Multiple Cause-of-Death Analysis

Questions and Answers

The IUSSP Scientific Panel on Declining Mortality and Multi-morbidity at Death has put together a series of Questions & Answers about Multiple Cause-of-Death (MCOD) Analysis, clarifying definitions, presenting aims and methods, addressing issues of data quality and international comparison and highlighting the contribution of MCOD to understanding COVID-19 mortality.

1- What are "multiple causes of death"? What about "contributing causes of death"?

Multiple causes of death (MCOD) refer to the entries listed in the medical part of the death certificate (International Form of Medical Certificate of Cause of Death). The Medical Certificate of Cause of Death is organized into two parts (Figure 1). Part I is devoted to the chain of causes directly leading to death. This includes the disease that initiated the train of events leading to death (also termed "underlying cause" or UC[1]) as well as consequences of this disease. Part II of the certificate is devoted to any significant conditions contributing to death "*but not related to the disease of condition causing it*".

Figure 1. International form of medical certificate of cause of death

INTERNATIONAL FORM OF MEDICAL CERTIFICATE OF CAUSE OF DEATH

Cause of death		Approximate interval between onset and death
I Disease or condition directly leading to death*	(a)	.....
	due to (or as a consequence of)	
Antecedent causes Morbid conditions, if any, giving rise to the above cause, stating the underlying condition last	(b)	.....
	due to (or as a consequence of)	
	(c)	.....
	due to (or as a consequence of)	
	(d)	.....
II Other significant conditions contributing to the death, but not related to the disease or condition causing it	.....	.....
	.....	.....
**This does not mean the mode of dying, e.g. heart failure, respiratory failure. It means the disease, injury, or complication that caused death.*		

[1] The selection of the UC relies on the International Classification of Diseases 10th Revision (ICD-10) rules. In general, it is the cause that initiated the train of events. There however are some very specific exceptions. As an example, the UC of a death due to liver cancer caused by a chronic liver disease is not the chronic liver disease but the liver cancer.

A contributing cause of death is a cause of death present in the death certificate but not listed as the underlying cause. It is possible to classify contributing causes into a few broad categories (See Désesquelles et al. 2012, Grippo et al. 2024):

- consequences or complications of the UC or of its therapy (also termed "precipitating cause"), including symptoms of the UC (e.g. epilepsy combined with brain cancer).

- risk factors for the UC (e.g. alcoholism or hypertension as risks factors for cardiovascular and other diseases).

- aggravating factors for the UC. Typically, this is the case for many chronic diseases (hypertension, diabetes…) mentioned in Part II of the death certificate (also termed "associated causes"). The mechanisms of the interaction with the morbid process in part I are not unique, as several exist. For instance, multi-morbidity may aggravate the patient's situation, increase his/her vulnerability to adverse events, make clinical care more complex[2], and increase the risk of complications of the UC, among other potential effects.

A growing number of countries produce multiple cause of death data (Bishop et al. 2023). Some countries have multiple cause-of-death data but only for very recent years. This information provides an exhaustive, generally good quality and relatively inexpensive source of data on multi-morbidity at death.

2- What do multiple causes of death add to the underlying cause of death? What are the aims of Multiple Cause-of-Death (MCOD) analysis?

The measurement of multiple causes of death can be considered complementary to the measurement of a sole underlying cause of each death. Mortality statistics based on the underlying cause (UC) of death have proven to be very powerful for understanding life expectancy trends as well as differences within and between countries. However, in the context of ageing populations and growing prevalence of multi-morbidity, an exclusive focus on the UC limits our understanding of the complexity of the processes leading to death as well as relationship between causes at death.

In addition, trends in the underlying cause of death are susceptible to biases due to changing or country-specific practices of medical doctors in the reporting of certain diseases (e.g. reporting in part I or II of the death certificate). This may be due to changes or variations in the diagnostic practices and the recognition about the role played by these diseases in death (see for instance the case of Alzheimer's disease and other dementias in Désesquelles et al. 2014 and Adair et al. 2022). These changes or variations have an impact on how frequently these diseases will be selected as the underlying cause of death. Multiple cause of death analysis can help to overcoming this bias.

2 As an example, polypharmacy increases the risk of adverse drug events and non-adherence to treatments.

The aims of the multiple cause-of-death analysis are becoming increasingly diverse, however, the general aims include the following:

- To reassess the contribution of causes in mortality, accounting for the different roles they play in death:

When the analysis is performed using the underlying cause only, the contribution of any given disease or condition in overall mortality is underestimated. Reassessing the burden of a given cause in mortality using multiple cause-of-death data is especially relevant for causes that are rarely selected as the UC. The analysis may take into account the specific role of each cause as stated on the death certificate (underlying or contributing causes or, in even greater detail, "originating", "associated" or "precipitating" causes - See Grippo et al. 2024).

- To examine how causes combine with each other to contribute to death:

Multiple cause-of-death analysis provides insight into the combinations of diseases that most frequently lead to death to gain a better understanding of the epidemiological profile of mortality. The analysis may take into account the specific role of each cause as stated on the death certificate. Multiple cause-of-death data can also be used to estimate probabilities of death if one or more causes of death were eliminated. In that case, multiple causes of death help overcoming the assumption of independence between causes that is normally used to estimate the impact of eliminating a cause of death, with the eventual aim of identifying disease patterns that can be considered quite independent of each other such as in the "lethal defect" model of Manton and al. (1976) or in the "relative susceptibility" model of Wong (1977).

- To assess the burden of multi-morbidity in mortality:

With increased life expectancy, death is more often the final stage of a long and complex morbid process involving more than one disease. From a public health perspective, multi-morbid patients represent a major challenge for health systems and caregivers. The number of causes listed on the death certificate can be used as an indicator of multi-morbidity but it does not account for causal relations between the reported causes. A more restrictive definition of multi-morbidity considers a process as multi-morbid if there is more than one independent morbid process described on the death certificate and/or contributing causes in Part II (Grippo et al 2024). It is possible to monitor multi-morbidity at death and to examine causes involved in those processes as well as characteristics of the decedents associated with it (e.g. age, sex…). However, it is not expected that the analysis of multi-morbidity at death provides similar results as the monitoring of multi-morbidity in the living population. The data on which these analyses rely are different both in terms of population (deceased persons vs. living people) and causes under study (causes that contributed to death vs. all causes diagnosed).

3- What are the factors impacting the quality of the multiple cause-of-death data? Can we compare countries using multiple cause-of death data?

The production of multiple cause-of-death data (including the underlying cause of death) relies on two steps that are both crucial for its quality. Firstly, the certifying physician reports

the chain of causes leading to death on the certificate. Secondly, this information is coded according to ICD-10 coding rules.

The extent and the impact of faulty certification is difficult to assess (several studies have investigated this issue. See e.g. Guralnick 1966; Speizer et al. 1977; Redelings et al. 2007) but both over- and under-reporting may occur. Certifying physicians may report diseases that were present at death but did not contribute to the morbid process; conversely, they may omit certain diseases that contributed to the death. When the underlying cause of the death (UC) is sufficient to explain the death, the physician may consider that there is no need to describe the clinical course of death in great detail. The certifying physician is required to make a decision about a single etiological sequence ending in death. The International form of medical certificate of cause of death is not adapted to the case of multi-morbid patients for whom the selection of one single etiological sequence is difficult.

The circumstances of the certification (i.e. place of the death and profile/expertise of the person who certifies the death[3]), the training of the certifiers, as well as how well they apply the skills learnt in training to completing death certificates in practice contribute to the quality of the certification. When the certifying person is the physician who treated the deceased person or when death occurs at the hospital, the information is likely to be more accurate. The availability of accurate information also depends on diagnostic behaviours. More generally, it reflects the state-of-the-art of medical knowledge. Certifying physicians are likely to report only contributing causes which, to their knowledge, possibly interact, with the result that the relationships between diseases already known to the certifying doctor are emphasised, creating a kind of 'confirmation bias'.

Inter-country heterogeneity in the reporting of causes of death is likely. In particular, reporting practices may be influenced by the format of the death certificate. Many countries use adaptations of the WHO recommended death certificate but slight deviations from the WHO certificate (size, number of lines, order of the reporting…) may have a strong impact on the reported data. This is probably partly reflected in the inter-country differences in the average number of entries on the death certificates.

The growing use of the multiple cause of death data by the research community will give the impetus for data collection improvements. Recent developments in the characterization of the causes reported of the death certificate along 4 categories (originating, precipitating, associated and ill-defined) (Grippo et al. 2024) can provide insights into the quality of the cause-of-death data and enable “cleaning” the data in an appropriate way given the objectives of the research.

Regarding coding, a growing number of countries use an automatic coding system to apply ICD-10 coding rules. This represents a major advance towards improved quality of multiple cause-of-death data. The ICD-10 coding rules can be applied systematically and uniformly, irrespective of the coding agent or the country and human intervention is only limited to

[3] General practitioner, medical examiner, coroner… The certification is not always and everywhere made by physicians.

problematic cases that cannot be processed automatically. IRIS (http://www.iris-institute.org) is a widely used coding system. However, not every country uses IRIS. As an example, the United States uses the MICAR-ACME system. Both systems are highly consistent and strictly follow all WHO rules for the coding of causes and the selection of the underlying cause of death.

4- How can multiple cause-of-death data be analyzed?

Methods and aims of MCOD are becoming more and more diverse (see Désesquelles et al 2012, Bishop et al 2023). Several general approaches have been developed, including the following:

- Compute indicators of the underestimation of the contribution of a given cause when the UC only is accounted for (e.g. Standardized ratio of multiple to underlying cause or SRMU - See Désesquelles et al. 2010). There are many examples of this approach for various diseases. Endocrine and metabolic diseases (i.e. diabetes), mental diseases (i.e. dementias) and infectious diseases are among the groups of causes whose contribution to mortality is most strongly re-evaluated upward through this approach.
- Compute indicators of the diversity of the causes of death, accounting for contributing causes. Indicators of diversity of causes of death have been developed to measure the extent to which individuals die from a set of rather similar or dissimilar causes of death. A recent study has examined cause-of-death diversity over time in the US accounting for multiple causes of death (See Trias-Llimós & Permanyer 2023).
- Compute indicators of the strength of the associations between causes. Some associations are very specific to the underlying cause. The Cause-of-death Association Indicator (CDAI) has been developed to measure the specificity of the associations (See Désesquelles et al. 2010). Strong associations between causes belonging to the same chapter of the International classification of diseases are commonly observed.
- Examine clusters of diseases (See, e.g. Barbieri et al. 2017) and networks of associations between diseases (See Egidi et al. 2018). One advantage of these methods is that associations examined are not limited to pairs of causes.
- Identify and analyse processes leading to death (simple /multi-morbid / ill-defined) based on the entire set of causes reported on the death certificates (See Grippo et al. 2020 & 2024). This can facilitate monitoring multi-morbidity at death and examining its relation with increasing/decreasing life expectancy.
- For some specific purposes, computations, though accounting for several entries per death certificate, require having each death counted only once. Weighting strategies for the entries have been developed to estimate mortality rates such that the sum of the weights for a given death is equal to one (See e.g., Moreno-Betancur et al. 2017, Bishop et al. 2023, Joshy et al. 2025).

Depending on the aims of the analysis, it can be useful to distinguish between causes in Part I and causes in Part II as they correspond to different roles in the morbid process (See Trias-Llimós et al. 2023). It may also be useful to distinguish between causes depending on the role they played in the lethal process (See Grippo et al. 2024). The results of multiple cause of death analyses can be visualised in several different ways depending on the intended purpose.

5- How can multiple cause-of-death data improve our understanding of mortality in the COVID-19 pandemic?

The characterization and understanding of the mortality related to COVID-19 have much to gain from analysing all entries on the death certificates (Petit et al. 2024). More precisely, it can be used to:

- Identify comorbidities to improve information on how people with COVID-19 die: By examining the co-occurrence of certain diseases or conditions with the reporting of COVID-19 on the death certificate, we can identify diseases/conditions more frequently than expected associated with COVID-19. Vulnerability of people with chronic conditions (i.e. cardiovascular diseases, diabetes or obesity) to the onset of severe COVID-19 and death has been established (Hong Liu et al 2020, Hacker et al 2021, Geng et al 2021). MCOD data allows us to analyse how these comorbidities and COVID-19 intervene in the process leading to death. It may be that COVID-19 is the primary cause (UC) and that the comorbidities contribute to the process leading to death; but the reverse situation is also possible, with COVID-19 aggravating a pre-existing disease/ condition.
- Quantify the full impact of COVID-19, including how it indirectly contributes to deaths. MCOD data can show how often COVID-19 is listed as a contributing rather than an underlying cause.
- Analyse temporal trends and geographical variations performed to investigate further the specificities of the interactions between COVID-19 with other diseases over time and across locations. This helps refine public health responses by identifying high-risk groups that require targeted measures.
- Understand longer-term trends in underlying causes of death during and after the pandemic: Given the interactions described above, trends in underlying causes of death for many chronic diseases such as dementia and cardiovascular disease have been distorted by COVID-19. To understand likely future trajectories of mortality from these causes, both underlying and contributing cause data should be analysed so that the impact of COVID-19 is properly accounted for. Ultimately, the analysis sheds light on the potential competition between COVID-19 and other causes of death.

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