Tuberculosis and Tuberculosis/HIV/AIDS–Associated Mortality in Africa: The Urgent Need to Expand and Invest in Routine and Research Autopsies

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Frequently quoted statistics that tuberculosis and human immunodeficiency virus (HIV)/AIDS are the most important infectious causes of death in high-burden countries are based on clinical records, death certificates, and verbal autopsy studies. Causes of death ascertained through these methods are known to be grossly inaccurate. Most data from Africa on mortality and causes of death currently used by international agencies have come from verbal autopsy studies, which only provide inaccurate estimates of causes of death. Autopsy rates in most sub-Saharan African countries have declined over the years, and actual causes of deaths in the community and in hospitals in most sub-Saharan African countries remain unknown. The quality of cause-specific mortality statistics remains poor. The effect of various interventions to reduce mortality rates can only be evaluated accurately if cause-specific mortality data are available. Autopsy studies could have particular relevance to direct public health interventions, such as vaccination programs or preventive therapy, and could also allow for study of background levels of subclinical tuberculosis disease, Mycobacterium tuberculosis–HIV coinfection, and other infectious and noncommunicable diseases not yet clinically manifest. Autopsies performed soon after death may represent a unique opportunity to understand the pathogenesis of M. tuberculosis and the pathogenesis of early deaths after initiation of antiretroviral therapy. The few autopsies performed so far for research purposes have yielded invaluable information and insights into tuberculosis, HIV/AIDS, and other opportunistic infections. Accurate cause-specific mortality data are essential for prioritization of governmental and donor investments into health services to reduce morbidity and mortality from deadly infectious diseases such as tuberculosis and HIV/AIDS. There is an urgent need for reviving routine and research autopsies in sub-Saharan African countries.

Tuberculosis and human immunodeficiency virus (HIV)/AIDS are frequently quoted as the 2 most important infectious causes of death in developing countries [1]. These surveillance data are derived from multiple sources of information, such as clinical records and death certificates. However, causes of death ascertained through these sources are known to be inaccurate. Autopsies provide the only means of defining the exact cause of death [2]. Autopsy data can provide disease and death statistics from the local community, country, and region for global surveillance of disease-specific mortality rates [1, 2]. Today, autopsies are performed for several purposes, including medical, legal, educational, and...
Table 1. Purpose and Usefulness of Routine and Research Autopsies

**Medical Reasons:** To Identify…
- Probable cause of death
- Manner of death
- State of health before death
- Pathology and extent of disease
- Missed pathology or abnormality before death
- Comorbidities
- Missed unusual presentations of common illnesses
- Whether treatment accorded was inappropriate

**Legal Reasons:** To Determine…
- Criminal causes of death (eg, homicide from any cause)
- Causes of unnatural or unexpected or sudden deaths (eg, suicide)
- Negligence in vehicle accidents (eg road, rail, air, marine accidents)

**Research Purposes**
- Prevalence and cause of death studies (hospital and community)
- Prevalence of coinfections and copathologies (HIV/tuberculosis/AIDS/noncommunicable diseases)
- Background level of noncommunicable diseases and infections in the community
- Death and disease statistics (hospital, region, and country)
- Investigation (clinicopathological and pathogenesis) of new diseases
- Evaluation of new diagnostics by providing a gold standard for more accurate tests than current gold standard for infectious diseases

**Educational/Training Purposes**
- Training of pathologists and anatomists
- Learning from errors in diagnosis and assisting in improving diagnostic algorithms
- Learning from medical management errors
- Provide a good index of quality of healthcare provided

**TYPES OF AUTOPSIES**

Autopsies [1, 2, 7, 8] are broadly classified into 3 main groups: (1) invasive autopsies, (2) noninvasive autopsies, and (3) verbal autopsies.

Invasive autopsies provide more accurate diagnostic information because they allow for direct access to organs and tissues for pathological examination. There are 3 types of invasive autopsies: (1) conventional whole-body examinations, (2) autopsies limited to a particular part of the body (necropsy), and (3) minimally invasive autopsies in which small amounts of tissue are obtained percutaneously using needles or via endoscopy through small skin incisions. Postmortem blood cultures fall under this group [9].

Noninvasive autopsies make use of specialist imaging techniques. With advances in technology, noninvasive autopsies are becoming common and include use of ultrasound (echoscopy), magnetic resonance imaging (MRI), multislice computed tomography (CT) [10], and positron emission tomography (PET)/MRI or PET/CT. These techniques identify site and extent of pathological abnormalities in cryptic areas and may allow for obtaining more targeted biopsies of lesions. All of these methods require adequate resources, trained staff, and sustainable pathology services, all of which are lacking in most developing countries, particularly those in sub-Saharan Africa.

Verbal autopsies are questionnaire and interview studies that attempt to ascertain the cause(s) of death in all age groups from information obtained from health staff, relatives, friends, and neighbors of the deceased [7]. These are conducted when invasive or noninvasive autopsies or valid premortem medical records are unavailable or when the corpse has been disposed of by burial or cremation [7, 11–16]. Due to resource constraints, inadequate pathology services, and lack of trained pathologists, verbal autopsies provide the only source of community mortality data in most sub-Saharan African countries.

**AUTOPSY TRENDS OVER TIME**

Autopsies were routinely performed on inpatient hospital deaths in the United States and Europe but have decreased steadily over the past 50 years [17–21]. Information previously gained from autopsy has gradually been replaced by biopsies and other refined minimally invasive surgical procedures. In the United Kingdom, the widespread media coverage and ensuing consternation over the undocumented retention of organs and tissue samples obtained at autopsy have also led to a reduction of autopsies being performed [19]. Routine autopsies are not performed in the majority of African countries. Apart from South Africa, routine autopsy rates have declined in most sub-Saharan African countries because of a number of reasons, such as lack of resources to maintain an effective pathology service, scarcity of trained pathologists, inadequate infrastructure, and difficulties in
obtaining consent for autopsies due to cultural beliefs and religious sensitivities. Even in more affluent countries like Nigeria, autopsy rates have declined. A 20-year (1984–2003) review of autopsy records at University College Hospital, Ibadan, Nigeria [20] showed that 3385 autopsies had been performed out of a total of 30,899 (9.1%) hospital deaths, thus giving an annual average autopsy rate of only 78% out of an average of 1626 deaths. The study also noted a large decline in autopsy rates at the hospital over the years from an average of 19% in 1984 to 3.6% in 2003. Thus, the actual data on the causes of deaths in the community (rural and urban) and in hospitals in most sub-Saharan African countries remain unknown, and the quality of cause-specific mortality statistics remains poor. Most mortality and causes-of-death data for adults, children, neonates, and mothers from Africa continue to be derived from verbal autopsy studies [11–16], the true value of which is doubtful. Thus, there is an urgent need to obtain more accurate cause-of-death data from sub-Saharan African countries by reviving routine autopsies within hospitals.

FUNDER NEGLECT OF AUTOPSY RESEARCH STUDIES

Prior to the 1990s, autopsy research studies and publications from African countries were uncommon. The beginning of the HIV/AIDS epidemic and the associated tuberculosis epidemic in sub-Saharan Africa was followed by alarmingly high death rates in adults and children [22–27], especially because antiretroviral therapy was not available at that time and the pathogenesis of many opportunistic infections was undefined. The increasing numbers of patients presenting with HIV-associated infections were difficult to diagnose and treat and posed major clinical management issues, taxing the resource-poor health services. Defining the actual causes of death to provide an evidence base for causes of mortality in HIV-infected individuals was deemed important because ascertaining the actual causes of death could lead to development of appropriate diagnostic and management algorithms, preventive measures, and therapy. Autopsies were the only way in which accurate data on the effects of the tuberculosis and HIV/AIDS epidemics on morbidity and mortality could be assessed, as illustrated by the sentinel autopsy studies on AIDS-related deaths from Botswana [25] and West Africa [26, 27].

However, funding agencies and governments did not consistently see the importance of serious investment into pathology and autopsy studies. As an example, in the late 1990s, an application by us for a small sum of money to a UK grant-making body to perform a 3-year autopsy study of hospitalized Zambian children dying of respiratory diseases obtained good reviewer comments but was rejected due to a panel decision [28]. Funding was eventually secured, and the largest autopsy study of inpatient children dying of respiratory illnesses was performed, yielding important and policy-relevant data published in a high-impact-factor journal [29]. The autopsy study of 264 Zambian children (137 boys [93 HIV-1 positive, 44 HIV-1 negative] and 127 girls [87 HIV-1 positive, 40 HIV-1 negative] aged between 1 month and <16 years) showed the 4 most common findings overall were acute pyogenic pneumonia (population-adjusted prevalence, 39.1%, 116 of 264), Pneumocystis carinii pneumonia (27.5%, 58 of 264), tuberculosis (18.8%, 54 of 264), and cytomegalovirus (CMV) infection (20.2%, 43 of 264). The 3 most frequent findings in the HIV–negative group were acute pyogenic pneumonia (50%), tuberculosis (26%), and interstitial pneumonitis (18%); in the HIV–positive group, the 3 most frequent findings were acute pyogenic pneumonia (41%), P. carinii pneumonia (29%), and CMV (22%). Tuberculosis was common in all age groups, irrespective of HIV-1 status. Most children dying from respiratory diseases had preventable or treatable infectious illnesses. The study concluded 4 things: (1) Most children dying from respiratory diseases have preventable or treatable infectious illnesses; (2) the presence of multiple diseases makes accurate diagnosis difficult; (3) World Health Organization (WHO) recommendations should therefore be updated with specific mention of HIV–1–positive children; and (4) improved diagnostic tests for bacterial pathogens, tuberculosis, and pneumonia were urgently needed. The study results demonstrated to WHO and the WHO International Management of Childhood Infections (IMCI) group the importance of respiratory infections, particularly tuberculosis, community-acquired pneumonia, and opportunistic infections, as important causes of death in young Zambian children. The data dismissed claims at that time that tuberculosis was not an important problem in African children. These data were used by regional African pediatricians and by the IMCI group to highlight the difficulties of making accurate respiratory diagnoses in HIV-infected children and to improve diagnostic algorithms for respiratory infections in children to avoid mortality from treatable causes of death. Other subsequent studies of sub-Saharan African children revealed similar data, confirming these findings [30, 31]. The results of our autopsy study led to a randomized clinical trial of co-trimoxazole for the prevention of acute bacterial infections in children [32], the results of which led to WHO recommending co-trimoxazole as prophylaxis in the management of HIV-infected children [33].

AUTOPSIES OF MATERNAL DEATHS FROM AFRICA

A substantial proportion of antenatal and postnatal women in sub-Saharan Africa are HIV infected, and many acquire active tuberculosis disease and die of codisease [34, 35]. Autopsies are not routinely performed on maternal deaths, and accurate data on the etiology of maternal deaths in sub-Saharan Africa do not exist. Thus, maternal mortality data from Africa countries are mainly based on clinical data or verbal autopsies. A clinical case note study of maternal deaths at the University Teaching Hospital (UTH) in
Lusaka, Zambia, indicated that tuberculosis, malaria, and HIV/AIDS were important nonobstetric causes of death. Autopsies are not routinely performed there, and these data need to be confirmed [36]. The 2-year retrospective study conducted between 1 January 1996 and 31 December 1997 was compared with available data published between 1974 and 1989. The maternal mortality ratio for UTH was calculated at 921 per 100,000 live births, a significant increase from the 118 noted in 1982 and 667 in 1989. These data showed that despite improved obstetric services, the maternal mortality ratios at UTH had increased 8-fold over the past 2 decades. Ordii and colleagues [37] performed a retrospective analysis of 139 maternal autopsies during the period October 2002 to December 2004 at Maputo Central Hospital, Mozambique. This analysis showed that major antemortem diagnostic errors were made in 56 (40.3%) maternal deaths. A high rate of false-negative diagnoses was also observed for infectious diseases, with sensitivities of 33.3% for HIV/AIDS-related conditions, 35.3% for pyogenic bronchopneumonia, 40% for pyogenic meningitis, and 50% for puerperal septicemia. It is only through autopsy studies that the accuracy of clinical diagnostic criteria can be improved. Furthermore, accurate data on exact causes of maternal deaths will lead to improved and targeted antenatal care focused on screening for common causes of deaths [38].

NEED FOR MORE TARGETED INVESTMENT INTO RESEARCH STUDIES

There is a need for more research autopsy studies in Africa in several important areas as outlined in Table 1. Autopsy research studies from Africa are few and limited to specific research questions [39, 40]. In the past 2 decades, only 20 research autopsy studies were published from sub-Saharan Africa (9 complete and 11 partial or minimally invasive), and these were reviewed recently [41]. Complete autopsies were performed in 593 HIV-positive adults and 177 HIV-positive children. An important finding was that postmortem diagnoses and causes of death were mainly due to treatable infectious diseases. Tuberculosis was the most frequent, present in 21%–54% of HIV-positive adults, and was considered the cause of death in 32%–45%. Overall, pulmonary infections (~66%) and central nervous system infections (~20%) accounted for the majority of pathology identified. A high discordance between clinical premortem and postmortem diagnoses was observed in these studies. This analysis emphasizes the unreliability of clinical diagnosis and cause-of-death data from clinical records and death certificates.

AUTOPSY STUDIES FOR UNDERSTANDING PATHOGENESIS OF TUBERCULOSIS AND TUBERCULOSIS/HIV/AIDS

Currently, a large amount of funding and resources are invested in interventions to reduce mortality from tuberculosis and tuberculosis/HIV/AIDS, and yet there are no accurate means of evaluating the effects of these interventions. Autopsies, biopsies, and open access to lung tissue performed a limited time after death may also provide a unique opportunity to understand the pathogenesis of Mycobacterium tuberculosis and learn about the success or failure of local immune responses in M. tuberculosis infections. Access to human lung tissue will help to address unanswered questions concerning immune surveillance and help to map the complexity of immune responses in latent M. tuberculosis infection, active tuberculosis disease (see article by Zumla and Maeurer in this supplement), and immunopathological reactions. Such samples could allow the capture of the real-time status of different stages of the latent M. tuberculosis infection vs active tuberculosis and help obtain a more realistic picture of the events that trigger and shape the profile of different clinical presentations of tuberculosis. Most available data on human cellular immune responses to M. tuberculosis have been obtained from conventional methods through analysis of peripheral venous blood samples or from active tuberculosis lesions from sick patients and thus may not reflect the relevant T-cell recognition patterns in situ. Access to postmortem tissue from acute deaths in the community [42] will enable us to more accurately address fundamental questions of protective immune mechanisms through immunological study of tissues from latent M. tuberculosis lesions, granulomas, and active M. tuberculosis lesions. Access to postmortem tissue will also enable study of deaths that occur soon after the initiation of antiretroviral therapy and those from the immune reconstitution inflammatory syndrome (IRIS) [43]. Furthermore, autopsy studies on acute deaths in the community due to acute illnesses, road traffic accidents, and accidental and self-induced deaths will allow for study of subclinical and background levels of tuberculosis, M. tuberculosis/HIV coinfection, and other infectious and non-communicable diseases not yet clinically manifest.

AUTOPSIES AS SOURCES OF ACCURATE CAUSE-SPECIFIC DEATH DATA

Current mortality statistics from WHO for specific disease-associated deaths in African countries are based on estimates from poorly kept hospital records, national returns from death certificates on which accurate causes of death are difficult to record, and verbal autopsy studies, all of which have major data gaps and limitations in estimating actual causes of death [8, 15, 16]. The importance, quality, and validity of the data obtained by use of verbal autopsies are subjective, often inaccurate, and misleading, and the information obtained is limited. Thus verbal autopsy studies from Africa and Asia have become a subject of intense debate. Most mortality and cause-of-death data from Africa and Asia being used by international agencies for surveillance and monitoring purposes have come from verbal autopsy studies that provide only approximate estimates of causes of death. There is
a need for parallel studies comparing data from verbal autopsy studies with conventional invasive autopsies to ascertain the actual concordance rates between the 2 autopsy methods. This would also allow for identifying which conditions and diagnoses give the greatest discrepancies and what diagnoses are being missed by verbal autopsy studies.

The true scale, distribution, and trends over time of lethal infectious and noncommunicable diseases remain undefined. More than 5 billion people worldwide live in resource-poor countries that lack adequate pathological services and a reliable system for issuing medical death certificates. The scale of any cause of death can only be ascertained by introduction of routine autopsies, which require large-scale investments into pathology services, training, and infrastructure. Autopsies can provide an accurate evidence base for funder and government investments on deadly infectious diseases. Autopsy studies of children would also provide cause-of-death data and would have particular relevance to direct public health interventions, such as vaccination programs or preventive therapy. It may also be possible to pool resources regionally and create sentinel surveillance sites in different regions.

There are other reasons why more investment is required into revamping autopsies in sub-Saharan Africa. Tuberculosis remains an important cause of death and is closely linked to the HIV/AIDS epidemic. The past decade has seen enormous efforts and investment into achieving tuberculosis control worldwide. Current investments into developing various interventions for lethal infectious diseases will need to be evaluated in terms of reduction in mortality rates. There are also several important issues regarding tuberculosis control, efficacy of current tuberculosis control efforts, epidemiology of tuberculosis in the community, pathogenesis, and mycobacterial latency that require autopsies to be conducted—for example, evaluating fatal IRIS reactions after initiation of antiretroviral therapy and determining the many scenarios of death in M. tuberculosis–HIV coinfected patients that are not caused by M. tuberculosis itself [44]. Donors and governments invest huge sums of money into health systems for targeted interventions in an attempt to reduce the mortality rates from common deadly infectious and noncommunicable diseases. With no accurate means of ascertaining the actual causes of death apart from autopsies, the impact of these huge investments cannot be accurately evaluated.

Routine autopsies will also allow for study of common diseases causing death in inpatient wards and in the wider community. Furthermore, autopsies conducted on those who die unexpectedly in the community will provide insight into study of background levels of noncommunicable diseases and of latent infections, subclinical infectious disease, or other cryptic diseases not yet clinically manifest. Clinical trials will benefit from ascertaining actual causes of death of participants that could be attributable to the trial intervention or to other natural causes. Donor investments must also provide parallel support for training and capacity building of local ethics committees, with focus on the important ethical issues of consent, tissue retention, and creation of biobanks from autopsy samples.

**IMPROVING AUTOPSY CONSENT RATES IN AFRICA**

Autopsies cannot be performed without the written consent of legal guardians, parents, or relatives. Obtaining consent is the most important enabling step in the autopsy procedure. Low autopsy rates in Africa have been attributed to cultural and religious objections and social taboos [40]. There is scanty published work from Africa on the subject of reasons for autopsy refusal. Consenting to necropsy examination is psychologically distressing at times of personal grief for relatives and doctors who often commonly consider the autopsy in terms of cadaver mutilation. In the autopsy study of Zambian children [29], we had a high refusal rate (75%) for autopsies from parents/guardians (891 of 1118) [45]. More than one-quarter (236 of 1118) of families declined because a death certificate had already been issued and arrangements to transport the body had been made and could not be delayed. A wide range of reasons were cited for refusal and pointed to the diverse and complex interaction of social, religious, and cultural factors affecting attitudes to autopsy examination. There are several ways in which autopsy consent rates can be increased. It becomes important to perform autopsies as a matter of urgency soon after death. This may not be possible within the current constraints on staffing and pathology services in most African countries; thus, more trained staff and adequate resources for pathology services are required. Staff training should include training in counseling and communication skills for requesting an autopsy examination in situations in which the staff must fully consider local beliefs and social and religious values and customs.

**CONCLUSIONS**

There is a growing and urgent need for reviving routine and research autopsies in sub-Saharan African countries. Recently WHO and The Global Fund have identified the need for better information to gauge their investments and tackle high mortality rates [46]. This can only be evaluated by the introduction of routine and research autopsies. The time is now ripe for donors, funders, and governments to seriously revisit the subject of the value of autopsies in sub-Saharan Africa, where millions of people die without the actual causes of death being accurately defined.

**Notes**

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