

Why is it important to correctly classify and report SARS-CoV-2 infections and COVID-19 deaths?

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Background. In a public health emergency such as the coronavirus disease 2019 (COVID-19) pandemic, mortality surveillance is crucial, as it guides the public health response and serves as a measure of its effectiveness. It is therefore critical that deaths are uniformly and accurately classified, calculated and reported.

Objective. To discuss the importance of making accurate COVID-19 diagnoses and correctly classifying COVID-19 deaths, drawing on the experience of the misclassification of HIV/AIDS deaths in South Africa (SA).

Method. We performed an electronic literature search on PubMed, Google Scholar and EBSCOhost to identify studies with key words such as coronavirus, COVID-19, SARS-CoV-2 and mortality or death. Relevant studies were reviewed for suitability and used in the development of the argument.

Results. In SA, from 6 May to 30 June 2020, an excess of 6 849 deaths were reported from natural causes among people >1 year old when using a revised base accounting for lower mortality during lockdown. Over this same period, the SA government reported 2 504 COVID-19 related deaths. Both overestimation and underestimation of deaths have significant implications for health policy and resource allocation, as was evident in SA when the misclassification of deaths during the period of HIV denialism led directly to fewer resources being spent on dealing with the prevention and treatment of HIV, which allowed the disease to spiral out of control.

Conclusion. To ensure an appropriate public health response to COVID-19, accurate data on SARS-CoV-2 infections and COVID-19-related deaths are needed. The SA National Department of Health should develop clear guidelines on classification of deaths, and share this information with all those responsible for certifying deaths.

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In December 2019, an outbreak characterised by a cluster of patients with respiratory disease associated with a novel coronavirus was reported in the city of Wuhan in the Hubei Province of the People's Republic of China.^[1] The virus has since spread worldwide, differentially affecting populations and regions, and on 11 March 2020, the World Health Organization (WHO) declared coronavirus disease 2019 (COVID-19) a pandemic.^[2]

South Africa (SA)'s COVID-19 experience started with an index patient identified on 5 March 2020 in KwaZulu-Natal Province. By 27 March, SA's first day of country-wide lockdown, positive cases had surpassed 1 000, and the country reported its first 2 COVID-19 deaths, 1 of which was later proven not to be COVID-19 related. In a public health emergency such as COVID-19, mortality surveillance is crucial, as it guides the public health response and serves as a measure of its effectiveness. It is therefore critical that deaths are uniformly and accurately classified, calculated and reported.

Making an accurate diagnosis

An accurate diagnosis is, of course, a prerequisite for any useful classification and reporting system. The following are the case definitions proposed by the WHO:^[3]

- Suspect case: a patient with acute respiratory illness and travel history to or residence in a location reporting community transmission of SARS-CoV-2 during the 14 days prior to symptom onset.
- Probable case: a suspect case in whom testing for SARS-CoV-2 is inconclusive, or a suspect case for whom testing could not be performed for any reason.
- Confirmed case: a person with laboratory confirmation of SARS-CoV-2, irrespective of clinical signs and symptoms.

A change in case definition has a major impact on the estimate of the size of the pandemic, as well as the number of infection-related deaths reported. In Wuhan, 1 290 (50% of initially reported cases)

cases were misclassified as non-COVID-19 deaths. The National Health Commission in China subsequently modified the COVID-19 case definition seven times between 15 January 2020 and 3 March 2020.^[4] Consequently, the number of SARS-CoV-2 polymerase chain reaction (PCR) tests reported as positive increased by 7.1, 2.8 and 4.2 times from version 1 - 2, 2 - 4 and 4 - 5, respectively.^[4] In addition, the number of COVID-19 deaths in China have been revised to be almost 50% higher than initially reported. These changes had a significant impact on the global response to COVID-19, as early models had been developed across the world based on the initial Wuhan case fatality rates. Another case in point is the USA, where, when the case-related death definition was changed on 14 April 2020 to include probable deaths, an additional 3 778 cases (from 11 March to 14 April 2020) were added to the number of COVID-19 deaths.^[5]

Another pitfall is that laboratory diagnosis is currently limited by the lack of a sensitive and specific antibody test, which is beset by the problem of the late appearance of antibodies, their seemingly rapid disappearance^[6] and potential cross-reactivity with other circulating coronaviruses. Coupled with this is the low sensitivity of the molecular tests currently used for diagnosis. While the PCR test has excellent specificity, it has a sensitivity of only 71%,^[7] and this is significantly influenced by the type and quality of the specimen received.^[8]

The number of tests available will also affect the number diagnosed with the disease. As the Italian health system became overwhelmed, SARS-CoV-2 testing became limited to patients with severe disease, and this increased the positivity rate of the test and, ultimately, the case fatality rate.^[9] This has already started playing out in SA, where the Western Cape Province has reported higher numbers than the other provinces, probably due to different approaches to testing.^[10]

Correctly classifying deaths

The definition of a COVID-19 death appears to be similar across the WHO and the countries predominantly affected by the pandemic (Table 1). Accordingly, anyone who dies while COVID-19 positive should be listed as a COVID-19 death, unless there is a clear alternative cause of death that cannot be related to SARS-CoV-2 infection. There are, however, some differences, specifically in terms of the need for laboratory confirmation. For instance, a positive PCR is required in the Italian case definition, but not in the WHO, USA or UK definitions, where clinical judgement is allowed.^[9] This difference creates discrepancies and makes comparison between countries difficult. For example, as of 21 April 2020, the USA reported 44 575 deaths, 5 862 of which were probable COVID-19 deaths without laboratory confirmation, accounting for 13.17%. The number of people who die *with* the coronavirus will of course be very different from the number who die *from* coronavirus, and this will have a considerable impact on the numbers reported. It is not clear which definition of COVID-19 death is used in SA, as no definition could be found on the National Institute for Communicable Diseases (NICD) or National Department of Health websites. Conversely, it is known that once the number of cases is high, especially in the context of an overwhelmed system, some patients will die before they are tested, post

Table 1. Definition and classification of COVID-19 deaths

| Country/ organisation | Definition of COVID-19 death |
|-----------------------------------|--|
| WHO ^[3] | A death due to COVID-19 is defined for surveillance purposes as a death resulting from a clinically compatible illness, in a probable or confirmed COVID-19 case, unless there is a clear alternative cause of death that cannot be related to COVID disease (e.g. trauma). There should be no period of complete recovery from COVID-19 between illness and death. |
| USA ^[5] | Coronavirus disease deaths are identified using the ICD-10 code U07.1. Deaths are coded to U07.1 when it is reported as a cause that contributed to death on the death certificate. These can include laboratory-confirmed cases, as well as cases without laboratory confirmation. If the certifier suspects COVID-19 or determines it was likely (e.g., the circumstances were compelling within a reasonable degree of certainty), they can report COVID-19 as 'probable' or 'presumed' on the death certificate. |
| England and Wales ^[11] | Medical practitioners are required to certify causes of death 'to the best of their knowledge and belief'. Without diagnostic proof, if appropriate and to avoid delay, medical practitioners can circle '2' in the MCCD ('information from post mortem may be available later') or tick box B on the reverse of the MCCD for ante-mortem investigations. For example, if before death the patient had symptoms typical of COVID-19 infection, but the test result has not been received, it would be satisfactory to give COVID-19 as the cause of death, tick box B and then share the test result when it becomes available. In the circumstances of there being no swab, it is satisfactory to apply clinical judgement. |
| Italy ^[9] | COVID-19-related deaths occur in patients who test positive for SARS-CoV-2 via RT-PCR, independently from pre-existing diseases that may have caused death. |

MCCD = medical certificate of cause of death; RT-PCR = reverse transcription polymerase chain reaction.

mortems are unlikely to be conducted and some will die at home.^[12] Limiting the number of COVID-19 deaths to only those with laboratory confirmation will skew the numbers in a downward direction. For instance, in the USA, as of 18 April, 10 834 (71.04%) patients had died of COVID-19 in inpatient healthcare settings (as shown in Table 2^[5]), and it is assumed that most of these patients would have been tested for SARS-CoV-2 upon admission. However, the remaining ~29% of patients who died before they were admitted, or who died in other institutions such as nursing homes, were unlikely to have been tested, and would therefore not have been counted if laboratory confirmation had been a requirement.

The problem with mortality rates

The method of determining mortality rates can lead to both an overestimation and an underestimation of the real numbers, and both can have considerable impact on the public health

response.^[14] Case fatality rates are subject to considerable selection bias, as the denominator is mostly unknown. An overestimation could erode public trust and lead to more stringent public health measures than are warranted, inevitably taking resources away from other important healthcare programmes, such as screening and prevention services. The NICD has already reported an ~48% average weekly decrease in tuberculosis (TB) testing, which will have a negative impact on the national TB control programme.^[15] On the other hand, underestimating COVID-19 deaths would mean that appropriate resources are not made available and control systems are not optimised, with the unsavoury consequence of an increase in preventable deaths.

One method that has been proposed to overcome some of these limitations is measuring excess mortality. For example, to calculate excess mortality in Italy, deaths from 2015 to 2019 during the months of

January to March were compared with deaths in 2020 during the same months by using a counterfactual time series analysis. This showed 52 000 deaths in the 2020 time period, more than a factor of 2 higher than the official number of deaths reported.^[16]

In SA, from 6 May to 30 June 2020, an excess of 6 849 deaths were reported from natural causes among people >1 year old when using a revised base accounting for lower mortality during lockdown (Fig. 1).^[13] Over this same period, the SA government reported 2 504 COVID-19 related deaths.^[17] A similar trend was observed in the USA, with 87 001 estimated excess deaths from 1 March to 25 April 2020.^[18] Over this period the USA reported 55 263 COVID-19 deaths.

Learning from the past

SA's history related to misclassification of deaths during the period when the existence of HIV was questioned is a useful example for understanding the importance

of correctly classifying deaths in a pandemic situation. In 2006, SA had one of the largest populations of people living with HIV in the world.^[19] It is estimated that, at that time, 47.5% of people who died in SA died of HIV-related disease.^[20] The official national statistics, as published by Statistics SA, however, reported that HIV disease accounted for just 2.4% of all deaths in the country, making it only the ninth leading cause of death.^[21] A study published in 2011 showed that many HIV-related deaths were misclassified between 1996 and 2006, with misclassification ranging from 87.8% to 94.3%.^[20]

The misclassification of deaths has significant implications for health policy and resource allocation.^[22] D'Amico *et al.*^[23] warned that biases could distort, limit or inhibit the value of mortality data as an epidemiological resource. This was accurately demonstrated in the SA case, as the government argued that they could not treat a disease that was only the ninth leading cause of death as a national priority. In his 2016 letter, President Thabo Mbeki wrote:

"Why did it come about that so much noise was made internationally about the 9th leading cause of death in our country, with not even so much as a whimper about the 1st leading cause of death, tuberculosis? Why would the SA government, knowing the health condition of its own population very well, have been expected so to focus on the 9th leading cause of death as virtually to treat as less urgent and important the first eight (8) leading causes of death, even taken together?"

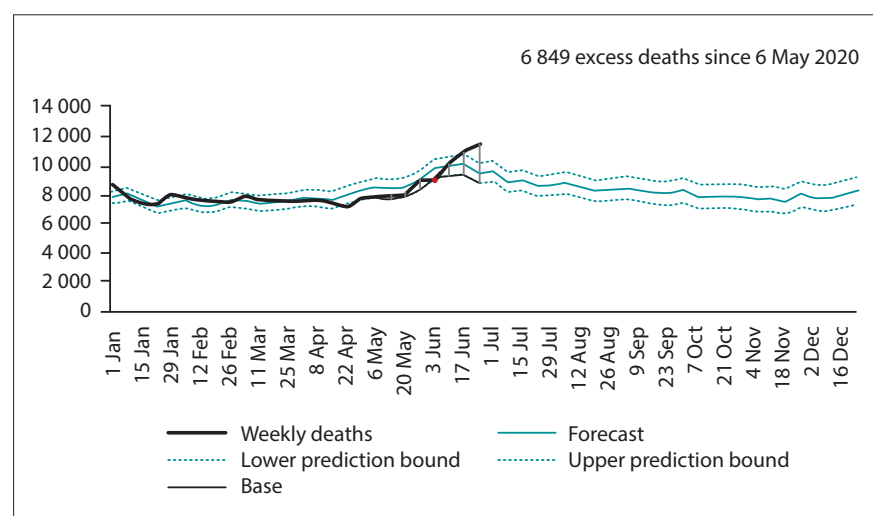


Fig. 1. South African weekly deaths from natural causes in people aged >1 year, 1 January - 30 June 2020. (Adapted from ^[14].)

Table 2. Place of death in the USA^[5]

| Indicator | All COVID-19 deaths (ICD-10 U07.1) | % |
|--|------------------------------------|-------|
| Healthcare setting, inpatient | 10 834 | 71.04 |
| Healthcare setting, outpatient or emergency room | 882 | 5.78 |
| Healthcare setting, dead on arrival | 21 | 0.14 |
| Deceased's home | 1 288 | 8.45 |
| Hospice facility | 162 | 1.06 |
| Nursing home/long-term care facility | 1 931 | 12.66 |
| Other | 132 | 0.87 |
| Total | 15 250 | 100 |

Misclassification of HIV-related deaths led directly to fewer resources being spent on dealing with the prevention and treatment of HIV. As a result of this denialism, the disease exploded from a prevalence of 14.2% in 1996 to 30.7% in 2016 among women attending antenatal care, more than 330 000 lives were lost because a feasible and timely HIV treatment programme was not implemented and 33 000 babies were born with HIV.^[24]

At the present stage it is unknown how the COVID-19 pandemic will manifest itself

in the SA population, where a large proportion of young people are immunocompromised due to HIV and malnutrition, among other causes, and many have risk factors for complications and death from COVID-19. This is further complicated by overlapping clinical syndromes as we enter the seasonal influenza and pneumonia season, and further complicated in HIV-infected people where infections such as *Pneumocystis jirovecii* pneumonia and *Mycobacterium tuberculosis* also have to be factored into the equation. As we deal with COVID-19, we need to be extra vigilant that we do not repeat the mistakes of the past.

Conclusion

To ensure an appropriate public health response to COVID-19, accurate data on COVID-19-related deaths are needed. Both underestimating and overestimating the number of infections and the case fatality rate can be detrimental to a proportionate public health response. An accurate antibody test might be beneficial, but no such test has yet been approved in SA, and the exact role of antibody testing has not been defined. In addition, given the limited capacity of the hospital and laboratory system, relying only on laboratory confirmation is not advisable. SA needs to develop clear guidelines on classification of deaths, and share this information with all those responsible for certifying deaths. Moreover, a universal classification system is needed for global surveillance.

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