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Editorial

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EDITORIAL

Minimally Invasive Autopsy: Welcoming a New Tool for Cause of Death Investigation in Children in Resource-constrained Countries

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INTRODUCTION

Despite large efforts and generous investments, mortality statistics and cause-of-death (CoD) estimates from resource-constrained countries remain, as of 2017, still unreliable. Models used to build estimates for poor countries, where the majority of preventable deaths still occur, have shown many flaws, and discrepancies in cause-attributable disease figures [1] have evidenced the shortfall of current methods, predominantly based on data derived from verbal autopsy or clinical records. With efforts targeting the improvement of civil and vital registration systems (CVRSs), counting the dead has become progressively easier [2, 3], but establishing the CoD for each person remains a major challenge, particularly among children. Routine and cause-specific disaggregated mortality data are however critical at the local level to help policymakers make rational health planning and prioritization decisions [4].

THE REBIRTH OF POST-MORTEM METHODS

Pathological autopsies are generally considered the gold standard methodology to investigate CoD, but their practice is globally decreasing [5], and in the majority of poor settings, their routine use and acceptability are severely limited or non-existent. In recent years, renewed interest in developing less invasive, and thus potentially more acceptable, post-mortem methods capable of providing similarly rich pathological and microbiological data so as to substitute the pathological autopsy has emerged. In rich countries, sophisticated imaging techniques (including computerized tomography scanning and magnetic resonance imaging) have been used to explore in detail stillbirths and neonatal deaths, and to guide fine needle biopsies for percutaneous tissue sampling, with the aim of studying the possible CoD [6–8]. In poorer settings, however, such an approach would remain impracticable, and for this reason, simpler methods had to be developed. In this respect, the use of fine needle biopsies to target specific organs, so as to permit targeted organ or pathology-specific investigations can be traced back to many decades ago. Décio Parreiras and Werneck Genofre developed in the year 1930 during a yellow fever outbreak in Brazil the 'Parreiras-Genofre Spindle' to be used for targeted post-mortem liver sampling [9]. Subsequently, although for a relatively short period

of time, this methodology became moderately popular for targeted post-mortem sampling across many tropical settings [10]. More recently, targeted fine needle biopsies of the brain's frontal lobe using the supraorbital approach have been used in research contexts for the confirmation of cerebral malaria [11]. These approaches, insufficient for a wider and less localized or disease-specific CoD investigation, were however the seed of what later would become the minimally invasive autopsy (MIA), a protocolized and systematic methodology targeting various organs and bodily fluids, and aiming to provide sufficiently good quality samples for pathological and microbiological investigations so as to substitute the complete pathological autopsy (Fig. 1).

THE MIA VALIDATION

The MIA approach for CoD investigation has been validated against the full pathological autopsy in a large multicentre study conducted in Mozambique and the Brazilian Amazon [12]. In this study, 343 in-hospital deaths, including stillborns, neonatal and child deaths and adults, were studied using the MIA approach [13–15]. In all cases, a full pathological autopsy, conducted by a second team of researchers, immediately followed the MIA. All samples obtained with the two procedures were investigated with a protocol that combined classic histopathology approaches [16] with intensive conventional and molecular microbiology investigations [17]. In all population groups studied, MIA performed well, allowing a good diagnosis of the underlying CoD. Not surprisingly, the MIA's diagnostic precision was good for infectious and oncologic CoD, but significantly declined for metabolic or cardiovascular diseases, and in children, it failed to adequately recognize congenital diseases. This study, difficult to replicate, laid the methodological foundations for future uses of this tool.

IS A MIA TOOL ACCEPTABLE IN THOSE PLACES WHERE THE FULL AUTOPSY WAS NOT?

Validating an innovative MIA approach for CoD investigation in poor settings would be a futile exercise if such a tool was not shown to have a significantly better acceptability profile than the full autopsy it aims to substitute. Socio-anthropological research

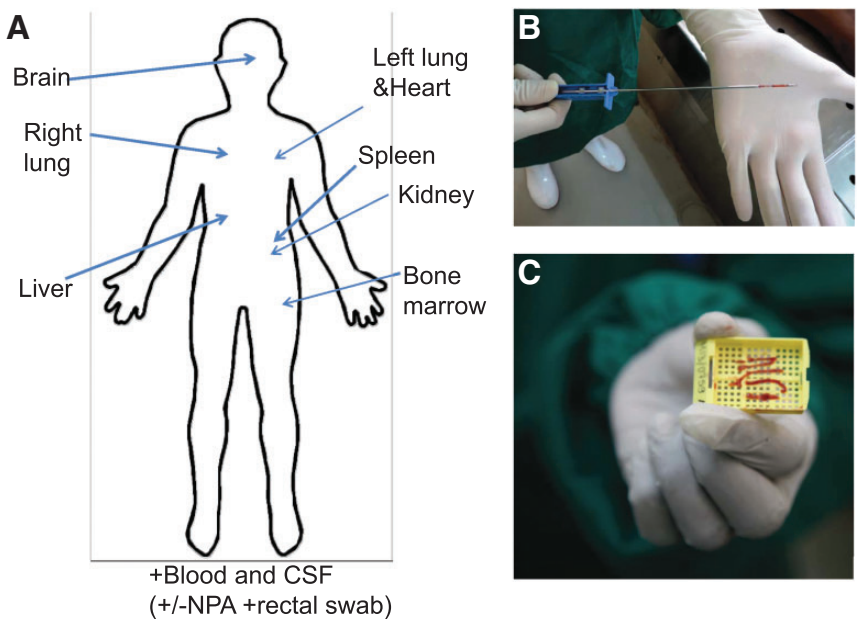

Fig. 1.(**A**) Schematic diagram of organs and bodily fluids targeted with MIA (CSF = cerebrospinal fluid; NPA = nasopharyngeal aspirate); (**B**) example of biopsy needle after obtaining tissue sample; (**C**) lung tissue cylinders obtained through a MIA.

was conducted as part of the aforementioned project in five different countries (Mozambique, Kenya, Gabon, Mali and Pakistan) to provide representative findings from different geographical, cultural and religious backgrounds, providing encouraging results of the differential acceptability of the MIA vs. more aggressive and invasive post-mortem methods [18]. The study anticipated also potential barriers and facilitators, not only at the health facility but also at the community level, where the majority of deaths still occur in low-income settings, essential for local tailoring of recommendations for future MIA implementation.

MIA CHALLENGES: THE CASE FOR SPECIFIC DISEASES AND ATTRIBUTION OF CAUSALITY

In addition to the difficulties shown in identifying non-infectious or oncologic diseases, the current MIA protocols may also fail to recognize certain common paediatric conditions without clear microbiological or histopathological signatures, such as, for instance, protein or energy malnutrition, anaemia or electrolyte or metabolic disturbances. This needs to be highlighted as an important research gap in terms of future MIA development, and creative thinking will be required to improve and innovate current sampling and investigation strategies, and laboratory methods. Additionally, the use of post-mortem methods has confirmed the stand-alone importance of certain diseases, and particularly certain infections, in terms of attributable or contributable mortality. However, post-mortem bacterial translocation and contamination phenomena, together with the inherent challenges of differentiating innoxious carriage from pathogenic presence, make the interpretation of microbiological findings challenging. The MIA approach facilitates the contextualization of isolated pathogens in relation to underlying histopathological changes, and thus could provide a more adequate evaluation of their contribution to the fatal event. However, attribution of causality remains as of today the Achilles' heel of the MIA.

THE FUTURE OF MIAS

The future wide-scale implementation of MIAs could provide confirmatory post-mortem evidence of the presence of diseases and pathogens, and help adjust global burden of disease estimates that currently remain highly speculative. While introducing new post-mortem methods is challenging, particularly in settings that have never used them before, the development and validation of the MIA have popularized and stirred a new impetus in the field of CoD investigation, opening new avenues that can facilitate the uptake and dissemination of such methods. MIAs will not eliminate the need to strengthen CVRS, or to conduct verbal autopsies, a method for CoD ascertainment with clear limitations at the individual level, but which remains useful from a public health point of view. MIAs may however contribute, as no other method has made until now, to increase our understanding of the major determinants of preventable mortality and the enormous inequities that surround survival in resource-constrained settings.

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