cause of death, namely InterVA (Interpretations of VA), Sweden (64), SmartVA (Tariff method), USA (65) and, InSilicoVA, USA (66). Based on the Bayesian-probabilistic modelling (64), the InterVA is the most widely used instrument, first developed and tested in 2003 with VA data from FilaBavi HDSS, Vietnam (67), and now conveniently applied in different settings,

The principle of the Bayesian probability models was primarily developed by Thomas Bayes in 1763 and have thereafter been extensively explored in different medical applications and have shown relatively effective applications (68, 69). In general, the Bayes' theorem is based on the premise that the probability of an event occurring given a particular circumstance is linked with the unconditional probability of that event and the conditional probability of the circumstance given the event. In this sense, if the event of interest was the cause of death and the conditional circumstance (indicators), representing various signs, symptoms and circumstances leading to death is part of that event, then for a predetermined set of possible causes of death $C_{1,..},C_m$ and another set of indicators $I_{1,..},I_n$, the Bayes' theorem for any particular cause C_i and indicator I_j represented as $P(C_i|I_j)$ can be calculated by:

Equation, 1:

$$P(C_i|I_j) = \frac{P(I_j|C_i) \times P(C_i)}{P(I_j|C_i) \times P(C_i) + P(I_j|\bar{C}_i) \times P(\bar{C}_i)}$$

Where $P(\bar{C}_i)$ is (1- $P(C_i)$)

For instance, if the probability that diarrhoea occurs in any death at the population level is 15% i.e. P(I) = 0.15, the probability of death from HIV/ AIDS at the population level is 10% i.e. P(C) = 0.1, and the probability of an individual who has died from HIV/ AIDS having suffered a diarrhoea is %85 i.e. P(I|C) =0.85. Hence using equation 1, it can be estimated that anyone who suffered from diarrhoea before death has a likelihood of %56.7 of dying of HIV/ AIDS.

Applying a set of unconditional probabilities for causes of death $C_{1,..,}C_m$, which is said to be $P(C_i|I_0)$, and a matrix of conditional probabilities $P(I_j|C_i)$ for indicators $I_{1,..,}I_n$ occurring at population level, make it possible to repeat this calculation process for each indicator that is linked with a particular death outcome. This methodological process used in the InterVA model, which is described in full elsewhere (64), typically results in the probabilities of most causes reducing, while a few likely causes are described by their increasing probabilities as successive indicators are processed.

For each VA record, InterVA generates up to three likely causes of death and their corresponding likelihoods (70), e.g. likely causes of death of person 'A' are; HIV/ AIDS (likelihood = 70%) or, TB (likelihood = 30%). These likelihoods can then be presented as CSMF (52). CSMFs are population-level estimates which refer to the proportion that each cause category contributes to the total number of deaths. For individuals where these likelihoods do not total to 100%, an 'indeterminate' residual is assigned (71).

One may argue that, deriving a realistic probability of cause of death may appear challenging, albeit recommendations by the VA community that a high degree of precision is not strictly necessary to build a workable model (67). Nevertheless, all versions from the InterVA family have been validated in large-scale international studies (72) and have generally shown that the InterVA models can in fact provide reliable and comparable results to use for population level estimates. Furthermore, InterVA has more recently been upgraded into the latest version InterVA-5 which fully complies with the WHO 2016 VA standards including complete list of all sixty four WHO causes of death groups (56).

1.10 Unfinished global agenda: towards widespread use of VA

Applied extensively within HDSSs or as reported in unregistered populations (73), the overall methodological developments have greatly increased the potential for the widespread use of computerized VA methods including other purposes than merely research applications. According to the new SDGs to achieve significant improvement in CRVS reporting by 2020, genuine interests for integrating VA into routine CRVS systems are established and declared by many countries as future agenda, shedding the light on potential practical and system-level perspectives (31). There are, however, challenges concerning some contextual aspects, such as the local perception of causes of mortality, as

well as other operational factors of the VA process within HDSSs, which are in part due to the nature of death. The trauma of death can influence willingness to report symptoms or detailing circumstances of event, and feelings of guilt during mourning may distort accounts of events preceding death (74). These accounts are also driven by informants' willingness to report relevant information of the illness during VA interviews, which are strongly influenced by local literacy of health and how communities perceive their causes of deaths. This may result in delayed or unreliable reports of death which may impact the overall VA assessment of cause of death. Hence, these problems are crucial for the VA community to explore. Furthermore, the WHO VA standard is a source of indicators for circumstances of deaths, such as causes related to social and health systems factors, beside the medical causes. Therefore, using the InterVA family of models may potentially facilitate an integrated novel and scalable approach for addressing the non-medical causes of death in the understanding of the survival pathway in a consistent way. These circumstantial factors are both modifiable and influential which can have significant impact on understanding critical limiting factors related to social and health systems contexts involved in the survival pathway. Throughout the past decade, there has been a significant development and updates in the WHO VA standard protocols with attempts to align with the automated tools which are more common to apply for VA analysis. The InterVA-5, the latest from the widely used InterVA family is now designed to fully comply with WHO VA 2012 standard and the WHO VA 2016 standard, but yet lack methodological assessments.

2 AIMS AND OBJECTIVES

Based on thorough literature reviews and consultancy with the VA research experts at the WHO, four research domains were identified as crucial for the development and widespread use of VA. Using the case of the Agincourt HDSS in South Africa, this thesis investigates challenges and recent advancements and applications of the VA method addressing relevant contextual, operational, health system and technical aspects that can influence the overall conclusion on causes of death, see figure 3. The first paper discusses the role of the community's perception in shaping their VA inputs during interviews and thus, the VA assessment of causes of death whereas, paper II undertakes operational and cultural factors that may potentially delay reporting of a death (i.e. longer recall period) which can impact the quality of VA inputs during interviews and reflect negatively on the final conclusion on causes of death. Paper III is concerned with the inclusion and assessment of a set of circumstantial questions (items) to the existing VA medical processing of causes death; including health system and social factors that may ultimately lead to deaths, potentially providing a complete picture on the cause of death. This novel approach is implemented in the most up-to-date automated tool from the InterVA family of which its advancement and performance are discussed in paper IV. A summary of the four objectives (papers) is listed hereunder:

1. Contextual: to explore the effect of pre-existing concepts of cause of death among VA respondents on the VA assessment, shedding the light on the health literacy in such settings. (Paper I)
2. Operational: to examine the impact of the resulted time lag between death and VA (recall period) on VA-determined cause of death, aiming for optimized VA process within HDSSs. (Paper II)
3. Social and Health system: to explore the concept of non-medical cause of death that may have influenced the death situation and consequently the VA conclusion. (Paper III)
4. Technical: to summarise and validate the recently updated version of the InterVA-5 which has now been modified to comprehensively use all inputs and classify all sixty four causes from the WHO 2016 VA. (Paper IV)

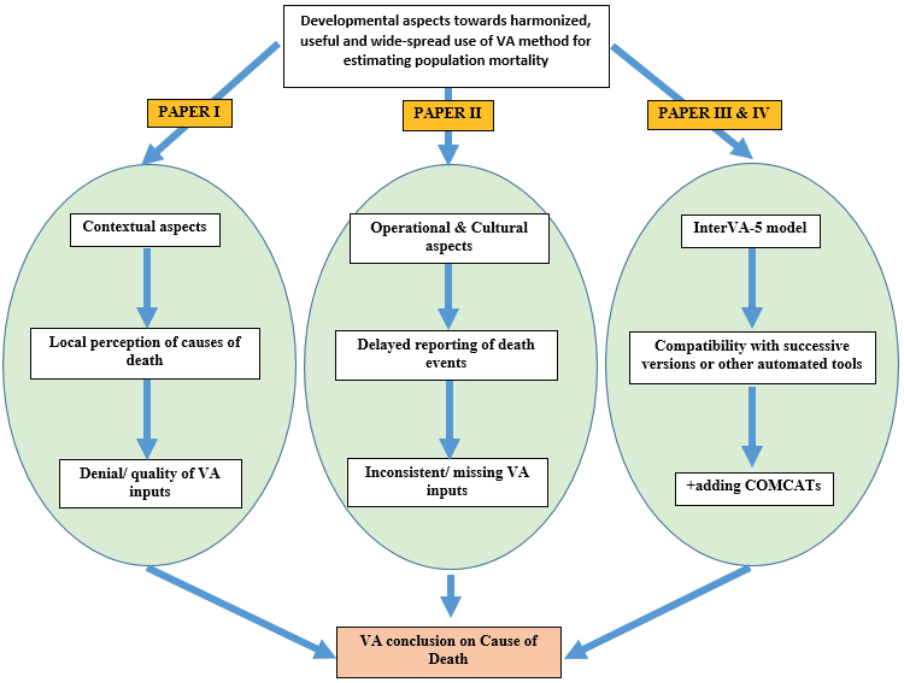

Figure 3. Outlines of the thesis studies

3 BACKGROUND

3.1 Local perceptions of causes of death in public health

In the introduction chapter, I referred to how individuals generally involve time value and cost throughout their decision-making process in health matters rather than appropriately weighing their associated risk behaviour which could ultimately cause or prolong their illnesses. This lay belief about health is driven by more complex theories and can impose further implications on peoples' health and well-being. Lay beliefs of health and illness are conceptual models used by individuals or communities to describe reasons for ill-health and causes of terminal deaths. During the past three decades, the focus on the divergence between lay-perception of health and diseases and the established medical understanding has helped to add complementary understanding about health issues and inequalities (75). This notion is important because, where cultures disagree about a pattern of symptoms of illness it can likely mislead different cultural groups in understanding conceptual models about health and the origin of illness and by association, mislead their understanding of the associated risk factors (76). For example, people from the Western countries tend to seek explanations for illnesses and emphasise biological concepts (77), whereas communities in Eastern countries appear to locate the origin of health and illness in the social or supernatural worlds (78). An African-American study in the US revealed that, a reason for refusal of using pregnancy prevention methods was that birth control was perceived as a plot against Blacks (79). Another Malaysian study involving medical students, hospital staffs and outpatients, showed that participants rationalized smoking by self-exempting beliefs such that drinking water or eating sour fruits immediately after smoking can make smoking healthier (80). This pattern of how local beliefs influence medical treatments and health intervention is persisting, as reported in more recent studies (81). In view of such cultural circumstances, one national and international health priority is set to understand intermediate factors between health and disease to support patients' decision making for improved health access and self-management and, empower them to seek and handle information responsibly (82, 83). In a more direct term, examining how lay people perceive causes of mortality or morbidity can illuminate how people make appropriate health decisions at home or at work, in the community, in the health system and the political arena, which defines the overall concept of health literacy (84).

Health literacy is context-driven and closely related to socioeconomic status (SES), thereby increasing risk for low health literacy among those who are most vulnerable. In a time when patients are more involved in obtaining information about their health, health literacy is becoming a more critical issue in public health. In 2004, the United States Governing Board of the National Research Council approved a project on the population's assessment of their ability to obtain, understand and use health information. The report concluded that, almost half of all American adults — 90 million people — experience difficulties understanding and thus, acting upon health information. It was reported that, even people with strong literacy skills, science teachers and some medical staff may have difficulties receiving, comprehending and applying health information or at least failing to adequately explain such details to other people, for example visiting patients (85). Another study from an industrialised setting associated limited health literacy with being poor, having minimal educational attainment or belonging to a particular racial or ethnic minority group (86). In resource-poor settings, where people are generally encircled by strong cultural values and traditional beliefs (27), the situation is more dramatic. Communities tend to describe their diseases in manners that cannot be sustained by local medical evidence, but which nevertheless persist since they form part of the conceptual knowledge of that community leading to the idea that health and illness literacy is simply lacking in some circumstances (75). Consequences of poor health literacy, particularly in resource-constrained settings, are not too difficult to come by. Focusing on South Africa which is, like other African countries, featuring a growing multiple burden of diseases, disease management is not routinely assessed through clinical governance (87, 88). Despite progressive economy and health policies, the South African health system, is deeply divided and inequitable (89, 90). In this unequal societal context (91), patients with low health literacy exhibit poor knowledge about their illness and likely to experience difficulties in accessing care or adhere to treatments. Keikelame et al.'s study on management of epilepsy in primary care settings in Cape Town found that, epilepsy is poorly managed and this is directly associated with health illiteracy, communication difficulties and poor doctor-patient relationships (92). In addition, South Africa is one of the countries with the highest burden of infectious diseases mainly HIV which commonly co-exists with TB of a high degree of symptoms overlapping (87). This can pose serious challenges for succeeding interventional programs or managing the effect of the combined use of antiretroviral and TB drugs. A study by Taylor et al which covered both rural and urban South Africa concluded that, despite decades of HIV/AIDS in South Africa, high school students' health literacy was inadequate and focused health education will be necessary to control transmission, prevention, early diagnosis and adherence to treatment for both HIV/ AIDS and TB infections (93). Other studies have inferred that individuals with low health literacy were less likely

to take and adhere to antiretroviral therapies (94, 95), pressing the need for further empirical research on lay perceptions of causes of illness across different cultural contexts. Nonetheless, health literacy is a complex phenomenon involving both access to and skilful use of health-related information. Achieving a comprehensive definition of health literacy that can distinct it from related domains is posing another challenge (96). Furthermore, attempts to employ traditional methods to assess community understanding of related causes of mortality in Africa has resulted in inconsistent outcomes (97-101). In fact, evidence of relying on lay reports as a basis for national estimates of cause-specific mortality is limited, with both lay reports and physicians failing to distinguish between common cause of death such as TB and HIV/AIDS in some instances (102). Nevertheless, no studies have yet sought standardised tools, such as VA, to explore people's perception of cause of death in African settings.

3.2 Pre-existing concepts of causes of death in the context of VA

In South Africa, HDSSs are featuring a widespread use of VA as a standardised and imperfect instrument in the absence of medical certification. To a large extent, VA method relies on lay informants to elicit a specific cause of death. The process of identifying appropriate respondent for the VA interviews still needs to be standardised, taking into account respondents' backgrounds and cultural factors (103). Experience suggests that close relatives or caregivers are most appropriate and rarely refuse to provide information, with some surveys reporting 100% response rates for VA interviews (104-106). The respondent's backgrounds and relationships are also reported to have effect on the quality of VA data. For instance, when reporting maternal-related deaths, male respondents tend to provide more detailed information compared to female respondent during the VA interview (107) whereas giving information on child's death showed that mothers are able to retrospectively report signs and symptoms but were unable to differentiate between degrees of severity (108). In more critical VA occasions, however, deliberate denial of prominent signs and symptoms by the respondents, such as those of chronic conditions like malnutrition or HIV/ AIDS, may suggest that some disease symptoms are not genuinely appreciated by lay communities which make it more difficult to measure. Nonetheless, one key underlying assumptions of VA is that, each disease category has a distinct pattern of symptoms that can be recognised, recalled, and reported accurately by lay respondents (109, 110). It is also

crucial to note that recognition and recall abilities of disease symptoms are two distinct phenomena, with little empirical evidence existing regarding respondents' ability to recognise symptoms. From technical and operational points of view, symptoms that are both poorly recognised and poorly recalled are likely to derive spurious conclusion during the VA process (111, 112). It is thus apparent that recognition, recall and reporting to a certain extent depends on cultural perception of symptoms (104, 113) as well as on social taboos and expectations (114). VA respondent's perceptions of cause of death may sway responses to specific questions in a VA interview, and thereby affect conclusions on causes of death (25). Examining local perception of cause of death, using the context of the HDSS, is therefore essential in situations where clinical and lay concepts and terms to describe specific symptoms are to coincide (115). This research study will be dealt with in paper I.

3.3 Operational aspects in HDSSs

HDSSs are platforms for research programs that illuminate causal pathways and assess health interventions across the life course. The dynamic and social transitions in South Africa, just like other African and Asian countries (116) where most HDSSs are localized, are associated with challenges. Furthermore, sex and age structure and cause of death patterns are changing in these settings, pressing more needs for consistent and prospective data (34). This entails routine updates of individual and household information on vital events and other background and characteristic details to describe populations of well-defined geographical boundaries. Local HDSS sites begin with a baseline census, usually at initial stages of their establishment. Following the baselines census, this routine is usually fixed at bi-annual or more or less frequent rounds. Information involving members of the population and their households, including a person's name, sex, date of birth, relationship to the head of the household, are key parameters collected and updated at regular intervals (34, 117). In this dynamic cohort, members of the population are added through birth or migration into the HDSS area and removed, but reported, through death or out-migration (figure 4). Other information are often collected, including economic status, marriage and divorce, educational attainment, and immunizations of children (34).

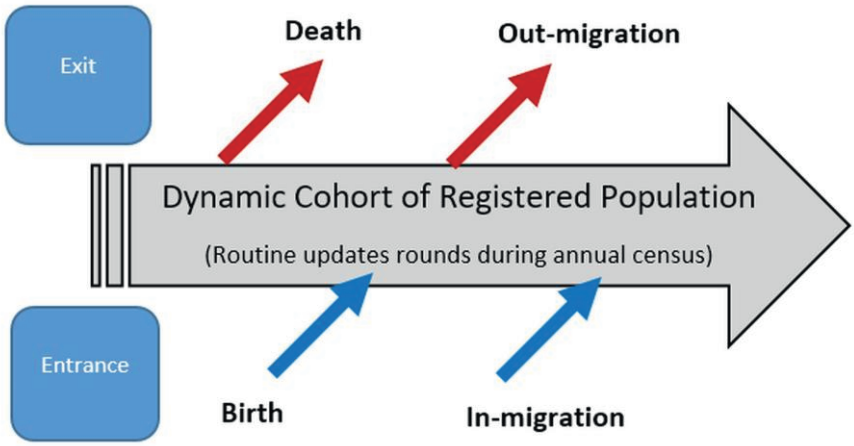

Figure 4. The dynamic population cohort in demographic surveillance systems

Deaths identified during the update rounds are followed up by specially trained field workers who conduct VA interviews with respondents, usually close relatives or caregivers. Although most HDSS sites collect VA data and provide population level cause-specific mortality data, such HDSS sources may not provide representative data for national estimates of cause-specific mortality. Hence, applications of VA in large cross-sectional surveys or in sample vital registration systems have been used to obtain national and sub-national level mortality estimates (56).

3.4 The Agincourt HDSS: routines and practices

Undertaking VAs within HDSSs adopts typical routine operational procedures, most often as fixed annual cycles (118). In the Agincourt HDSS in South Africa, the annual census round and the VA interviews are undertaken strictly between August and November (although some VAs continue into December to finish off), which leads to the dominant short-period of five months during the dry season. As a result of the HDSS annual cycle of operation, there is a usual range from about one month (recognised mourning period during which VA interviews are not conducted) to around one year between death and the VA interview, but this can extend to a longer period in a minority of cases, for example if deaths are missed in update rounds (26). Although true cause of

death is assumed independent of any time lag, seasonal variations in the various underlying aetiologies of some causes of death are plausible. This could likely confound the relationship between time of year, when death occurred, and recall period as a result of the annual cycle of documenting and following up deaths in HDSSs, impacting the overall VA conclusion. Cultural factors can also contribute to the delayed reporting of deaths, and these can be associated with the nature of the death. For instance families are commonly reluctant to report neonatal deaths or disclose information about stigma- or shame-related causes such as the case of HIV/AIDS (52, 62).

As a result of these operational and cultural aspects, delays in following-up deaths can occur in the Agincourt HDSS, prolonging the time between death and VA. Longer recall times may influence ways in which original events are remembered, and thus affect responses to specific questions in a VA interview, which may influence conclusions on cause of death (25, 62, 119). In a study where VA was repeated, inconsistent disclosure of signs and symptoms were reported depending on the backgrounds and characteristics of the respondents (119). Although no standard procedures have been practised or suitably tested (120), experience suggest an optimal range from 3 months to 24 months after death, preceded by a "condolence visit" to inform and prepare the families for interviews (119, 121). The question as to what constitutes a reasonable elapse between death occurring and VA being undertaking has been asked, but evidence on the effect of recall and its consequence on VA assessments remains scarce. Hence, understanding the impact of recall on cause of death outcomes can be useful for optimising the application of VA. This is a topic of research will be dealt with in paper II.

3.5 Circumstantial causes of mortality

Not until fairly recently, in response to fatally ill children, efforts to understand deaths linked to particular social contexts emerged to track process and determinants of quality of healthcare provided and care seeking from home to health facility, which defines the overall concept of social autopsy (SA) (122). SA involves assessment of factors such as knowledge, behaviours, accessibility and quality of care often using a range of qualitative and mixed-methods approaches (123, 124). SA provides unique opportunities to review social determinants of avoidable mortality. It effectively uncovers the pathway to survival in the most constrained-settings and provides complementary information to medical cause of death needed for assisting planning, resource allocation and health policy making. If applied in representative and large-scale populations, SA can provide data to facilitate national and global

estimates of social, cultural, and health systems determinants of mortality and to advocate for the resources needed to overcome these problems. Unlike VA however, SA is not a method that lends itself to large-scale implementation or automated processing. Albeit recent efforts to use SA jointly with VA to add understanding to some social and resources-related care-seeking barriers in some African countries (125, 126), these approaches were only applied in the form of cross-sectional national survey (VASA study) and limited to maternal and child health.

Medical research usually pays more attention to biological processes of particular illness rather than the ultimate death. From an epidemiological point of view, establishing causality between mortality (or morbidity) and putative risk factors typically begins with identifying a biological problem in the host but further assess its social determinant to establish a causal inference. Although many of the technology instruments required to recognise the principal biomedical causes of death of individuals in resource-poor settings are available, these can be significantly restricted for large parts of the population in some settings. Household resources are one key factor for reaching healthcare, however, how health systems facilitate their services for patients to have ease of accessing care and receive fair and quality care is an important piece in the overall survival puzzle (127).

Mosley and Chen's 1984 framework for the study of child survival in developing countries organised determinants of mortality as proximate (biological), intermediates (health systems) and distal (social) (128). In their model, intermediate factors can considerably mediate the pathway between social conditions and health outcomes, a view that is also consistent with other recent models where social norms and values of inequality for accessing advantaged health care services have recently evolved (129-131). Similarly influenced by Mosley and Chen's framework, child survival strategies during the 1990s emerged toward integrated concepts and acknowledgement of community and health system factors for relevant public health activities including health promotions, interventional programs and treatment. This was consequently matured into the development of the Pathway to Survival framework in 1995 recognizing the inequitable access to health services and the established correlation between child mortality and household resources (127). Hence, adopting Mosley and Chen's concept does not undervalue the usefulness of aetiology-specific classification of a particular cause of death, but emphasises social and health system as well as medical roots of the risk. In light of this theoretical opportunity for explaining the pathway between social condition and health outcomes, health system factors were employed as new key indicators in health measurements. Factors associated with health systems

are viewed as meaningful components of the overall care processes and circumstances and events at and around the time of death. This has motivated the literature search on VA and SA to seek relevant questions on care processes prior to a death (132). This is more relevant in settings where vulnerable groups such as immigrants, children or those with chronic illnesses, like HIV/ AIDS, are at increased risk of receiving sub-optimal health care. Thus, understanding the health-care needs of this group as well as their perceptions of the health-care system is crucial (133). Correspondently, SA consists of modifiable questions that can contribute to the same deaths investigated by VA. In contrast, VAs for maternal deaths have earlier on and more frequently examined the social contributors to death alongside the medical causes. In view of the methodological transition of VA for use in CRVS systems, using standardised and robust methods like VA provides a unique opportunity to significantly progress understanding of how circumstances and events at and around the time of death contribute to social exclusion from health systems (132). This is grounded on the assumption that deaths assessed in VA are likely to occur among individuals facing social exclusion from access to health systems. The advancement with this research will likely develop a pragmatic and scalable approach that does not only produce the same level of details as SA or the more recent approach of 'confidential enquiry' (134), but that can also be easily and cheaply applied to large numbers of deaths to generate information on critical limiting factors related to social and health systems contexts. Hence, this approach has the potential of incorporating relevant set of Circumstances Of Mortality CATegories (COMCAT) to the overall VA process for assigning specific causes of death. The COMCAT is therefore, a novel concept that will be introduced and discussed in details in paper III. The COMCAT system is integrated into the latest version from the InterVA family, InterVA-5, which is built on the earlier InterVA-4 model and expanded the knowledge base required using a mixture of data analysis from the training Population Health Metrics Research Consortium (PHMRC) VA reference dataset, as well as expert inputs. The development, comparability and consistency of InterVA-5 model in processing existing data is dealt with in paper IV.

4 METHOD

This research is based on a broad list of methodological applications, primarily using surveillance data from the Agincourt HDSS but also including international reference datasets for the assessments performed in paper IV. Table 2 below provides and overview of the research designs and methodologies applied in this research.

Table 2. Overview of research designs and applied methods in this thesis.

	Paper I	**Paper II**	**Paper III**	**Paper IV**
Source and size of study population	Agincourt HDSS *n*= 11,228	Agincourt HDSS *n*=10,882	Agincourt HDSS *n*=1,247	Dataset 1 (PHMRC*): *n*=6,130 and dataset 2 (AMSVA*): *n*=4,009
Year	1992-2011	1992-2011	2012-2014	2007-2010
Statistical analysis	Kappa statistics and CCC⸸ (135) were employed to assess the agreement between VACoD§ and RRCoD§ at both individual- and population-levels, respectively. Multiple logistic regression was used to examine the agreement by the profile of the deceased	Katz-adjusted log method (136) was used to investigate causes of death subject to seasonal variation whereas multiple logistic regression was applied to examine the association of derived-causes of death by different recall periods.	Descriptive statistics of the distribution of COMCAT proportions by causes of death.	The CCC method was used for the agreement of CSMF from InterVA-5 with the older model (InterVA-4) and with other methods (Tariff-2.0) and WHO VA standards.
InterVA model used	InterVA-4	InterVA-4	InterVA-5	InterVA-5

*PHMRC=Population health metrics research consortium and, AMSVA=Afghanistan Mortality Survey verbal autopsy
⸸Concordance correlation coefficient
§VACoD=Verbal autopsy-derived causes of death and, RRCoD=Respondent-reported cause of death

4.1 Study context

4.1.1 A brief history of development in rural South Africa

In response to international advocates for local health services based on the Primary Health Care (PHC), the Department of Community Health of Wits University in Johannesburg initiated a Health Service Department Unit (HSDU) in 1982 in what is now Bushbuckridge, Mpumalanga province in South Africa. During that period and throughout to the early 1990s, the health planning and services in South Africa was vastly influenced by the legacy of apartheid (137). Political, economic, and ownerships policies were strictly ordered according to race, gender, and age-groups, affecting the organisation of social life, access to basic resources for health, and health services (91). Immediately after its democracy in 1994, however, South Africa saw major health system restructurings included the combination of 14 previously divided health departments into one national health system (138). Despite progressive and inclusive health policies, South Africa is being challenged by institutional transformation and promotion of equity in health development, leaving the health system deeply divided with persistent disconnects between policy and implementations (91, 139). A multi-country review to assess the determinants of over- and under-achievements in health suggested that poor health outcomes and long-standing social determinants of ill-health in South Africa can be attributed to the rapid increase of the dual HIV and TB epidemics but also to the poorly developing PHC (138). Nonetheless, a sweeping system of national health insurance and re-engineering of PHC are now underway to serve universal, equitable and affordable health care coverage. This is aligned with a national consensus to prioritise health research, surveillance and improved information system (89).

4.1.2 The Agincourt HDSS: history and structure

Ten years following the establishment of the HSDU in Bushbuckridge, the Agincourt HDSS research site was formed as part of the Bushbuckridge demonstration district health initiative (137), to introduce and evaluate decentralised PHC programmes and further educate evolving national and district health planning (140). Although the site's priorities were set to work in community-oriented primary care and census studies supporting demographic and health surveillance, the introduction of population registration (i.e. annual census) was politically sensitive and required demanding justification to community members and leaderships. However, support to perform these

activities were later granted on the premise that proposed projects should typically contribute to visible health service improvements and, research findings are to be regularly shared with local communities (137). Today, the Agincourt HDSS provides the basis for the Rural Public Health and Health Transitions Research Unit of the Medical Research Council (MRC) and the co-founding University of Witwatersrand (Wits) (118).

The Agincourt HDSS site (http://www.agincourt.co.za) is located in rural South Africa close to the Mozambique border and spread over 450 km^2. It comprises an open dynamic cohort of 114,765 individuals (2015 mid-year population figure) living in nearly 21,000 households across 32 villages (141). Two thirds of the inhabitants belong to the Shangan-speaking Tsongo ethnic group and one third are of Mozambican origin. In fact, the appeal of the Agincourt as the study site lay in its dynamic feature and diverse population which resulted from constant in- and out-migrations of Mozambican immigrants (formerly as refugees during the Mozambican civil war but as temporary immigrants preceding the ´90s). The act of migration can typically encompass the "movement" of ethnic groups, culture, economy, diseases and social values and beliefs.

The area has a total of 28 primary schools and 19 high schools, yet the education standards remain low with consistently poor rate of school enrolments (141, 142). Approximately 6% of adults possess some tertiary education but only about the half of those actually complete their education (143). Nonetheless, regional reports suggest that South African women has a literacy rate close to 80% (144). Unemployment is considerably high driving as much as third of the area population of both sexes to seek temporary migration for work opportunities– whether on nearby farms or in the mines or even in the manufacturing and service industries of larger towns. Alternatively, villagers commonly grow crops to supplement their daily diets. The act of temporary migration usually involve travelling out of the study site for less than 6 months in a 12-month period (145). Albeit increased unemployment rate, the SES of the population has relatively improved over the past two decades, largely due to the government's social grant system, including child-support grant, the disability grant, the old-age pension, the war-veterans grant and the crisis related grant (146).

Figure 5. The map of Agincourt HDSS in rural North-East South Africa. The site covers 32 villages and a population of 114,765 people in 2015. Reproduced from the public domain Encyclopedia Britannica, Inc. (147)

Villages within the Agincourt site are connected to one another via a network of roads that are partly tarred whereby smaller roads and footpaths link households (141). Following some substantial developments including electrification and the completion of some dams, most houses have electricity (although too expensive to use) as well as access to a communal water tap, or in fewer households, running water within their dwelling. Summers are usually hot (up to 40^{o} C), but milder winters (5-27^{o} C) with usually a low rainfall (550-700 mm per year) in the season from May to September, falling mostly during the summer months of October to April (142). During periods with heavy rains, some road can experience erosion and flooding making transportation more difficult (141).

South Africa is undergoing a major epidemiological transition and given its representative profile, the Agincourt sub-district is no different. Early reports on life expectancy in the Agincourt area documented rates of 57.4 years for females (in 2006) and 50.0 years for males (in 2008). More recent estimates which were performed in 2012 revealed improved life expectancy rates both for females (67.7 years) and males (60.9 years) (44). Infectious causes dominated cause of death for the past 20 years in the Agincourt, driven primarily by HIV/ AIDS, but includes other leading infectious diseases like TB, malaria and acute respiratory diseases. Although a growing number of people living with HIV (PWH) are receiving long-term antiretroviral treatment, which has markedly contributed to the increased life expectancy in this area, this prevailing mortality patterns suggest critical needs for chronic-care services that cut across conventional categories of the so-called "quadruple burden" of disease, which now involves different forms of NCDs, trauma and violence and maternal causes for ill-health. (87). Nonetheless, early results on cause of death have laid the enhanced targeting of district interventions and potential research areas (137).

4.1.3 The health system in the Agincourt HDSS

In the Agincourt sub-district, there is an existing community health centre with a 24-hour acute maternity care. Though it is a considerably large health centre, it has limited number of beds to merely accommodate patients for 48-hours observation (141). In addition, there are six satellite clinics that are all staffed by nurses and provide free PHC services during regular working hours (142). Medical services include immunizations, treatment for minor trauma and routine medications for chronic illnesses as well as infectious diseases including the HIV initiation of antiretroviral therapy (141). In addition to these on-site health centres, there are three district hospitals located 25-60 km from the site that are also accessible by the Agincourt inhabitants through direct visits or referrals from the sub-district's PHC facilities (118). Patients commonly use public transport to commute to these remote hospitals (141). In general, people from the Agincourt site tend to seek both public and private health professionals as well as traditional healers for their illnesses (148), with national reports suggesting 80%-85% of South African seek traditional healers (149). Hence, this structural profile of the Agincourt site helps attract regional epidemiologists and facilitate research that can explore associations of mortality and socio-economic determinants with health systems development.

Figure 6. Vaccinations in one of The Agincourt community health centers. Adapted from the South African Health News Services public domain (150).

4.1.4 Data system in the Agincourt HDSS

Demographic and health surveillance involving comprehensive baseline census were carried out between 1992 and 1993 followed by routine annual updates (four updates between 1992 and 1998 followed by routine annual update rounds starting from 1999) (142). Trained fieldworkers, who scrutinise GIS (geographic information system)-based maps listing every dwelling (143), conducted home visits to collect information on all special events such as births, deaths and migrations. Other population profile, such as age, sex, resident, household relationships, refugee status and antenatal or delivery health seeking habit have helped to define catchment areas, vulnerable groups and potential users of medical services. The Agincourt data system is designed in the form that each individual is linked to a household following an entity called a "*membership episode*" which documents information on when and how a person joined or left the household. A similar entity named "*resident episode*" reports the start and end of a period of residence. These "*episodes*" are dynamic and subject to changes due to different individual activities (e.g. marriage). However, it is always the case that new individuals are added to the population through birth and in-migration and leave through death and out-

migration after enumeration. Based on these data, all health indicators related to vital events and the risk of dying and survival can be calculated (143). High appreciation of data process and data management is also maintained in the Agincourt HDSS to assure high quality data. These data processes refer to all type of activities involving data collections, entry, storage and analysis while also facilitating definitions of key variables for researchers and DSS managers (151).

Figure 7. Fieldworkers mapping households where deaths has been notified to follow with VA, Agincourt HDSS, South Africa. Reproduced from the Agincourt MRC/Wits Rural Public Health and Health Transitions Research Unit (152).

4.1.5 The Agincourt Short-Form VA instrument

It is acknowledged that there may be a desire to expand the VA instrument to address locally relevant conditions. However, this change should only be undertaken if unlikely to affect the comparability of VA results. For example, adding or changing questions related to household characteristics or environmental or behaviour risk factors. Similarly, changes of VA questions concerning usage of particular health context are also suitable to implement in the VA standards. Interestingly, the 2007 WHO VA standards contained sets of questions to address contact with health services, their locations, quality of care and treatment provided (51). Hence, following a series of pilot interviews and research in the Agincourt HDSS, the VA questions were refined for meaning and flow, and were subsequently integrated in 2012 into the short-form WHO VA standards (SF-VA). Consequently, a total of ten circumstantial questions on key aspects of care seeking and utilisation were defined in the SF-VA instrument, namely, circumstantial indicators for causes of death (table 3). Thereafter, the SF-VA standard was adopted in the Agincourt HDSS as part of the routine census activities (132), and was carried forward into the latest WHO VA 2016 standard, providing opportunity to assist understanding of relevant health systems, socio-economic and cultural circumstances of death. Following three annual census rounds in 2012, 2013 and 2014 in the Agincourt site where the SF-VA had been used, VA data has become a rich source for analysing circumstantial causes of mortality, beside the medical CSMFs.

Table 3. The ten circumstantial questions from the latest WHO VA 2016 standard, v1.4.

Questions	**Description** (Respondent's answer: Yes , No, Don't Know or, refused to answer)	**Corresponding information provided to the respondent during the VA interview**
Q1	In the final days before death, did she/he travel to a hospital or health facility?	The main concept is "hospital" which by definition is a 24/7 service. But in some countries there are smaller facilities which are not hospitals, but do offer 24/7 services, so those are included– but not lesser facilities which have no emergency service.
Q2	Did she/he use motorised transport to get to the hospital or health facility?	This is answered if the person who died travelled to a hospital or health facility by means of motorised transport (car, truck, tractor, motorcycle, scooter or ambulance) during the final illness.
Q3	Were there any problems during admission to the hospital or health facility?	This is answered if the person who died travelled to a hospital or health facility, and then had problems on arrival (delays, paperwork, queues, no staff)
Q4	Were there any problems with the way she/he was treated (medical treatment, procedures, inter personal attitudes, respect, dignity) in the hospital or health facility?	This is answered if the person who died travelled to a hospital or health facility, and then had problems with how they were treated (medical treatment, procedures, inter-personal attitudes, respect, dignity)
Q5	Were there any problems getting medications, or diagnostic tests in the hospital or health facility?	This is answered if the person who died travelled to a hospital or health facility, and then had problems obtaining essential items (drugs, medications or other prescriptions, blood products, and/or diagnostic tests

		such as lab tests and X-rays, either within the facility or needing to be bought elsewhere).
Q6	Does it take more than 2 hours to get to the nearest hospital or health facility from the deceased's household?	This is answered if the person who died lived in a household from where it would reasonably take more than 2 hours to reach the nearest 24-hour health facility by the means of transport available to the household members
Q7	In the final days before death, were there any doubts about whether medical care was needed?	This is answered if there were doubts among those assisting in the final illness (family members, etc.) about whether the final illness was sufficiently serious to need treatment at a health facility
Q8	In the final days before death, was traditional medicine used?	This is answered if a major part of treatment for the final illness was provided by any kind of traditional or alternative practitioner (herbal remedies, massages, drinks, foods, amulets, spells or blessings provided by traditional healers, witch doctors or shaman)
Q1	In the final days before death, did anyone use a telephone or cell phone to call for help?	This is answered if a telephone of any kind (working landline, or cell phone charged and with credit) was used by those assisting in the final 24 hours of the illness for example to call for help or arrange transportation
Q10	Over the course of illness, did the total costs of care and treatment prohibit other household payments?	This is answered if the total costs incurred in the final illness were sufficiently great to mean that other kinds of household expenses (food, fuel, travel, education etc.) could not be met, or caused debt or sale of household assets

4.2 Integrated approach to processing VA: the InterVA-5 model

In line with the existing concept that InterVA products are made available on an open-source basis, the InterVA-5 software is the most recent version which corresponds to the 2016 international WHO VA standard. The overall design of InterVA-5 adheres to the general architecture pattern observed in the InterVA-4 software. However, the recent advancements take into account: changes occurred in cause categories between WHO-2012 and WHO-2016, expansion (splitting) of the VA items in the WHO-2016 standard compared to the WHO-2012 and, adjusting for some outstanding issues reported by InterVA-4 users. In addition, the InterVA-5 model is now upgraded to further incorporate a knowledge base relating to the novel COMCAT system. Given that, the specific aim of formulating the WHO VA 2016 was to achieve harmonisation across various existing VA tools (153), this interest was maintained during the development of the InterVA-5 model which is built to be fully compatible with previous WHO VA standards as well as other methods for interpreting VA data like the Tariff-2. Table 4 summarises the input indicators for the WHO-2016, WHO-2012 and Tariff standards.

Table 4. Numbers of InterVA-5 input indicators for WHO-2016, WHO-2012 and Tariff-2 standards

	WHO-2016	WHO-2012	Tariff-2
Background	27	23	14
General	183	120	127
Neonates/infants	79	49	42
Women of reproductive age	54	43	24
Circumstances	10	10	-
Total	**353**	**245**	**207**

In general, all InterVA models follow a simple input format of binary questions, citing the "yes" option as the prime response item (64). InterVA-5 is therefore upgraded to use a substantive response for each item, which can be "yes" or "no", allowing the processing of assigning likelihoods for each cause category on the basis of substantive responses recorded in the VA data. On occasions where WHO VA items presented in different formats (such as response item with continuous values), InterVA-5, like preceding InterVA versions, takes pre-determined categories and implements each category as a binary item. The InterVA-5 is designed to accommodate an overall of 353

binary indicators corresponding to the 305 items from the WHO VA 2016 needed for assigning causes of death, figure 8. Thus, using InterVA-5 for analysing WHO VA 2016 data record could either succeed a conversion step; applying a convenient script to transform the 305 WHO-2016 items into the 353 items required in the CSV format file, or alternatively seeking a tablet data collection approach which is directly designed for the InterVA-5 format.

Two independent datasets were employed in the evaluation of InterVA-5 model. The PHMRC reference dataset was used as a comparator for the InterVA-5 cause of death assignments, and the Afghanistan 2010 national mortality survey dataset, was used to assess the performance of the new model when processing data aligned with WHO-2016, WHO-2012 and Tariff-2. The PHMRC only contain 70% of the VA input indicators (248/ 353) and, albeit experiencing some differences both of principle and details, including differences in some case-definitions, the PHMRC is undoubtedly an important VA reference data source with the advantage of including causes of death attributed by tertiary hospitals in LMICs (154). The Afghanistan 2010 national mortality survey dataset, which was collected independently of any of the WHO-2016, WHO-2012 or Tariff-2 protocols, covered 73.4% (259/ 353) of the InterVA-5 items.

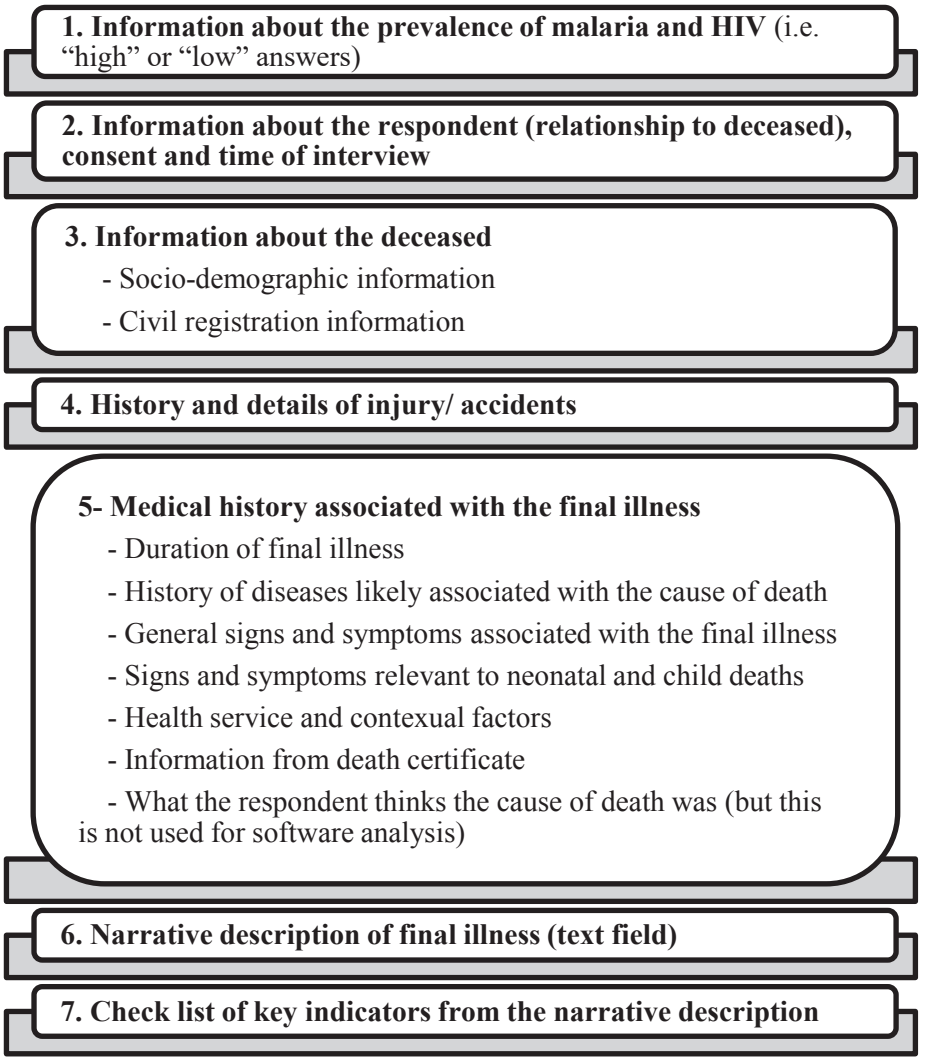

Figure 8. List of standard indicators routinely captured during VA interviews. Note age, sex, information about the season and the local prevalence of HIV and malaria are crucial to include for the automated analysis

4.3 Data analysis of circumstantial causes of mortality

Based on Mosely and Chen's conceptual framework adopted in the InterVA-5 model, individual records from the ten circumstantial questions at and around the time of death were used to derive COMCAT that can be routinely categorising deaths investigated using VA, table 3. The InterVA-implemented process for deriving COMCAT follows exactly the same Bayesian-based model for calculating CSMFs. The system assigns a probability to each individual for up to six COMCAT categories plus the multiple. This analysis is grounded on the premise that, in post-processing the six COMCAT categories, if any one of the six achieves a probability exceeding 50%, it can be attributed as the main circumstantial category related to a particular death, and if no category reaches 50%, then the seventh "multiple" COMCAT category will be assigned. Table 5, outlines the six COMCATs including the multiple category. The COMCAT-integrated approach in the InterVA-5 tool does not affect the CSMF calculations but may potentially have additionally-useful epidemiological applications (155). The InterVA-5 system also produces detailed output of the probabilities for all six COMCAT categories, which can be utilised in more detailed analyses if desired. The COMCAT system is a novel methodological development and has no obvious external comparator for consideration. Records from VA interviews collected from 2012-2014 at the Agincourt HDSS, including the ten circumstantial indicators, are one of the few available datasets for demonstrating the method. Furthermore, stratifying the COMCAT outputs by age and sex can help illustrate the system's functionality and plausibility in routinely exploring circumstantial causes of death and further inform future developments. Paper III from this thesis demonstrates the COMCAT approach as implemented in InterVA-5 using the Agincourt HDSS large population-based dataset as a proof of principle, with no intention to draw epidemiological conclusions from these analyses.

Table 5. Circumstances Of Mortality CATegories (COMCAT) factors

COMCAT factor	Description
Traditions	Harmful traditional practices or beliefs influenced health seeking behaviour
Emergencies	Sudden, urgent or unexpected conditions led to death
Awareness	Lack of recognition of symptoms or disease severity influenced health seeking behaviour
Resources	Inability to mobilise and use resources (e.g. material, transport, financial) hindered access to health care
Systems	Problems occurred despite accessing health care (e.g. related to admissions, treatments and medications)
Inevitability	Death occurred in circumstances that could not reasonably have been averted (e.g. very elderly or recognised terminal conditions)
Multiple	None of the above categories predominantly affected the pathway to death

4.4 Ethical clearance

No primary data collection nor specific additional ethical clearance was required for this study. The Agincourt HDSS data follow on-going ethical clearance which has been granted by the University of Witwatersrand's Committee for Research on Human Subjects (Nos. M960720 & M110138). The principle of informed consent was fully respected with the right for refusal or withdrawal from interviews at both individual and household levels. Community consent from civic and traditional leadership was secured at the start of surveillance in 1992 and is reaffirmed from time to time.

5 RESULTS

If the global health community has indeed agreed on VA as the most expedient method to use, whether independently in registered population or integrated into routine CRVS to fill in mortality gaps (31, 156), what is the impact of major domains that fall primarily under health system, operational process and the local knowledge of causes of ill-health on the overall VA conclusion of causes of death? At such growing international attention as well as the rapid methodological transition of VA, a series of studies, which constitutes this dissertation, has undertaken methodological examinations of relevant contextual, operational and technical domains that are important for the widespread use of this method. Although VA has experienced thorough and continuous examination in past decades, this empirical research provides unique design for assessing these outstanding domains and facilitate useful future applications. Using the newly upgraded InterVA-5 model as an integrated approach for processing WHO-2016 VA data, this research further proposes a novel approach for enhancing VA adding COMCAT to incorporate health systems and social dimensions to the conventional understanding of a death. Correspondently, this dissertation appears to be timely in view of the latest advancements of the WHO VA standard protocols (56) and the ongoing global discussion of integrating VA into routine CRVS systems (31). In addition, the availability of the PHMRC VA reference dataset, and other internationals data, independent of the WHO VA protocol, provided useful resources to assess the advancement of the VA automated tool and its harmonisation over time and space. The four original publications appended at the end of this thesis discuss more detailed findings for the specific objectives. Nevertheless, the main results of the four papers presented in this thesis are summarised under the corresponding sections below.

5.1 Local perception of causes of mortality

Paper I, the study of agreement between VA-derived causes of death (VACoD) and respondents-reported cause of death (RRCoD), showed that communities in LMICs like South Africa were a less consistent source of information on cause-specific mortality in relation to VA and depend on the informant's characteristics and the cause of death. During the twenty-year period 1992-2011, about 40% of all mortality with VA findings (n=11,228) had no specific RRCoD of which 46.1% of these deaths were HIV or TB related, as illustrated in Figure 9.

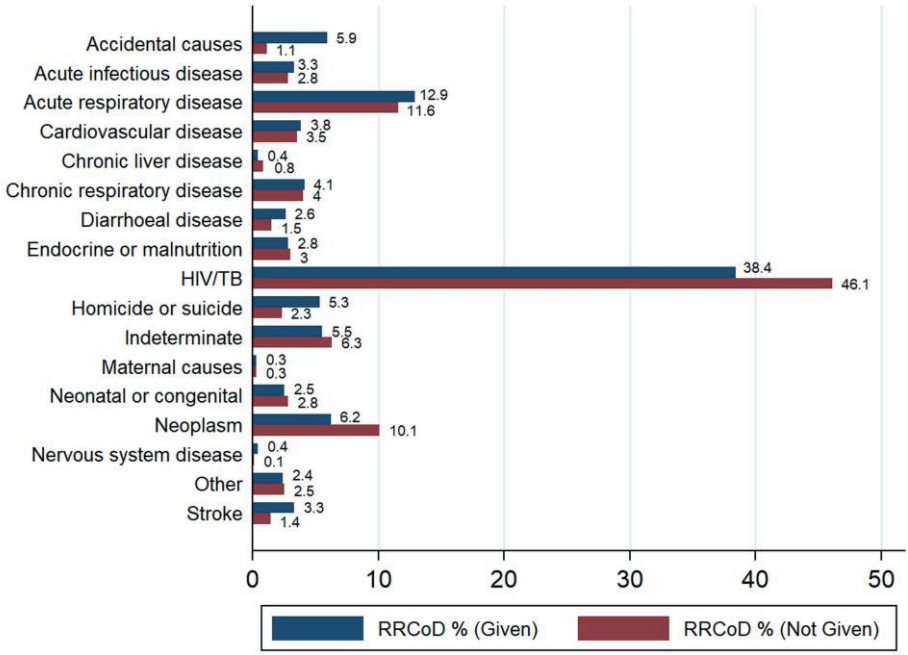

Figure 9. Proportions of deaths as assigned to VACoD, for a total of 6,721 (59.9%) deaths in the Agincourt HDSS, South Africa with given RRCoD compared to 4,507 (40.1%) without given RRCoD (all deaths, n=11,228). VACoD=verbal autopsy of causes of death, RRCoD=respondent-reported causes of death. Reproduced from Paper I (25)

An overall agreement of 30.9% was recorded between VACoD and RRCoD which unsurprisingly associated causes such as accidents, homicides and suicides with minimal needs for understanding underlying biomedical reasoning. Careful investigation of the derived agreement using multiple regression analysis is presented in table 6 which showed that increased perception of causes of deaths was generally associated with deaths occurring in the 15-49 years old group, longer illness duration and, deaths occurring outside home. The regression analysis also pointed out an interestingly improved local perception of causes of death occurring in more recent time periods (2002-2006), but when total deaths doubled in later years, no significant difference from baseline measurement in 1992 was observed.

Table 6. Background characteristics for 6,721 deaths in the Agincourt HDSS, South Africa, showing multivariable OR for agreement between RRCoD and VACoD including "unknowns". Adapted from Paper I (25).

Background characteristics		Number of deaths (%)	OR (95% CI)
age group	0-14 (child)	1,322 (19.7)	Ref
	15–49 (reproductive	2,560 (38.1)	1.46 (1.15-1.86)*
	50-64 (adult)	1,429 (21.3)	1.06 (0.81-1.38)
	>65 (elder)	1,405 (20.9)	0.98 (0.74-1.29)
sex	male	3,573 (53.2)	Ref
	female	3,148 (46.8)	1.04 (0.93-1.17)
origin	Mozambican origin	2,061 (30.7)	Ref
	South African origin	4,660 (69.3)	1.09 (0.96-1.24)
respondent	child	867 (12.9)	Ref
	parent	2,418 (36.0)	0.89 (0.72-1.10)
	spouse/sibling	2,132 (31.7)	1.12 (0.92-1.36)
	other	1,304 (19.4)	1.16 (0.95-1.42)
years of education	none	2,707 (32.8)	Ref
	1 to 7	1,465 (21.8)	1.14 (0.96-1.34)
	8 to 15	1,591 (23.7)	1.11 (0.92-1.34)
	other/too young	1,458 (21.7)	0.86 (0.68-1.09)
period of death	1992-1996	766 (11.4)	Ref
	1997-2001	1,161 (17.3)	1.03 (0.83-1.29)
	2002-2006	1,802 (26.8)	1.26 (1.02-1.55)*
	2007-2011	2,992 (44.5)	1.21 (0.99-1.48)
cumulative household deaths	1 person	2,744 (40.8)	Ref
	2 people	2,137 (31.8)	1.01 (0.89-1.15)
	3 people or more	1,840 (27.4)	1.07 (0.93-1.22)
illness duration	< 2 weeks (acute)	1,530 (22.8)	Ref
	> 2 weeks (chronic)	4,026 (59.9)	1.16 (1.01-1.34)*
	unknown	1,165 (17.3)	3.59 (2.96-4.34)*
previous illness	no	4,522 (67.3)	Ref
	yes	2,199 (32.7)	1.12 (0.98-1.28)
	none	775 (11.5)	Ref

therapeutic approach	Western only	2,576 (38.3)	1.14 (0.93-1.40)
	traditional only	164 (2.4)	0.67 (0.43-1.06)
	Western and	2,457 (36.6)	0.98 (0.79-1.21)
	unknown	749 (11.1)	1.23 (0.97-1.55)
place of death	home	2,795 (41.6)	Ref
	hospital	3,071 (45.7)	1.18 (1.04-1.34)*
	other locations	855 (12.7)	1.56 (1.30-1.88)*

** Odds ratio significantly different from unity; OR = Odds ratios; VACoD = verbal autopsy causes of death; RRCoD = respondent-reported cause of death*

In a parallel analysis, population-level CSMFs derived from VA using the InterVA-4 model were compared to CSMFs acquired from RRCoD by estimating their absolute difference (with 95% CI), as presented in table 7. Significant absolute difference were observed and varied across almost all cause categories except the circulatory diseases, maternal and endocrines and some of the external causes. Largest absolute difference were seen among most common causes such as HIV, TB, and acute respiratory (pneumonia) as well as the indeterminate. Bewitchment as RRCoD was reported for 865 cases, which had no possibility of being designated as a VA cause.

Table 7. CSMF from VACoD and RRCoD for 6,721 deaths in Agincourt HDSS, South Africa. Reproduced from paper I (25).

Cause of death category	Cause-specific mortality fraction		
	VACoD	RRCoD %	difference % (95% CI)
HIV/TB	36.5	13.3	-23.2 (-24.6 to -21.8)*
Indeterminate	12.4	34.1	21.7 (20.3 to 23.1)*
Acute respiratory disease	10.9	0.4	-10.5 (-11.3 to -9.7)*
Neoplasm	5.3	3.7	-1.5 (-2.2 to -0.8)*
Accidental causes	5.3	8.3	3.0 (2.2 to 3.8)*
Homicide or suicide	4.8	5.3	0.5 (-0.2 to 1.2)
Chronic respiratory disease	3.6	0.9	-2.7 (-3.2 to -2.2)*
Cardiovascular disease	3.4	3.7	0.3 (-0.3 to 0.9)
Stroke	3.0	3.0	0.1 (-0.5 to 0.6)
Acute infectious disease	2.8	1.2	-1.6 (-2.1 to -1.1)*
Endocrine or malnutrition	2.5	2.7	0.2 (-0.3 to 0.7)
Diarrhoeal disease	2.5	6.8	4.3 (3.6 to 5.0)*
Neonatal or congenital	2.2	0.6	-1.6 (-2.0 to -1.2)*
Others	2.1	0.4	-1.7 (-2.1 to -1.3)*
Chronic liver disease	0.4	0.7	0.3 (0.1 to 0.6)*
Nervous system disease	0.4	1.9	1.5 (1.1 to 1.9)*
Maternal	0.3	0.3	0.0 (-0.2 to 0.2)
Bewitched	0.0	12.8	12.8 (12.0 to 13.6)*

**Difference is significantly different from zero.*

5.2 Effect of recall time on the cause of death

The impact of recall time on the VACoD was assessed in paper II. Recall time between a death occurring and a VA interview had a median recall time of 7 months and ranged between 1-48 months. The majority (83%) of all deaths had VAs conducted within 12 months of the event. Overall, VA proved to be robust against operational and cultural factors that can cause delays in reporting deaths. Closer inspection of the distribution of recall times by causes is illustrated in Figure 10 which showed a tendency towards longer recall time for deaths of neonatal or over 65-year groups.

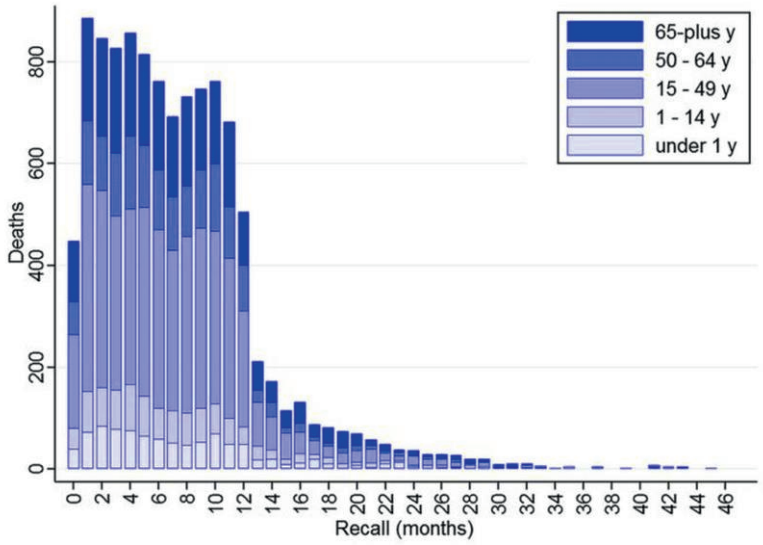

Figure 10. The distribution of deaths by VA recall time (months) and age groups between 1992 and 2011, Agincourt HDSS, South Africa. Reproduced from the work of Hussain-Alkhateeb L et al (paper II) published in Emerging Themes in Epidemiology (BMC) (26).

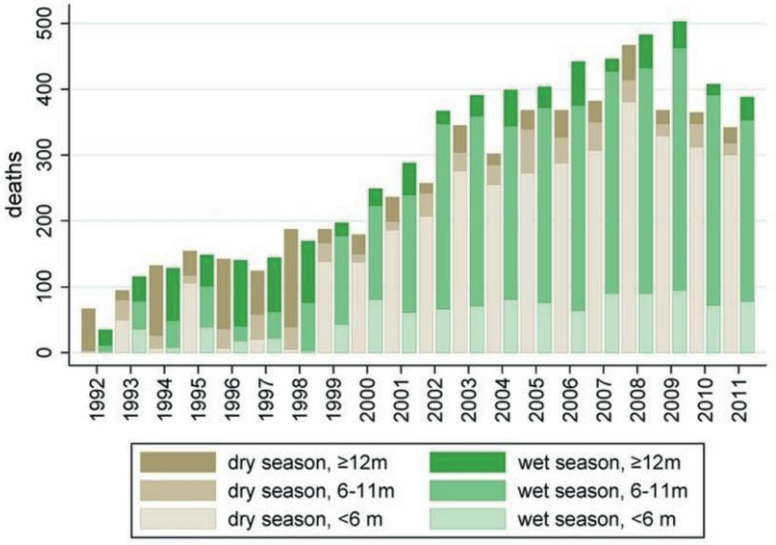

Figure 11. Distribution of deaths by year of death and season (dry or wet), by recall time (months) for VA interviews between 1992 and 2011, Agincourt HDSS, South Africa. Retrieved from the work of Hussain-Alkhateeb L et al (paper II) published in Emerging Themes in Epidemiology (BMC) (26).

The range of recall time relies on the mechanism of annual update round that HDSSs routinely follow. Deaths occurring around the time of the annual update round are followed up just over a year later leading to the majority of recalls under six months relating to deaths in the dry seasons which can have confounding consequences, see Figure 11.

Further analysis showed that pneumonia, diarrhoeal diseases and other unspecified NCDs were confounded by season with CSMF ratio significantly different between the two recall periods (< 6 months and ≥ 6 months), thus highlighting the importance of adjustment in a multivariate analysis (see paper II for results on CSMF ratio). Crude and adjusted regression models concluded that only trivial recall effects were associated with VAs undertaken anytime during the first year following death, and remained of minimal effects during the second year, with exemption made for the neonatal deaths (table 8.).

Table 8. Logistic regression analysis to examine the effect of recall period on the VA assessment (yes/ no) of all cause of death groups in Agincourt, South Africa during 1992-2011. Reproduced from Paper II (26)

Cause of Death (*n*)	Model	Recall Periods [a]		
		3-5 Months OR (p-value)	**6-11 Months** OR (p-value)	**≥12 Months** OR (p-value)
HIV/ TB (*n*=3,759)	Crude	0.96 (0.423)	1.00 (0.897)	0.66 (0.000)*
	Adjusted [b]	0.94 (0.339)	1.01 (0.885)	0.87 (0.065)
Acute Respiratory (n=712)	Crude	0.90 (0.287)	0.74 (0.001)*	0.78 (0.018)*
	Adjusted [b]	0.93 (0.467)	0.92 (0.468)	0.88 (0.340)
Other Infectious (n=405)	Crude	1.10 (0.453)	0.93 (0.564)	1.40 (0.009)*
	Adjusted [b]	1.07 (0.605)	0.87 (0.336)	1.03 (0.862)
Neoplasm (n=609)	Crude	0.90 (0.313)	1.13 (0.165)	1.15 (0.173)
	Adjusted [b]	0.85 (0.140)	0.88 (0.247)	0.99 (0.961)
Other NCDs (n=1429)	Crude	1.10 (0.166)	1.00 (0.990)	0.91 (0.225)
	Adjusted [b]	1.10 (0.181)	1.04 (0.584)	1.07 (0.466)
Neonatal (n=187)	Crude	0.97 (0.876)	0.74 (0.102)	1.69 (0.004)*
	Adjusted [b, c]	1.17 (0.504)	1.49 (0.114)	2.58 (0.000)*
External (n=641)	Crude	0.95 (0.712)	1.20 (0.074)	1.68 (0.000)*
	Adjusted [b]	0.99 (0.936)	1.14 (0.326)	1.27 (0.097)
Indeterminate (n=3140)	Crude	1.12 (0.085)	1.09 (0.119)	1.56 (0.000)*
	Adjusted [b]	1.12 (0.089)	1.06 (0.425)	1.03 (0.701)

[a] <3 months recall is the reference group

[b] Odds ratios were adjusted for: year of death, season (wet/ dry), age, education, nationality, nationality and place of death

[c] Age group factor was removed from the adjusted model

OR = odds ratio

5.3 Circumstances Of Mortality CATegories (COMCAT)

The COMCAT analysis presented 6+1 categories and their attributed deaths; 'Tradition', 'Emergency', 'Awareness', 'Resources', 'Health System', and 'Inevitability' plus the 'Multiple' (where no COMCAT reached 50%). Overall results from the COMCAT analysis ranked limited household resources to access health care services the most common circumstantial category for peoples' health in South Africa, which accounted for quarter of all deaths. This was followed by limitations related to communities' awareness of causes of death (23%) and inadequate health system response (19%). Emergency-classified events corresponded to 13.4% of deaths, and an equal proportions of deaths interrelated with inevitable causes. Traditional practices in Agincourt HDSS communities showed lower attribution to the pathway of death (2.3%) – see paper III for all proportions of COMCATs.

Figure 12 illustrates COMCAT ranks by causes of death according to their CSMFs. Listing the first six leading causes of death or their groups, HIV/ AIDS, pneumonia and the circulatory disease group, such as stroke and cardiovascular diseases ranked top in the list followed by TB, neoplasm and road traffic accidents, respectively. HIV/ AIDS-related deaths, the leading cause in this population, were linked to limited household resources to access health (37%) and to a certain extent to categories related to limited local awareness (30%) and health system response (24%). Deaths due to acute respiratory causes like Pneumonia were corresponding to poor awareness of disease symptoms and severity (33%) whereas deaths from circulatory diseases were linked to inevitability causes (stroke 41% and cardiac causes 28%). TB-related deaths attributed to categories of 'health system' (37%) but most deaths from the neoplasm group (41%) corresponded to awareness-related categories leaving the road traffic accidental deaths to bind with the 'emergency' category.

Albeit almost equal distributions of CSMFs across sex group, COMCATs were unevenly distributed between both sexes. Table 9 illustrates percentages of CSMFs and COCMAT by sex and age-groups which shows that 28.7% of deaths among females were characterized by limited household resources to access healthcare services compared to 21.3% of deaths in the males group. In a parallel comparison, 27.6% of deaths among males and 18.4% among females were linked to local awareness of illnesses. Age is a reasonably important factor in understanding the pathway of death with findings from the COMCAT analysis attributing a range between 36.8%-47.4% of deaths among the under-14 yrs. group, including infants, to limited recognition of diseases

symptoms and severity. Almost half of neonatal deaths were corresponding to health systems aspects and 32.5% of deaths among the elderly group (>65 yrs.) was related to inevitable causes.

Table 9. CSMF and COMCAT categories by age and sex of the deceased

		COMCAT						
Characteristic	CSMF	Traditions	Emergency	Awareness	Resources	H. Systems	Inevitability	Multiple
Sex								
Male	48.1	2.2	17.2	27.6	21.3	18.1	10.9	2.6
Female	51.9	2.4	9.9	18.4	28.7	20.3	15.5	4.9
Age								
Neonatal	2.3	0.00	25.8	6.5	9.7	48.4	0.0	9.7
Infant	2.9	2.6	21.1	36.8	22.4	10.5	0.0	6.6
1-4 yrs.	4.3	4.4	21.7	45.2	13.0	10.4	0.0	5.2
5-14 yrs.	1.5	5.3	15.8	47.4	15.8	10.5	5.3	0.0
15-49 yrs.	44.4	2.9	17.2	19.5	31.2	22.8	3.3	3.1
50-64 yrs.	14.4	1.3	14.1	26.0	25.8	16.2	12.8	3.9
>65 yrs.	30.1	1.6	4.6	21.7	19.7	15.8	32.5	4.0

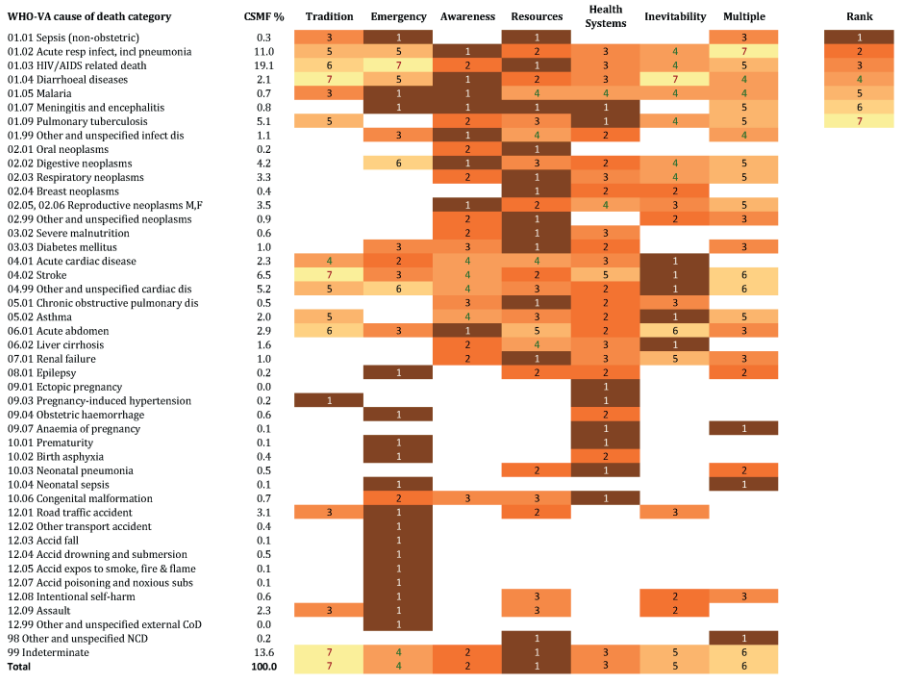

Figure 12. Ranks of COMCATs (rank; 1-7) by the WHO VA causes of death categories.

5.4 How did the InterVA-5 model perform?

Evaluating the overall performance of InterVA-5 and its alignment with previous versions is essential for maintaining a reliable, cheap and fast approach to derive conclusion on causes of death and to enforce the ability for handling a range of VA input formats. Whilst this research focuses on how InterVA-5 performs with VA data collected under the WHO VA 2016 protocol, some earlier VA archives with substantial proportion of WHO-2016 materials were used to suffice as relevant material for evaluating the new model.

Figure 13A presents the agreement between CSMFs for WHO-2016 cause categories from the hospital causes and InterVA-5, stratified by the 5-plus and under-5 age groups. Concordance correlation coefficient (CCC), a measure of equivalence between two sources (135), estimated a 91.3% of agreement (95%CI: 85.6 to 97.0) for the under-5 age group and 86.2% (95% CI: 79.6 to

92.9) for the 5-plus age group. In its assessment of having backwards compatibility with WHO-2012 and InterVA-4 as well as its performance against Tariff-2 method, figures 13B and 13C demonstrate CCCs for InterVA-5 by each input source. For InterVA-4, 96.8% (95%CI: 94.8 to 98.8) for the younger age group and 95.5% (95%CI: 92.9 to 98.1) for the older age group were reported and, for Tariff-2, 93.3% (95%CI: 89.2 to 97.3) for the under-5 age group and 86.7% (95%CI: 79.9 to 93.5) for the 5-plus age group were estimated by the CCC analysis. Figure 13D shows the Afghanistan dataset as processed by InterVA-4 and compared with InterVA-5 processing of the InterVA-4 subset of inputs. Findings from this analysis to investigate version continuity and the effects of intentional changes in the model, figure 13D shows that CCC was 94.3% (95%CI: 91.3 to 97.4), excluding intended changes.

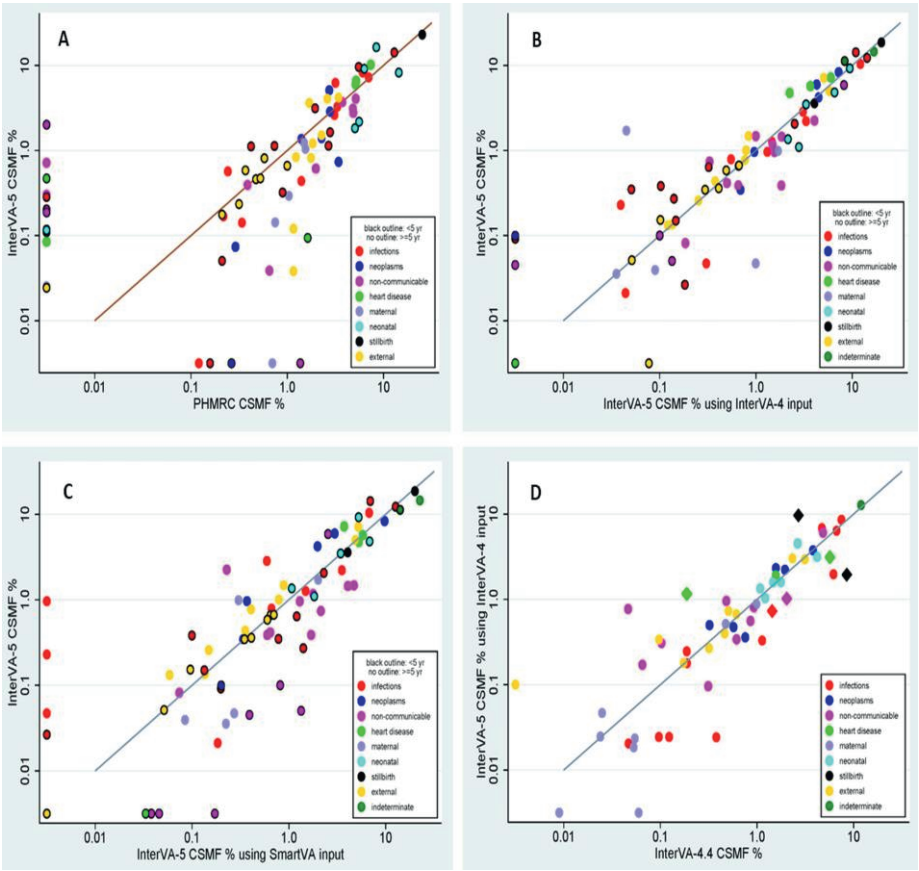

Figure 13. Part A presents the cause-specific mortality fractions (CSMF) by age for 6,130 deaths from the Population Health Metrics Research Consortium (PHMRC) verbal autopsy reference dataset, with PHMRC cause of death determined from clinical data at tertiary hospitals involved in final care, and processed by the InterVA-5 model from PHMRC verbal autopsy data, against the line of equivalence. Parts B, C and D present the CSMF by age for 4,009 deaths from the Afghanistan Mortality Survey verbal autopsy dataset, with cause of death determined by the InterVA-5 model using WHO-2016 and, WHO-2012 input datasets (in part B), Tariff-2 input datasets (in part C) and InterVA-4 (version4.04) model using WHO-2012 input datasets (in part D), all against the line of equivalence. Diamond-shaped markers represent causes intentionally revised in the InterVA-5 model.

6 DISCUSSION

6.1 Striving for robustness

The increasing role of patients, families and communities in defining public health outcomes is well established and its disciplines are wide spread (157), and VA is not a different concept where families of the deceased are crucial in this process.

In LMICs, health programs are substantially funded by external sources, mainly private donors and agencies of high-income countries. Therefore, one determinant of the priorities set by both private donors and development agencies is the perception of populations living in high-income countries about which diseases are legitimate for global health intervention (158). Hence, integrated-process in registered populations to elicit perspectives of local communities on leading causes of death are advantageous and several projects such as methods adopting a community-based participatory research (159) and a participatory action research (PAR) (160) are underway. Those approach strive to link evidence with action plans and can be useful in extending partnership between respective communities, researchers and health authorities. Similarly for the process of VA, systematic assessment of pre-existing concepts about causes of deaths among VA respondents is crucial for documenting mortality and providing reliable patterns of death for public health planning. Recognising symptoms and signs that are highly correlated with common causes of deaths can potentially assist local communities to identify corresponding risk factors leading to deaths. Furthermore, it may reflect on how lay beliefs influence care-seeking in these settings which stresses the need for a better understanding of pre-existing concepts of cause of death among the locals in order to reasonably judge the health outcomes derived from available methods like VA.

The study of agreement between VACoD and RRCoD in paper I showed that about half of the actual HIV/ AIDS deaths were not reported by VA respondents, followed by causes related to neoplasm and acute respiratory, respectively. Although South Africa has the highest literacy rate in the continent reaching as high as 80% (144), the small proportion of medically plausible causes of death provided by respondents is not surprising and may reflect a rate of 'health literacy' in South Africa (161, 162). Interestingly, the majority of VA respondents who denied giving plausible medical causes were likely being informed by medical professionals during past hospital visits about the ultimate causes that led to the death they witnessed. Recognising medical signs can be equally challenging even in industrialised populations,

however, in this research we are more concerned with denial of signs associated with common causes and occasions where families are being informed about the true causes by medical professionals. This is an important piece of information when assessing national health estimates that rely primarily on local surveys, and likewise for examining the quality of the VA conclusion on causes of death. As the case with PCVA, the automated InterVA tool depends on the provided sign and symptom indicators for calculating probabilities of specific causes which may be disturbed if the degree of information or recall bias is ample.

In the same agreement study (paper I), almost two third of all deaths in Agincourt recorded specific RRCoD during the VA interview (including 'do not know' reports) with an overall 30.9% of agreement with VACoD. The basis for the difference in acknowledging deaths by families is not easy to interpret and can be associated with cultural factors and the type of death. In fact, HIV/ AIDS, and by association TB and pneumonia may be viewed socially sensitive conditions and people would favour secrecy (25). Local communities can also consider some causes of deaths to be limited to their local communities and tend to accuse them for deaths caused by other diseases. This local belief is plausible in settings where most deaths of PWH is led by TB, which reaches a co-infection rate of up to 73% (163), and can further justify the averseness of reporting deaths. In a cross-sectional study in Cape Town, South Africa, 95% of all respondents interviewed from the randomly selected 1020 households carried the view that, all TB patients will also develop HIV, with respondents further agreeing that people with TB tend to hide their disease status to avoid negative comments from the members of their community (163). Another social determinant of population health is reflected by a markedly lowered perception of causes of death among VA informants being associated with HIV/ TB deaths among elderly people. This may be relevant and explains the social prejudice against social groups or the failure of kinship network to render effective care for social groups with special needs (164). This is also reflected in the results outlined in table 10. Albeit several cross-national studies have acknowledged VA as a consistent and robust method to use in settings where the certification of deaths is otherwise incomplete, local misconceptions of mortality showed that "health literacy" is another equally important piece in the overall public health puzzle and remains vital to routinely study for effective health policies and planning.

Table 10. Multivariate logistic regression of the age group of the deceased and the 'agreement' between VACoD and RRCoD as outcome variable for the HIV/ TB causes

Factor	**HIV/ TB *(n*=4864)**
Age	**OR (95% CI) §**
0-14 (child)	Ref
15–49 (reproductive-age)	2.59 (1.43-4.66)*
50-64 (Adult)	1.30 (0.70-2.44)
>65 (older age)	0.42 (0.21-0.84)*

**Significantly different from unity*
§Adjusted for; sex, age, nationality, respondent, years of education, SES, time of death, illness duration and place of death.

The low reporting of specific causes of mortality in the Agincourt communities could nevertheless echo a degree of stigmatisation or depict some cultural beliefs, which does not seem to exempt causes with greatest burden (paper I). Stigma is the most cited reason for the lack of response to health prevention programs and the provision of treatment (165) and in the case of the VA process, of the disclosure and routine reporting of deaths. It is an expression of relationships which conveys familial values that influence the community's perception and interpretations of meaning, or the acceptance and rejections of particular diseases such as HIV/ AIDS or TB. Stigma is the result of fear and societal blame rather than ignorance and can likely be overcome with educational interventions (166). Reluctance to report local deaths could also involve economical and historical conditions that have privileged physical and mental appearance in society (167). The negative impact of apartheid on native South African identity has a major role in shaping families and communities' responses to interventional programs and routine public health actions. In addition, the pandemic of HIV/AIDS in South Africa put tremendous pressure on millions of households as the primary wage earners or the caretakers fall sick and eventually die (168), consequently leading to the fact that HIV/ AIDS worsens poverty through loss of work time and income which severely impact a household's wealth (169). Understanding the cultural, historical and economical aspects that could influence public health practices requires a systematic understanding of the context and local perceptions within which these fears, blames and reluctance are expressed (170). A study which was conducted among around 500 PWH in Cape Town found that individuals who had not been tested for HIV held significantly more stigmatising attitudes towards PWH than did those who had been tested (171). Therefore, the opportunity of having a systematic assessment of local perceptions of causes

of death using VA would enable us to negotiate and develop strategies that could help explain the complex nature of communities' behaviours and provide appropriate health interventional programs. It can also be helpful in ensuring relevant VA process for assigning causes of deaths in those settings. The multiple regression model was useful in identifying contexts for the poor underlying medical causes in Agincourt communities. Essentially, deaths occurring at home is associated with lowered perception of specific cause of death. Deaths occurring at home are less likely to be reported or assigned medically plausible causes since contact with healthcare facility is most probably not being sought prior deaths. What constitutes a deterrent from seeking healthcare facilities prior to deaths is a distinct circumstantial domain that fall into health systems and social factors and gaining insight into how this domain affects mortality may augment the conceptualisation process of cause of death needed for public health planning. This is however, a separate analysis and discussion that will be dealt with in more details in later sections.

VA respondents' perceptions of causes of death may sway responses to specific questions during the VA interviews, and thereby affect the overall conclusions on causes of death. This deliberate denial of common causes has other operational implications in running larger public health plans like the HDSS. In HDSSs, updating and verifying existing data or documenting new events such as births and deaths are carried out via routine annual update rounds and are subsequently followed up by trained field workers to conduct VA interviews (118). In occasions where families are more reluctant to disclose deaths during update rounds, deaths missed in these round visits may therefore be discovered and recorded in subsequent rounds, consequently have a longer recall period before conducting VA. This overlap between cultural and operational acts within HDSSs can allocate specific causes in longer recall intervals which could influence the overall VA conclusions on causes of deaths. Figure 10 shows that wider recall periods were correlated with neonatal deaths or among elderly, and this was related to the causes of death. Cultural factors can impact this pattern, particularly in this African setting where myths and superstitions can likely influence communities' behaviours (52). Paper I from this report quantified this view and showed that bewitchment as RRCoD was reported for 865 cases with no possibility of being designated as a VACoD, and 40% of these bewitched records (according to families) were in fact associated with HIV/ TB according to the VACoD. The local non-biomedical viewpoint about causes of death can nonetheless be clearly illustrated when assessing communities' perceptions of causes of death using standardised and consistent methods like VA (paper I).

Moreover, these HDSS annual cycles could potentially lead to confounding between time of year and recall period, which could be important for causes of deaths subject to seasonal variation. Paper II presents results of this variation as illustrated in figure 11, showing that, the majority of recalls under six months were related to deaths in the dry season. Analysis from paper II (not presented here) provides a more in-depth understanding of these seasonal variations, which were associated with three causes of deaths: acute respiratory, diarrhoeal infections and, some forms of NCDs. Seasonal variations in the various underlying aetiologies of these causes were very plausible reflecting the importance of running a more advanced analysis in some instances. The multiple regression analysis presented in table 8 attempts to adjust for potential confounding to give a more relevant conclusion from the data, and showed that only neonatal deaths were less consistent with different recall periods. Although the basis for the difference among neonatal causes may not be easy to determine, it is likely to be associated with reluctance to disclose this form of death. Study I on the agreement has contributed to this finding showing a lower perception of neonatal causes and thus, less likely to be reported, mainly if occurred at home. Albeit increasing attention on recall ability and its relation to specific causes including neonatal is reported (74, 111), operational aspects within HDSSs are currently scare and can be crucial for evaluating the overall conclusion on causes of death.

Agreements of individual and population patterns of causes of death between physicians reviewing VAs are reported to be high or at least reasonable in many studies (38, 60, 110, 172-174) but less satisfying in some other reports (175-177). Although this may depend on the overall quality of specific details of VAs as well as the physician trainings, physicians' prior knowledge of local diseases is associated with high consistency during the VA assessment. If a cause of death is not expected in certain demographic groups, physicians will not readily code such cause and often focus on the symptoms that are locally present, leading to the exclusion of other possible causes (60, 74, 103, 174). Unlike the PCVA method, automated tools like InterVA are highly consistent, but would still demand unbiased VA inputs by respondents for completing the VA assessment. In a fairly large proportion of death cases in study I, respondents could not provide eligible cause of death or simply stated that they did not know any relevant cause of death for their deceased. These respondents-given records were corresponding to records assigned by VA as indeterminate cases, reflecting a degree of respondents' inconsistencies as communities can misperceive connections between symptoms and disease pathways (178). However, whether VA data are interpreted by PCVA or using automated tools, it is important that interviewers receive thorough training to be able to evaluate the medical data they are collecting. Although the training of fieldworks currently lacks standardised methods, a limitation being

acknowledged by the VA community, the closed-questions sections are least affected in this process (103, 105, 179, 180). These items (interview questions) are primarily used in the automated models like InterVA. Paper I shows that using systematic assessment of communities' perception of causes of deaths can provide useful contextual information for VA interviewers, and thus reduces the effects of non-harmonised VA trainings across geo-locations. This claim is apparent in view of the observed trend of agreement over the 20-year period of death, as illustrated in table 6, which may facilitate consistent and repeatable evaluation of local viewpoints of causes of deaths at low cost. Paper IV assesses the performance and compatibility of the latest model from the InterVA family against preceding versions as well as other software, utilising data from the WHO VA 2016 standards and other independent sets of records. The findings derived from the tool assessment are also encouraging with potential for tracking mortality patters over time and across various sites, which can have critical public health implications.

VA specifically seeks to address epidemiologic needs at a population level, emphasising reliable estimates of CSMFs for defined populations rather than certainty at the individual level. Interestingly, discrepancies between two sources, such as physicians, are more apparent at individual-level assessment of VAs but have only minimal impacts on overall population-level CSMFs where misclassifications of causes of death appear to be bidirectional (181-183). The population-level CSMFs are derived using multiple rather than single causes of death which can reflect on the interaction of different diseases that lead to death (49). This approach is useful in general but more specifically in settings where disease overlaps can commonly occur in marginalised groups such as children, elderly or in the case of South Africa among PWH. For instance, if a fatally ill child suffered from diarrhoea and an acute lower respiratory infection, it is likely that it was the combination of the two that ultimately led to death, and thus treating or preventing one of the diseases may have prevented the death. According to fairly recent studies, the ability of the applied Bayesian probability method to reach a workable VA model for estimating population-level CSMFs does not require a high degree of precision (67, 155) suggesting that the results presented in this thesis are more useful for local health planning and the community participatory role.

True validation of VA assessment of cause of death against an absolute gold-standard is lacking, which is a major limitation (62). Nevertheless, the correlation of VACoD with other sources such as the PHMRC reference data applied in paper IV using hospital diagnosis, is considered useful in illuminating some of the limitation of VA. This in return addresses the issue of VA being used as the "gold-standard" in paper I, which can be considered a limitation. Although in principle only post-mortem examinations (autopsy) can

be regarded as a true gold-standard, the issue of assuming VA as the gold-standard in the agreement study is likely to be minor since methodological developments should not be considered in terms of merely absolute validity, but rather in terms of consistency, comparability, and adequacy for the purpose (62). In addition, VA is the common reference materials of causes of mortality in the study area with potential to integrate into CRVS systems, and given the protocol of VA interviews, this can ensure a reasonably good compatibility of data collection process across various geo-locations. Similarly, in the second study (paper II) where a reference standard is absent, proving that some recall periods have superior performance in relation to others is difficult when only using statistical tools. However, one can show that recall periods can at least have equal effects on the VA assessment, which is the approach we followed in this research to avert possible limitations.

6.2 Novelty and beyond: towards integrated approach to processing VA

VA has an increasingly invaluable role in strengthening health systems (184) as its conventional medical model remains the prime source for conceptualising the pathway to death in settings that lack CRVS. Whilst VA method transitions towards routine application, incorporating social and health systems circumstances of deaths can add value to the VA process as an attractive proposition with only minimal effort and cost. This is also relevant in the context of the increasing global attention towards health systems performance (185). In that sense, both the family and healthcare centres are two key contexts that cannot be avoided by ill people (157), which stresses the need for a better understanding of these important contexts in order to reasonably judge the health outcomes.

D'Ambruoso et al.'s initial report on the new ten indicators – first piloted in the WHO-2012 standard and carried forward in the WHO-2016 standard – revealed multiple problems with access to healthcare services at the time of death, with a large number of ill-persons also face social exclusion. This may occur in deeply unequal societies where limiting factors that are stemming from social and health system contexts have critical role in survival (132). The novel COMCAT work in paper III builds on the original report from the new ten circumstantial questions. Hence, applying the probabilistic modelling approach implemented in the InterVA-5 version would enable consistency and repeatability for the sake of comparability over time and place, as currently in assigning medical causes of death. This is indeed one of the added-value

features implemented in the InterVA-5 which specifically ensures compatibility with preceding InterVA versions and other common automated models, as illustrated in paper IV.

The demonstration of COMCAT using the case of Agincourt HDSS appears to be plausible, although it cannot be said at this stage to be useful nor even necessarily correct in any absolute sense. Overall findings from the COMCAT analysis in paper III ranked limited resources to access healthcare services as the most common category, followed by poor community's awareness of illness severity and inadequate health system response, all of which generally underlie social institutions. Although COMCATs mark six distinct dimensions of circumstantial causes of mortality, plus the multiple category, the inter-correlation of COMCATs is clear and interesting, and the categories seem to reinforce one another. For instance, if healthcare is unaffordable then patients are likely to deny the disease severity and avoid seeking help or travelling to facilities at and around the time of death. In fact, repeated claims for care that are typically unaffordable and unsuccessful may normalise the exclusion of those who lack the resources needed during acute situations (186). This also corresponds to the argument presented in paper I where reluctance to report deaths was also linked to economic factors suggesting that, although community behaviour towards heath is a complex phenomenon, using multidisciplinary analysis could guide pathways to understanding causes of deaths. On the contrary, patients with chronic illnesses are more likely to experience distress due to costs or other medical problem along the care pathway since they have many more presentations for care in the management of long-term conditions. Hence, records without any given medically-plausible cause of death that may occur due to conditions with acute onsets can potentially be explained by the COMCAT system. For example, the acute respiratory disease category (pneumonia) showed to be least perceived among communities in the Agincourt HDSS with 1.1% of agreement against VACoD (see paper I) - albeit ranking second highest CSMF among all cause categories. This corresponds to the COMCAT analysis, where awareness of disease severity and symptoms were the most common category with 33% of pneumonia deaths being contributed by this category (see paper III).

Ranking what constitutes social conditions attributed to deaths has the potential to guide public health attention via routine feedback to health planners. This can likely assist in focusing limited resources on more direct and probably more cost-effective interventional programs that have otherwise been neglected. The inevitability category (such as old age or recognised terminal illness) derived from the COMCAT system is important and can further adjust the understanding of how circumstantial causes of mortality can

relatively motivate the definition of ill-health within a functioning health system. Furthermore, the work on the COMCAT anticipated to allocate a "multiple" category to incorporate other possible factors leading to deaths that could not fall into any of the six COMCATs. Nevertheless, the COMCAT system is inextricably linked outside the 'multiple' category and in the existing realities of healthcare seeking and utilisation specifically at and around the time of death. This view is typically addressed in the Agincourt HDSS setting and can by extension exist in other LMICs.

Albeit various attempts to derive estimates that are usually based on non-fatal outcomes (187), robust and consistent indicators relying on definitive health outcomes like mortality for tracking health system performance will be more effective. This is particularly relevant in the context of the unfinished global health agenda of the SDGs and Universal Health Coverage (UHC), which will involve major investments in health by many countries. In this sense, causes of deaths linked to the healthcare of individuals can be regarded as important proxy of accessibility to- and quality of healthcare services which can serve as a robust benchmark of health system performance (187). Many international reports have associated patients' accessibility to high quality healthcare with substantial improvement in health outcomes including chronic infectious diseases like HIV/ AIDS or TB (188), maternal and neonatal illness as well as a range from the NCDs like stroke and cardiovascular diseases (189-193). Nonetheless, a more recent Lancet international report concluded that, estimating mortality in LMICs that should not be fatal if effective medical care was present is timely since current approaches are merely focusing on high-income countries and, completely failing to seek standardised and consistent approach for comparability and repeatability. COMCAT is therefore, an example of a tool able to contribute directly to that process.

The COMCAT system is designed to serve as an affordable tool to inform priority settings. It has the potential to address local viewpoints of common causes of mortality (194), and to highlight the role of the health system and local communities as important stakeholders in the process of defining population health particularly in settings with marginalised societal groups (195, 196). This is the first time that the circumstances of mortality indicators have been developed for computation in a system compatible with InterVA and analysed within a large population dataset. The intention in making COMCAT available as a routine component of the InterVA-5 model is that it should be widely used, reported, and very likely discussed and further developed and refined. This novel system has no obvious comparator to refer to, however, it addresses urgent health system and policy research questions posed by the global health community as top priorities (196). Although the COMCAT model is not designed to substitute the role of SA or confidential

enquiry methods in detailing essential social and contextual determinants of health, the advancement with reports from this study hints at significant benefits when using this model into routine applications. In a parallel initiative, the primary health care systems in many LMICs are undergoing a genuine process of revitalisation giving more priority for community-based function with plans to integrate with and steer by the health departments. Correlatively, the interaction between the CSMF and the corresponding COMCAT from the VA may augment the public health action plans suggesting that the COMCAT analysis is assessing new dimensions of burden of disease that may exist in this area.

In principle, physicians can process VA data to assign individual cause of death, and their involvements as medical expertise may bring additional nuances to these mortality cases. However, considering cost, time and consistency issues as well as the possibility of reaching a future impact on the estimated 20 million undocumented deaths annually, automated models are likely to serve as more feasible approach to fill in the gap. The introduction of the ten circumstantial questions in the WHO-2012 as well as the recent modifications of the WHO VA standard into a harmonising consensus WHO-2016 instrument, while maintaining the ten circumstantial questions, has been convenient and timely. It has certainly provided a useful platform to advance the established practice of providing analytical models for VA data that not only correspond to international WHO VA standards and has the COMCAT embedded into its new design, but has also been developed to specifically harmonise various existing VA standards capable of handling a range of input formats. The lack of absolute reference for the assessment of the different VA approaches has on the other hand been a longstanding challenge (62, 104). In this research, however, the use of the PHMRC reference dataset, although by no means is perfect which primarily depends on non-representative tertiary hospital population, revealed a comprehensive and promising picture on the overall performance of InterVA-5. Findings from the empirical research, discussed in paper IV suggest that, InterVA-5 is the sole model with features compatible with the WHO-2016 standard, both in the form of VA interview input items and in the derived causes of death categories. Interval-5 is additionally useful by demonstrating ability to reasonably handle data from previous WHO VA and Tarrif-2 standards. The new InterVA-5 version, as assessed in paper IV, appeared to perform reasonably well against the WHO-2012 standard and other common methods. This would typically allow for trend and pattern testing of mortality data and facilitate a useful geo-location comparability to guide health policy making at regional and global levels.

7 CONCLUSION

Despite noticeable achievements in global health, many countries remain with very insufficient CRVS systems and fail to document representative proportion of national births and deaths, just like countries with HDSSs. Therefore, causes of deaths are currently not established, which threaten effective local health actions and diminish the chance of achieving corresponding SDGs (42). In this sense, the attainment of the CVRS is unlikely to happen in the short term and VA can in the meantime serve as the most expedient method to yield sufficiently reliable information on causes of mortality for health policies. Hence, this thesis provides a continuity to important assessment of VA methods to ensure reliable and wider spread applications and, in view of the recent methodological advancement and the increased global attention for the use of VA into a national routine registrations of vital data.

While the examination of local perception of causes of death is interesting, national health planners, regional epidemiologists as well as the global health community should continue to use the rigorous and standardised VA as an alternative to national surveys for providing complete picture on causes of deaths in places where routine registration is by no means valid. Although the ultimate goal set by the global health community should be towards relative certainty in accounting for individual health globally, the HDSS concept meanwhile continues to generate and publish solid population-based data needed for health planning. The sensitivity of VA due to routine operational procedures within HDSSs as well as other cultural aspects, as tested in this work, appears to be of minimal effect which strengthens the role of HDSSs in new strategies set by the INDEPTH for engaging with many SDGs (42). Given this strategic plan, the novel COMCAT concept introduced in this thesis, though yet at very early stages, is very timely, plausible and likely to provide comprehensive picture by contributing information on health systems and social circumstances causes to death outcomes. The compatibility of the integrated InterVA-5 model, from the widely used InterVA family, brings a degree of harmonisation across various VA data sources which is unlike preceding models or other methods, the InterVA-5 can track mortality patters over time and space flourishing the VA applications in various settings.

8 FUTURE PERSPECTIVE

This thesis discussed a number of timely and important issues, and findings are likely to assist future VA applications stretching to global estimates of causes of mortality. However, progression with this research also warrants future research and implementations, which are crucial for the perspective of mortality surveillance. The COMCAT concept for instance, is yet not fully understood and should experience a cycle of validations in various settings to weigh its reliability throughout the overall VA assessment. Nonetheless, the HDSS system does not record full information on social and health systems determinants, which is a crucial next step to implement or possibly expand in a systematic manner. Albeit promising outcome revealed from the examination of the InterVA-5 model, a larger-scale dataset from the WHO-2016 should be employed to better inform about the performance of this integrated tool.

Furthermore and in view of the interest established by the INDEPTH to engage HDSSs, and by association VA, in the assessment of global health indicators including a considerable list from the SDGs, it is crucial to expand the routine surveillance to additionally capture heath exposures information of relevance to some globally-recognised epidemics and transitional diseases. For instance, climate and entomological indicators are viewed to be necessary for explaining mortality (& morbidity) patterns of major diseases at global levels. Viral diseases transmitted via Aedes mosquitoes like Zika, dengue and chikungunya as well as the tubular-interstitial chronic kidney disease (CKD) and other respiratory diseases from the NCDs are currently increasing in frequency over time and space, affecting people's health and burdening resource-constrained health systems. The inclusion of such environmental, entomological and potentially some social media data, a shining source for people's mobility, is particularly important for research capacity building as well as the future application of the VA tool.

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"*No one who achieves success does so without acknowledging the help of others. The wise and confident acknowledge this help with gratitude*." ~Alfred North Whitehead

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REFERENCES

1. Sutherland I. John Graunt: a tercentenary tribute. Journal of the Royal Statistical Society Series A (General). 1963:537-56.
2. Adams RH. The Parish Clerks of London: A History of the Worshipful Company of Parish Clerks of London: Yourdon Press; 1971.
3. Bellhouse D. London Plague Statistics in 1665. Journal of Official Statistics. 1998;14(2):207.
4. Högberg U, Wall S. Secular trends in maternal mortality in Sweden from 1750 to 1980. Bulletin of the World Health Organization. 1986;64(1):79.
5. Byass P. Person, place and time—but who, where, and when? : Sage Publications Sage UK: London, England; 2001.
6. Declich S, Carter AO. Public health surveillance: historical origins, methods and evaluation. Bulletin of the World Health Organization. 1994;72(2):285.
7. Nash LL. Inescapable ecologies: A history of environment, disease, and knowledge: Univ of California Press; 2006.
8. Susser M, Susser E. Choosing a future for epidemiology: I. Eras and paradigms. American Journal of Public Health. 1996;86(5):668-73.
9. Harper K, Armelagos G. The changing disease-scape in the third epidemiological transition. Int J Environ Res Public Health. 2010;7(2):675-97.
10. Tawfik L, Kinoti S. The impact of HIV/AIDS on health systems and the health workforce in sub-Saharan Africa. Washington (DC): SARA Project, USAID Bureau for Africa. 2003.
11. Tawfik L, Kinoti SN. The impact of HIV/AIDS on the health workforce in developing countries. document de base préparé pour Le Rapport sur la santé dans le monde. 2006:8.
12. Heller R, Page J. A population perspective to evidence based medicine:“evidence for population health”. Journal of Epidemiology & Community Health. 2002;56(1):45-7.
13. Jeffery RW. Risk behaviors and health: Contrasting individual and population perspectives. American Psychologist. 1989;44(9):1194.
14. Byass P. The imperfect world of global health estimates. PLoS Med. 2010;7(11):e1001006.
15. Beaglehole R, Bonita R. Challenges for public health in the global context-prevention and surveillance. Sage Publications Sage UK: London, England; 2001.
16. Dlamini L, LMququ, PKhawula, MHattingh, CMpambo-Sibhukwana, T. Burden of Health & Disease in South Africa: Medical Research Council briefing Parliamentary Monitoring Group2016. Available from: https://pmg.org.za/committee-meeting/22198/. (accessed 15 January 2018)

17. Byass P. The unequal world of health data. PLoS medicine. 2009;6(11):e1000155.
18. Setel PW, Macfarlane SB, Szreter S, Mikkelsen L, Jha P, Stout S, et al. A scandal of invisibility: making everyone count by counting everyone. The Lancet. 2007;370(9598):1569-77.
19. Byass P. Who needs cause-of-death data? PLoS Medicine. 2007;4(11):e333.
20. Lancet. Counting Births and Deaths. Lancet; 2015.
21. Lancet. Who Counts? : Lancet; 2007.
22. World Health Organization. World Health Statistics 2017: Monitoring Health for the SDGs Sustainable Development Goals: World Health Organization; 2017.
23. Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. The Lancet. 2013;380(9859):2095-128.
24. Cleland J. Demographic data collection in less developed countries 1946-1996. Popul Stud (Camb). 1996;50(3):433-50.
25. Hussain-Alkhateeb L, Fottrell E, Petzold M, Kahn K, Byass P. Local perceptions of causes of death in rural South Africa: a comparison of perceived and verbal autopsy causes of death. Global health action. 2015;8.
26. Hussain-Alkhateeb L, Petzold M, Collinson M, Tollman S, Kahn K, Byass P. Effects of recall time on cause-of-death findings using verbal autopsy: empirical evidence from rural South Africa. Emerging themes in epidemiology. 2016;13(1):10.
27. Huy TQ, Johansson A, Long NH. Reasons for not reporting deaths: a qualitative study in rural Vietnam. World health & population. 2007;9(1):14-23.
28. Hill K. Making deaths count. Bulletin of the World Health Organization. 2006;84(3):162-.
29. Shrivastava SR, Shrivastava PS, Ramasamy J. Assessing the status of United Nations Millennium Development Goals. Annals of Tropical Medicine and Public Health. 2016;9(2):87.
30. Byass P, Kabudula CW, Mee P, Ngobeni S, Silaule B, Gómez-Olivé FX, et al. A successful failure: missing the MDG4 target for under-five mortality in South Africa. PLoS medicine. 2015;12(12):e1001926.
31. de Savigny D, Riley I, Chandramohan D, Odhiambo F, Nichols E, Notzon S, et al. Integrating community-based verbal autopsy into civil registration and vital statistics (CRVS): system-level considerations. Glob Health Action. 2017;10(1):1272882.
32. Evans T, AbouZahr C. INDEPTH@ 10: celebrate the past and illuminate the future. Global Health Action. 2008;1(1):1899.
33. Berkelman RL, Sullivan P, Buehler JW. Public health surveillance. Oxford textbook of public health, Volume 2: the methods of public health. 2009(Ed. 5):699-715.

34. Bawah A, Houle B, Alam N, Razzaque A, Streatfield PK, Debpuur C, et al. The Evolving Demographic and Health Transition in Four Low- and Middle-Income Countries: Evidence from Four Sites in the INDEPTH Network of Longitudinal Health and Demographic Surveillance Systems. PLoS One. 2016;11(6):e0157281.
35. Mahapatra P, Shibuya K, Lopez AD, Coullare F, Notzon FC, Rao C, et al. Civil registration systems and vital statistics: successes and missed opportunities. The Lancet. 2007;370(9599):1653-63.
36. Mikkelsen L, Phillips DE, AbouZahr C, Setel PW, De Savigny D, Lozano R, et al. A global assessment of civil registration and vital statistics systems: monitoring data quality and progress. The Lancet. 2015;386(10001):1395-406.
37. Hill K, Lopez AD, Shibuya K, Jha P, group MoVEw. Interim measures for meeting needs for health sector data: births, deaths, and causes of death. The Lancet. 2007;370(9600):1726-35.
38. Huong DL, Minh HV, Byass P. Applying verbal autopsy to determine cause of death in rural Vietnam. Scand J Public Health Suppl. 2003;62:19-25.
39. Chandramohan D, Maude GH, Rodrigues LC, Hayes RJ. Verbal autopsies for adult deaths: their development and validation in a multicentre study. Tropical Medicine & International Health. 1998;3(6):436-46.
40. Sankoh O, Byass P. The INDEPTH Network: filling vital gaps in global epidemiology. International journal of epidemiology. 2012;41(3):579-88.
41. DSouza S. A population laboratory for studying disease processes and mortality--the Demographic Surveillance System Matlab Comilla Bangladesh. Rural demography. 1981;8(1):29-51.
42. Sankoh O, Byass P. New INDEPTH strategy for the SDGs using robust population data. The Lancet Global Health. 2017;5(7):e647-e8.
43. Ramsay M, Crowther N, Tambo E, Agongo G, Baloyi V, Dikotope S, et al. H3Africa AWI-Gen Collaborative Centre: a resource to study the interplay between genomic and environmental risk factors for cardiometabolic diseases in four sub-Saharan African countries. Global Health, Epidemiology and Genomics. 2016;1.
44. INDEPTH. International Network for the Demographic Evaluation of People and their Health iSHARE. 2015. Available from: http://www.indepth-network.org/member-centres. (accessed 15 January 2018)
45. Garenne M, Fauveau V. Potential and limits of verbal autopsies. Bull World Health Organ. 2006;84(3):164.
46. World Health Organization. WHO: Lay reporting of health information. Geneva: World Health Organisation; 1978.
47. Lozano R, Freeman MK, James SL, Campbell B, Lopez AD, Flaxman AD, et al. Performance of InterVA for assigning causes of death to verbal autopsies: multisite validation study using clinical diagnostic gold standards. Popul Health Metr. 2011;9:50.

48. Desai N, Aleksandrowicz L, Miasnikof P, Lu Y, Leitao J, Byass P, et al. Performance of four computer-coded verbal autopsy methods for cause of death assignment compared with physician coding on 24,000 deaths in low-and middle-income countries. BMC medicine. 2014;12(1):20.
49. Soleman N, Chandramohan D, Shibuya K. Verbal autopsy: current practices and challenges. Bulletin of the World Health Organization. 2006;84(3):239-45.
50. Baiden F. Setting international standards for verbal autopsy. Bulletin of the World Health Organization. 2007;85(8):570-1.
51. World Health Organization. Verbal autopsy standards: ascertaining and attributing case of death. Geneva: World Health Organization; 2007. Available from: http://www.who.int/whosis/mort/verbalautopsystandards/en/. (accessed 15 January 2018)

52. Fottrell E, Tollman S, Byass P, Golooba-Mutebi F, Kahn K. The epidemiology of 'bewitchment'as a lay-reported cause of death in rural South Africa. J Epidemiol Community Health. 2012;66(8):704-9.
53. World Health Organization. Verbal Autopsy Standards: Ascertaining and attributing causes of death: the 2012 WHO verbal autopsy instrument. Geneva: World Health Organization; 2012. Available from: http://www.who.int/healthinfo/statistics/verbalautopsystandards/en/index.html. (accessed 15 January 2018)

54. World Health Organization. Verbal Autopsy Standards: Ascertaining and attributing causes of death: the 2014 WHO verbal autopsy instrument. Geneva: World Health Organization; 2014. Available at http://www.who.int/healthinfo/statistics/verbalautopsystandards/en/index1.html. (accessed 15 January 2018)

55. Nichols EK, Byass P, Chandramohan D, Clark SJ, Flaxman AD, Jakob R, et al. The WHO 2016 verbal autopsy instrument: An international standard suitable for automated analysis by InterVA, InSilicoVA, and Tariff 2.0. PLoS Med. 2018;15(1):e1002486.
56. Organization WH. Verbal autopsy standards: the 2016 WHO verbal autopsy instrument: Geneva:World Health Organization; 2016. Available from: http://www.who.int/healthinfo/statistics/verbalautopsystandards/en/. (Accessed 15 January 2018)
57. Leitao J, Desai N, Aleksandrowicz L, Byass P, Miasnikof P, Tollman S, et al. Comparison of physician-certified verbal autopsy with computer-coded verbal autopsy for cause of death assignment in hospitalized patients in low-and middle-income countries: systematic review. BMC medicine. 2014;12(1):22.

58. Serina P, Riley I, Stewart A, Flaxman AD, Lozano R, Mooney MD, et al. A shortened verbal autopsy instrument for use in routine mortality surveillance systems. BMC Med. 2015;13:302.
59. King C, Zamawe C, Banda M, Bar-Zeev N, Beard J, Bird J, et al. The quality and diagnostic value of open narratives in verbal autopsy: a mixed-methods analysis of partnered interviews from Malawi. BMC Med Res Methodol. 2016;16:13.
60. Kamali A, Wagner HU, Nakiyingi J, Sabiiti I, Kengeya-Kayondo JF, Mulder DW. Verbal autopsy as a tool for diagnosing HIV-related adult deaths in rural Uganda. Int J Epidemiol. 1996;25(3):679-84.
61. Bird J, Byass P, Kahn K, Mee P, Fottrell E, editors. A matter of life and death: practical and ethical constraints in the development of a mobile verbal autopsy tool. Proceedings of the SIGCHI Conference on Human Factors in Computing Systems; 2013: ACM.
62. Fottrell E, Byass P. Verbal autopsy: methods in transition. Epidemiol Rev. 2010;32(1):38-55.
63. Byass P, Kahn K, Fottrell E, Collinson MA, Tollman SM. Moving from data on deaths to public health policy in Agincourt, South Africa: approaches to analysing and understanding verbal autopsy findings. PLoS Med. 2010;7(8):e1000325.
64. Byass P, Chandramohan D, Clark SJ, D'Ambruoso L, Fottrell E, Graham WJ, et al. Strengthening standardised interpretation of verbal autopsy data: the new InterVA-4 tool. Global health action. 2012;5.
65. Serina P, Riley I, Stewart A, James SL, Flaxman AD, Lozano R, et al. Improving performance of the Tariff Method for assigning causes of death to verbal autopsies. BMC medicine. 2015;13(1):291.
66. Clark SJ, McCormick T, Li Z, Wakefield J. InSilicoVA: a method to automate cause of death assignment for verbal autopsy. arXiv preprint arXiv:150402129. 2015.
67. Byass P, Huong DL, Van Minh H. A probabilistic approach to interpreting verbal autopsies: methodology and preliminary validation in Vietnam. Scandinavian Journal of Public Health. 2003;31(62 suppl):32-7.
68. Byass P, Corrah P. Assessment of a probabilistic decision support methodology for tropical health care. Proceedings of Medinfo-89 Amsterdam: North-Holland. 1989:995-1000.
69. Bayes T. Essay towards solving a problem in the doctrine of chances: University Press; 1958.
70. InterVA. [www.interva.net].
71. Streatfield PK, Khan WA, Bhuiya A, Alam N, Sié A, Soura AB, et al. Cause-specific mortality in Africa and Asia: evidence from INDEPTH health and demographic surveillance system sites. Global health action. 2014;7.
72. Byass P, Herbst K, Fottrell E, Ali MM, Odhiambo F, Amek N, et al. Comparing verbal autopsy cause of death findings as determined by

physician coding and probabilistic modelling: a public health analysis of 54 000 deaths in Africa and Asia. Journal of Global Health. 2015;5(1).
73. Godefay H, Abrha A, Kinsman J, Myleus A, Byass P. Undertaking cause-specific mortality measurement in an unregistered population: an example from Tigray Region, Ethiopia. Global health action. 2014;7.
74. Snow RW, De Azevedo IB, Forster D, Mwankuyse S, Bomu G, Kassiga G, et al. Maternal recall of symptoms associated with childhood deaths in rural East Africa. International journal of epidemiology. 1993;22(4):677-83.
75. Swami V, Arteche A, Chamorro-Premuzic T, Maakip I, Stanistreet D, Furnham A. Lay perceptions of current and future health, the causes of illness, and the nature of recovery: explaining health and illness in Malaysia. British journal of health psychology. 2009;14(3):519-40.
76. Rogers WS. Explaining health and illness: An exploration of diversity: Harvester Wheatsheaf New York; 1991.
77. Herzlich C. Health and illness: A social psychological analysis: Academic Press; 1973.
78. Swami V, Furnham A, Kannan K, Sinniah D. Beliefs about schizophrenia and its treatment in Kota Kinabalu, Malaysia. International Journal of Social Psychiatry. 2008;54(2):164-79.
79. Bird ST, Bogart LM. Conspiracy beliefs about HIV/AIDS and birth control among African Americans: implications for the prevention of HIV, other STIs, and unintended pregnancy. J Soc Issues. 2005;61(1):109-26.
80. Jackson AA, Manan WA, Gani AS, Carter YH. Lay beliefs about smoking in Kelantan, Malaysia. 2004.
81. Suhami N, Muhamad MB, Krauss SE. Why Cancer Patients Seek Islamic Healing. Journal of religion and health. 2016;55(5):1507-18.
82. Barney LJ, Griffiths KM, Banfield MA. Explicit and implicit information needs of people with depression: a qualitative investigation of problems reported on an online depression support forum. BMC psychiatry. 2011;11(1):88.
83. Keikelame MJ, Swartz L. Lost opportunities to improve health literacy: observations in a chronic illness clinic providing care for patients with epilepsy in Cape Town South Africa. Epilepsy Behav. 2013;26(1):36-41.
84. Shaw A, Ibrahim S, Reid F, Ussher M, Rowlands G. Patients' perspectives of the doctor-patient relationship and information giving across a range of literacy levels. Patient Educ Couns. 2009;75(1):114-20.
85. Kindig DA, Panzer AM, Nielsen-Bohlman L. Health literacy: a prescription to end confusion: National Academies Press; 2004.
86. Sudore RL, Yaffe K, Satterfield S, Harris TB, Mehta KM, Simonsick EM, et al. Limited literacy and mortality in the elderly: the health, aging, and body composition study. Journal of general internal medicine. 2006;21(8):806-12.
87. Tollman SM, Kahn K, Sartorius B, Collinson MA, Clark SJ, Garenne ML. Implications of mortality transition for primary health care in

rural South Africa: a population-based surveillance study. The Lancet. 2008;372(9642):893-901.
88. Pillay-van Wyk V, Msemburi W, Laubscher R, Dorrington RE, Groenewald P, Glass T, et al. Mortality trends and differentials in South Africa from 1997 to 2012: second National Burden of Disease Study. The Lancet Global Health. 2016;4(9):e642-e53.
89. Mayosi BM, Lawn JE, Van Niekerk A, Bradshaw D, Karim SSA, Coovadia HM, et al. Health in South Africa: changes and challenges since 2009. The Lancet. 2012;380(9858):2029-43.
90. Mooney GH, McIntyre DE, De Costa CM. South Africa: a 21st century apartheid in health and health care. Med J Aust. 2008;189(11-12):637.
91. Coovadia H, Jewkes R, Barron P, Sanders D, McIntyre D. The health and health system of South Africa: historical roots of current public health challenges. The Lancet. 2009;374(9692):817-34.
92. Keikelame MJ, Hills RM, Naidu C, de Sa A, Zweigenthal V. General practitioners' perceptions on management of epilepsy in primary care settings in Cape Town, South Africa: an exploratory pilot study. Epilepsy Behav. 2012;25(1):105-9.
93. Taylor M, Jinabhai C, Sathiparsad R, de Vries H. South African high school students' health literacy and behaviour concerning HIV/AIDS, STIs, and TB (HAST). International Journal of Infectious Diseases. 2014;21:247.
94. Waldrop-Valverde D, Ownby RL, Wilkie FL, Mack A, Kumar M, Metsch L. Neurocognitive aspects of medication adherence in HIV-positive injecting drug users. AIDS Behav. 2006;10(3):287-97.
95. Kalichman SC, Rompa D. Functional health literacy is associated with health status and health-related knowledge in people living with HIV-AIDS. J Acquir Immune Defic Syndr. 2000;25(4):337-44.
96. Wawrzyniak AJ, Ownby RL, McCoy K, Waldrop-Valverde D. Health literacy: impact on the health of HIV-infected individuals. Curr HIV/AIDS Rep. 2013;10(4):295-304.
97. Mugure G, Karama M, Kyobutungi C, Karanja S. Correlates for cardiovascular diseases among diabetic/hypertensive patients attending outreach clinics in two Nairobi slums, Kenya. 1937.
98. Nuwaha F. People's perception of malaria in Mbarara, Uganda. Tropical Medicine & International Health. 2002;7(5):462-70.
99. Chizimba R, Christofides N, Chirwa T, Singini I, Ozumba C, Sikwese S, et al. The Association between Multiple Sources of Information and Risk Perceptions of Tuberculosis, Ntcheu District, Malawi. 2015.
100. Sambo M, Lembo T, Cleaveland S, Ferguson HM, Sikana L, Simon C, et al. Knowledge, Attitudes and Practices (KAP) about Rabies Prevention and Control: A Community Survey in Tanzania. PLoS neglected tropical diseases. 2014;8(12):e3310.

101. O'Neill S, Gryseels C, Dierickx S, Mwesigwa J, Okebe J, d'Alessandro U, et al. Foul wind, spirits and witchcraft: illness conceptions and health-seeking behaviour for malaria in the Gambia. Malar J. 2015;14:167.
102. Reniers G, Araya T, Davey G, Nagelkerke N, Berhane Y, Coutinho R, et al. Steep declines in population-level AIDS mortality following the introduction of antiretroviral therapy in Addis Ababa, Ethiopia. AIDS (London, England). 2009;23(4):511.
103. Soleman N, Chandramohan D, Shibuya K. Verbal autopsy: current practices and challenges. Bull World Health Organ. 2006;84(3):239-45.
104. Kahn K, Tollman SM, Garenne M, Gear JS. Validation and application of verbal autopsies in a rural area of South Africa. Tropical Medicine & International Health. 2000;5(11):824-31.
105. Gajalakshmi V, Peto R. Verbal autopsy of 80,000 adult deaths in Tamilnadu, South India. BMC Public Health. 2004;4:47.
106. Chandramohan D, Soleman N, Shibuya K, Porter J. Ethical issues in the application of verbal autopsies in mortality surveillance systems. Trop Med Int Health. 2005;10(11):1087-9.
107. Gajalakshmi V, Peto R, Kanaka S, Balasubramanian S. Verbal autopsy of 48 000 adult deaths attributable to medical causes in Chennai (formerly Madras), India. BMC Public Health. 2002;2:7.
108. D KALTER H, GRAY RH, BLACK RE, GULTIANO SA. Validation of postmortem interviews to ascertain selected causes of death in children. International journal of epidemiology. 1990;19(2):380-6.
109. Mirza NM, Macharia WM, Wafula EM, Agwanda RO, Onyango FE. Verbal autopsy: a tool for determining cause of death in a community. East Afr Med J. 1990;67(10):693-8.
110. Snow RW, Armstrong JR, Forster D, Winstanley MT, Marsh VM, Newton CR, et al. Childhood deaths in Africa: uses and limitations of verbal autopsies. Lancet. 1992;340(8815):351-5.
111. Freeman JV, Christian P, Khatry SK, Adhikari RK, LeClerq SC, Katz J, et al. Evaluation of neonatal verbal autopsy using physician review versus algorithm-based cause-of-death assignment in rural Nepal. Paediatric and Perinatal Epidemiology. 2005;19(4):323-31.
112. Snow B, Marsh K. How useful are verbal autopsies to estimate childhood causes of death? Health policy and planning. 1992;7(1):22-9.
113. Baqui AH, Black RE, Arifeen S, Hill K, Mitra S, Al Sabir A. Causes of childhood deaths in Bangladesh: results of a nationwide verbal autopsy study. Bulletin of the World Health Organization. 1998;76(2):161.
114. Marsh DR, Sadruddin S, Fikree FF, Krishnan C, Darmstadt GL. Validation of verbal autopsy to determine the cause of 137 neonatal deaths in Karachi, Pakistan. Paediatr Perinat Epidemiol. 2003;17(2):132-42.
115. Baqui AH, Black RE, Arifeen SE, Hill K, Mitra SN, al Sabir A. Causes of childhood deaths in Bangladesh: results of a nationwide verbal autopsy study. Bull World Health Organ. 1998;76(2):161-71.

116. Myer L, Ehrlich RI, Susser ES. Social epidemiology in South Africa. Epidemiol Rev. 2004;26:112-23.
117. Baiden F, Hodgson A, Binka FN. Demographic surveillance sites and emerging challenges in international health. Bulletin of the World Health Organization. 2006;84(3):163-.
118. Kahn K, Collinson MA, Gómez-Olivé FX, Mokoena O, Twine R, Mee P, et al. Profile: Agincourt health and socio-demographic surveillance system. International journal of epidemiology. 2012;41(4):988-1001.
119. Byass P, D'Ambruoso L, Ouedraogo M, Qomariyah SN. Assessing the repeatability of verbal autopsy for determining cause of death: two case studies among women of reproductive age in Burkina Faso and Indonesia. Popul Health Metr. 2009;7:6.
120. Dowell SF, Davis HL, Holt EA, Ruff AJ, Kissinger PJ, Bijoux J, et al. The utility of verbal autopsies for identifying HIV-1-related deaths in Haitian children. AIDS. 1993;7(9):1255-9.
121. Lulu K, Berhane Y. The use of simplified verbal autopsy in identifying causes of adult death in a predominantly rural population in Ethiopia. BMC Public Health. 2005;5:58.
122. Kalter HD, Salgado R, Babille M, Koffi AK, Black RE. Social autopsy for maternal and child deaths: a comprehensive literature review to examine the concept and the development of the method. Popul Health Metr. 2011;9:45.
123. Källander K, Kadobera D, Williams TN, Nielsen RT, Yevoo L, Mutebi A, et al. Social autopsy: INDEPTH Network experiences of utility, process, practices, and challenges in investigating causes and contributors to mortality. Population health metrics. 2011;9(1):44.
124. Waiswa P, Kalter HD, Jakob R, Black RE. Increased use of social autopsy is needed to improve maternal, neonatal and child health programmes in low-income countries. Bulletin of the World Health Organization. 2012;90(6):403-A.
125. Bensaid K, Yaroh AG, Kalter HD, Koffi AK, Amouzou A, Maina A, et al. Verbal/Social Autopsy in Niger 2012-2013: A new tool for a better understanding of the neonatal and child mortality situation. J Glob Health. 2016;6(1):010602.
126. Koffi AK, Libite PR, Moluh S, Wounang R, Kalter HD. Social autopsy study identifies determinants of neonatal mortality in Doume, Nguelemendouka and Abong-Mbang health districts, Eastern Region of Cameroon. J Glob Health. 2015;5(1):010413.
127. Claeson M, Waldman RJ. The evolution of child health programmes in developing countries: from targeting diseases to targeting people. Bulletin of the World Health Organization. 2000;78(10):1234-45.
128. Mosley WH, Chen LC. An analytical framework for the study of child survival in developing countries. Population and development review. 1984;10:25-45.

129. Dixon-Woods M, Cavers D, Agarwal S, Annandale E, Arthur A, Harvey J, et al. Conducting a critical interpretive synthesis of the literature on access to healthcare by vulnerable groups. BMC Med Res Methodol. 2006;6:35.
130. Freedman LP. Achieving the MDGs: health systems as core social institutions. Development. 2005;48(1):19-24.
131. Gilson L. Trust and the development of health care as a social institution. Social science & medicine. 2003;56(7):1453-68.
132. D'Ambruoso L, Kahn K, Wagner RG, Twine R, Spies B, Van Der Merwe M, et al. Moving from medical to health systems classifications of deaths: extending verbal autopsy to collect information on the circumstances of mortality. Global Health Research and Policy. 2016;1(1):2.
133. Abera Abaerei A, Ncayiyana J, Levin J. Health-care utilization and associated factors in Gauteng province, South Africa. Global Health Action. 2017;10(1):1305765.
134. van den Akker T, Bloemenkamp KW, van Roosmalen J, Knight M. Classification of maternal deaths: where does the chain of events start? The Lancet. 2017;390(10098):922-3.
135. Lawrence I, Lin K. A concordance correlation coefficient to evaluate reproducibility. Biometrics. 1989:255-68.
136. Fagerland MW, Lydersen S, Laake P. Recommended confidence intervals for two independent binomial proportions. Statistical methods in medical research. 2015;24(2):224-54.
137. Tollman SM. The Agincourt field site evolution and current status. South African Medical Journal. 1999;89(8).
138. Naledi T, Barron P, Schneider H. Primary health care in SA since 1994 and implications of the new vision for PHC re-engineering. South African health review. 2011;2011(1):17-28.
139. Bradshaw D, Groenewald P, Laubscher R, Nannan N, Nojilana B, Norman R, et al. Initial burden of disease estimates for South Africa, 2000. South African Medical Journal. 2003;93(9):682-8.
140. Kahn K, Tollman SM, Collinson MA, Clark SJ, Twine R, Clark BD, et al. Research into health, population and social transitions in rural South Africa: Data and methods of the Agincourt Health and Demographic Surveillance System1. Scandinavian Journal of Public Health. 2007;35(69 suppl):8-20.
141. Wagner RG. The Burden of Epilepsy: using population-based data to define the burden and model a cost-effective intervention for the treatment of epilepsy in rural South Africa: Umeå University; 2016.
142. Kahn K. Dying to make a fresh start: mortality and health transition in a new South Africa: Folkhälsa och klinisk medicin; 2006.
143. Tollman SM. Closing the gap: applying health and socio-demographic surveillance to complex health transitions in South and sub-Saharan Africa: Folkhälsa och klinisk medicin; 2008.

144. Kickbusch IS. Health literacy: addressing the health and education divide. Health promotion international. 2001;16(3):289-97.
145. Collinson MA, White MJ, Bocquier P, McGarvey ST, Afolabi SA, Clark SJ, et al. Migration and the epidemiological transition: insights from the Agincourt sub-district of northeast South Africa. Glob Health Action. 2014;7:23514.
146. Twine R, Collinson MA, Polzer TJ, Kahn K. Evaluating access to a child-oriented poverty alleviation intervention in rural South Africa. Scand J Public Health Suppl. 2007;69:118-27.
147. The map of Agincourt HDSS in rural North-East, South Africa. https://kids.britannica.com/students/assembly/view/166031: Encyclopædia Britannica, Inc.; 2015.
148. Thorogood M, Connor M, Lewando-Hundt G, Tollman S, Ngoma B, Team SP. Secondary prevention of stroke--results from the Southern Africa Stroke Prevention Initiative (SASPI) study. Bulletin of the World Health Organization. 2004;82(7):503.
149. Petzer K, Mngqundaniso N. Patients consulting traditional health practioners in the context of HIV/AIDS in urban areas in KwaZulu-Natal, South Africa. African Journal of Traditional, Complementary and Alternative Medicines. 2008;5(4):370-9.
150. The South African Health Services. www.health-e.org.za: South African Health E-News; 2017.
151. Fottrell E. Dying to count: mortality surveillance in resource-poor settings. Global health action. 2009;2(1):1926.
152. Mapping household deaths for Verbal Autopsy. http://www.agincourt.co.za/: Agincourt MRC/Wits Rural Public Health and Health Transitions Research Unit; 2017.
153. Nichols EK, Byass P, Chandramohan D, Clark SJ, Flaxman AD, Jakob R, et al. The WHO 2016 verbal autopsy instrument: an international standard suitable for automated analysis by InterVA, InSilicoVA, and Tariff 2.0. PLOS Medicine (in press); 2017.
154. Byass P. Usefulness of the Population Health Metrics Research Consortium gold standard verbal autopsy data for general verbal autopsy methods. BMC medicine. 2014;12(1):23.
155. Byass P, Fottrell E, Dao LH, Berhane Y, Corrah T, Kahn K, et al. Refining a probabilistic model for interpreting verbal autopsy data. Scand J Public Health. 2006;34(1):26-31.
156. AbouZahr C, De Savigny D, Mikkelsen L, Setel PW, Lozano R, Lopez AD. Towards universal civil registration and vital statistics systems: the time is now. The Lancet. 2015;386(10001):1407-18.
157. Airhihenbuwa C, Okoror T, Shefer T, Brown D, Iwelunmor J, Smith E, et al. Stigma, culture, and HIV and AIDS in the Western Cape, South Africa: An application of the PEN-3 cultural model for community-based research. Journal of Black Psychology. 2009;35(4):407-32.

158. Siegel KR, Feigl AB, Kishore SP, Stuckler D. Misalignment between perceptions and actual global burden of disease: evidence from the US population. Global health action. 2011;4(1):6339.
159. Hullur N, D'Ambruoso L, Edin K, Wagner RG, Ngobeni S, Kahn K, et al. Community perspectives on HIV, violence and health surveillance in rural South Africa: a participatory pilot study. Journal of global health. 2016;6(1).
160. Brooks C, D'Ambruoso L, Kazimierczak K, Ngobeni S, Twine R, Tollman S, et al. Introducing visual participatory methods to develop local knowledge on HIV in rural South Africa. BMJ Global Health. 2017;2(3):e000231.
161. Mangesho P, Shayo E, Makunde W, Keto G, Mandara C, Kamugisha M, et al. Commnity knowledge, attitudes and practices towards tberculosis and its treatment inMpwapwa District, central Tanzania. Tanzania Journal of Health Research. 2007;9(1):38-43.
162. Montgomery MR. Perceiving mortality decline. Population and Development Review. 2000;26(4):795-819.
163. Cramm JM, Finkenflügel HJ, Møller V, Nieboer AP. TB treatment initiation and adherence in a South African community influenced more by perceptions than by knowledge of tuberculosis. BMC public health. 2010;10(1):72.
164. Niehaus I. Death before Dying: Understanding AIDS Stigma in the South African Lowveld*. Journal of Southern African Studies. 2007;33(4):845-60.
165. Shisana O. South African national HIV prevalence, HIV incidence, behaviour and communication survey, 2005: HSRC press; 2005.
166. Deacon H, Stephney I, Prosalendis S. Understanding HIV/AIDS stigma: A theoretical and methodological analysis: HSRC press; 2005.
167. Fassin D, Schneider H. The politics of AIDS in South Africa: beyond the controversies. BMJ: British Medical Journal. 2003;326(7387):495.
168. Arndt C, Lewis JD. The HIV/AIDS pandemic in South Africa: Sectoral impacts and unemployment. Journal of International Development. 2001;13(4):427-49.
169. Fitzpatrick L, McCray E, Smith DK. The global HIV/AIDS epidemic and related mental health issues: The crisis for Africans and Black Americans. Journal of Black Psychology. 2004;30(1):11-23.
170. Okoror TA, BeLue R, Zungu N, Adam AM, Airhihenbuwa CO. HIV positive women's perceptions of stigma in health care settings in Western Cape, South Africa. Health care for women international. 2014;35(1):27-49.
171. Kalichman SC, Simbayi LC. HIV testing attitudes, AIDS stigma, and voluntary HIV counselling and testing in a black township in Cape Town, South Africa. Sexually transmitted infections. 2003;79(6):442-7.
172. Ronsmans C, Vanneste AM, Chakraborty J, Van Ginneken J. A comparison of three verbal autopsy methods to ascertain levels and causes of

maternal deaths in Matlab, Bangladesh. International journal of epidemiology. 1998;27(4):660-6.
173. Gajalakshmi V, Peto R. Verbal autopsy of 80,000 adult deaths in Tamilnadu, South India. BMC public health. 2004;4(1):47.
174. Joshi R, Lopez AD, MacMahon S, Reddy S, Dandona R, Dandona L, et al. Verbal autopsy coding: are multiple coders better than one? Bull World Health Organ. 2009;87(1):51-7.
175. Garenne M, Fontaine O. Assessing probable causes of death using a standardized questionnaire: a study in rural Senegal. 1990.
176. Fottrell E, Byass P, Ouedraogo TW, Tamini C, Gbangou A, Sombié I, et al. Revealing the burden of maternal mortality: a probabilistic model for determining pregnancy-related causes of death from verbal autopsies. Population Health Metrics. 2007;5(1):1.
177. Quigley MA, Chandramohan D, Setel P, Binka F, Rodrigues LC. Validity of data-derived algorithms for ascertaining causes of adult death in two African sites using verbal autopsy. Tropical Medicine & International Health. 2000;5(1):33-9.
178. Komaroff AL. Symptoms: In the head or in the brain? Annals of internal medicine. 2001;134(9_Part_1):783-5.
179. Bang AT, Bang RA. Diagnosis of causes of childhood deaths in developing countries by verbal autopsy: suggested criteria. The SEARCH Team. Bull World Health Organ. 1992;70(4):499-507.
180. Ronsmans C, Vanneste AM, Chakraborty J, Van Ginneken J. A comparison of three verbal autopsy methods to ascertain levels and causes of maternal deaths in Matlab, Bangladesh. Int J Epidemiol. 1998;27(4):660-6.
181. Edmond KM, Kirkwood BR, Amenga-Etego S, Owusu-Agyei S, Hurt LS. Effect of early infant feeding practices on infection-specific neonatal mortality: an investigation of the causal links with observational data from rural Ghana. The American journal of clinical nutrition. 2007;86(4):1126-31.
182. Joshi R, Lopez AD, MacMahon S, Reddy S, Dandona R, Dandona L, et al. Verbal autopsy coding: are multiple coders better than one? Bulletin of the World Health Organization. 2009;87(1):51-7.
183. Quigley MA, Chandramohan D, Setel P, Binka F, Rodrigues LC. Validity of data-derived algorithms for ascertaining causes of adult death in two African sites using verbal autopsy. Trop Med Int Health. 2000;5(1):33-9.
184. D'Ambruoso L, Boerma T, Byass P, Fottrell E, Herbst K, Källander K, et al. The case for verbal autopsy in health systems strengthening. The Lancet Global Health. 2017;5(1):e20-e1.
185. Ghebreyesus TA. All roads lead to universal health coverage. The Lancet Global Health. 2017;5(9):e839-e40.
186. D'Ambruoso L. Relating the construction and maintenance of maternal ill-health in rural Indonesia. Global health action. 2012;5(1):17989.

187. Barber RM, Fullman N, Sorensen RJ, Bollyky T, McKee M, Nolte E, et al. Healthcare Access and Quality Index based on mortality from causes amenable to personal health care in 195 countries and territories, 1990–2015: a novel analysis from the Global Burden of Disease Study 2015. Lancet. 2017.
188. Collaborators GT. The global burden of tuberculosis: results from the Global Burden of Disease Study 2015. The Lancet Infectious Diseases. 2017.
189. Dye C, Fengzeng Z, Scheele S, Williams B. Evaluating the impact of tuberculosis control: number of deaths prevented by short-course chemotherapy in China. International journal of epidemiology. 2000;29(3):558-64.
190. Borgdorff MW, Floyd K, Broekmans JF. Interventions to reduce tuberculosis mortality and transmission in low-and middle-income countries. Bulletin of the World Health Organization. 2002;80(3):217-27.
191. Campbell OM, Graham WJ, group LMSSs. Strategies for reducing maternal mortality: getting on with what works. The lancet. 2006;368(9543):1284-99.
192. Ebrahim S, Harwood R. Stroke: epidemiology, evidence, and clinical practice: Oxford University Press, USA; 1999.
193. Nolte E, Bain C, McKee M. Diabetes as a tracer condition in international benchmarking of health systems. Diabetes care. 2006;29(5):1007-11.
194. Jamison DT, Summers LH, Alleyne G, Arrow KJ, Berkley S, Binagwaho A, et al. Global health 2035: a world converging within a generation. The Lancet. 2013;382(9908):1898-955.
195. Mills A. Strengthening health systems: the role and promise of policy and systems research: World health organization (WHO). Alliance for health policy and systems research; 2004.
196. Kruk ME, Yamey G, Angell SY, Beith A, Cotlear D, Guanais F, et al. Transforming global health by improving the science of scale-up. PLoS biology. 2016;14(3):e1002360.