



health

Department:
Health
REPUBLIC OF SOUTH AFRICA



Date:	25 April 2022		
To:	Dr MJ Phaahla, MP Honourable Minister of Health	From:	Ministerial Advisory Committee (MAC) on COVID-19

MONITORING COVID-19 BETWEEN ACUTE OUTBREAKS AND DECIDING ON APPROPRIATE AND TIMELY RESPONSES

Problem Statement and Task to Committee

1. What are the most sensitive and feasible indicators that would identify an acute COVID-19 outbreak at the earliest possible time point?
2. Once a potential new acute outbreak is identified, how can the likely clinical impact (particularly in terms of severe disease) be determined in a timely manner?
3. If a new acute outbreak does occur, what actions should be taken to mitigate the severity of the outbreak? Can this be done without declaring a national state of disaster?

Background/Current Information

Although the possibility of a new variant of SARS-CoV-2 with increased transmissibility, immune escape characteristics, and/or increased virulence, cannot be discounted entirely, future planning needs to be based on the most likely scenarios. COVID-19 is most likely to become endemic, with periodic acute outbreaks. A mitigation approach is therefore needed, with the ability to pivot to a more interventional stance if needed.

In the mitigation phase of the epidemic, the primary focus needs to be on identifying an **acute outbreak of COVID-19 that is of national importance**. An acute outbreak of this nature may be defined as “widespread transmission of SARS-CoV-2, causing a high burden of severe disease, hospitalisation or death, including amongst those with prior infection or vaccination.” Although a high caseload may be associated with a high number of cases of severe disease, recent experience with the Omicron variant has shown that this is not inevitable.¹⁻³ Given the high levels of population immunity to COVID-19 in South Africa – a consequence of both vaccination and past infections - a future acute outbreak may not necessarily be associated with a high burden of severe disease. Although a high caseload should prompt some public health actions (e.g. focusing on health systems preparedness), it is the early evidence of an increased burden of severe disease that should trigger immediate action.

In keeping with a “mitigation” approach, it is critical to have a clear plan of action for the period between acute outbreaks, in order that future outbreaks can be detected and responded to in the shortest time possible, and that a response can be tailored to the likely national importance of the outbreak. The capacity to mount an even more rigorous response, if warranted, must also be ensured in the longer term.

Evidence review and recommendations

QUESTION 1: What indicators would indicate an acute outbreak of national importance?

An intrinsic difficulty with the choice of indicators is that measures of severe disease lag behind increased caseload by 1-2 weeks. Thus the earliest indicators of an acute outbreak (see table below) are paradoxically the least useful in establishing whether further action needs to be taken, and later indicators of severity, while more useful, may not provide sufficient time to act effectively. The various indicators therefore need to be analysed as a group, understanding their advantages and disadvantages.

Bearing this in mind, the following indicators need to be considered at a subdistrict (if possible), district, provincial and national level:

INDICATOR	ADVANTAGES	DISADVANTAGES
Total COVID-19 caseload	Easy to monitor, provided that private and state laboratories continue to submit data to the National Institute for Communicable Diseases (NICD) or an equivalent body on a regular basis. COVID-19 is listed as a category 1 notifiable medical condition, so reporting should be done within 24 hours of a diagnosis.	A rising caseload does not necessarily indicate that a high burden of severe disease is likely. This indicator is also vulnerable to changes in testing volumes and strategies.
Percentage SARS-CoV-2 test positivity	Easy to calculate provided that private and state laboratories continue to submit data to the NICD or an equivalent body on a regular basis.	A rising percentage does not necessarily indicate that a high burden of severe disease is likely. This indicator is also vulnerable to changes in testing strategies, as well as changes in reporting practices (e.g. if positive tests are more likely to be reported than negative results, or if only polymerase chain reaction (PCR) and not antigen rapid diagnostic tests (Ag RDTs) are reported). The rate of change in the percentage test positivity over a 7 day period may be a more sensitivity indicator, but cutoff values would need to be agreed. Monitoring within a province where there is consistency of testing strategies may give a more accurate indication of caseload change.

<p>Changes in cycle threshold (Ct) value of SARS-CoV-2 PCR tests</p>	<p>This is a standard component of RT-PCR test reporting, but needs to be tracked nationally, and at disaggregated levels of the health system.</p>	<p>A falling Ct, which indicates rising viral loads, does not necessarily indicate that a high burden of severe disease is likely. As this is a new method, it is not well validated and thresholds have not been well established. It is also vulnerable to changes in testing strategies. It is only applicable to RT-PCR test results.</p>
<p>Wastewater surveillance of SARS-CoV-2 RNA levels⁴</p>	<p>This is an efficient sampling technique, as a single test gives a snapshot of SARS-CoV-2 burden from the community, town or city. Variants can be sampled <i>en masse</i>.</p>	<p>A rise in SARS-CoV-2 in wastewater does not necessarily indicate an increase in the burden of severe disease. This approach requires a dedicated surveillance programme (currently led by South African Medical Research Council). Only certain sites are sampled, and some houses are not connected to sewerage, so there is a risk of selection bias and patchy coverage. Single individuals may contribute to more than one catchment area through travel. Thresholds are not well defined, so interpretation of results is difficult due to uncertainties in viral shedding patterns. At present only 88 facilities are being sampled, using varying methods. Interpretation is also vulnerable to environmental changes, including dilution by rain run-off.</p>
<p>COVID-19 hospitalisations and Intensive Care Unit (ICU) admissions</p>	<p>This metric may indicate the burden of severe disease. Currently, all hospitalisations are reported on a voluntary basis to DATCOV, and all public and private hospitals are reporting.</p>	<p>These data are vulnerable to changes in testing strategies and volumes in hospitals. They also do not necessarily distinguish between admission <i>due to</i> COVID-19 and admission <i>with</i> (incidental) COVID-19 infection. Although DATCOV is reported to cover 100% of hospitals, the completeness and accuracy of data has been questioned.</p>

<p>Total hospitalisations & ICU admissions</p>	<p>This metric can offer a compelling indication of burden of severe disease, if paired with a contemporaneous rise in caseload.</p>	<p>This measure may underestimate disease burden in an acute outbreak, if other competing diagnoses are not being admitted to hospital. It also requires a dedicated hospital surveillance system with quick reporting of all admissions, something which is not currently reported to DATCOV. Private hospitals have not always been open to reporting on all admissions.</p>
<p>Oxygen utilisation trends</p>	<p>Offers a sensitive and specific marker of COVID-related severe disease burden.</p>	<p>This requires centralised reporting, but also needs to take into account the variety of oxygen supply mechanisms across different types of facilities and locales. It also assumes that oxygen therapy remains a sensitive indicator of severe COVID-19 disease with a new variant. Its specificity may be suboptimal in the face of outbreaks of other respiratory viruses (e.g. influenza).</p>
<p>Genomic surveillance programmes</p>	<p>A new variant detected at rapidly rising frequency may offer early indication of a possible new variant of concern or a new sublineage. Analysis may also provide early indications of variants or sublineages which may be at high risk of immune escape (when combined with an analysis of reinfection hazards) or increased transmissibility.</p>	<p>A rise in frequency of a new variant or sublineage does not necessarily indicate that a high burden of severe disease will occur. Such surveillance programmes may be vulnerable to delays in processing and are expensive. Limited sampling may bias interpretation of the results. Early extrapolation of genotypic characteristics to phenotypic effects in a human population is currently difficult and potentially inaccurate.</p>
<p>Analysis of <i>in vitro</i> immune response to new variants</p>	<p><i>In vitro</i> data can provide an indication of immune escape from either vaccination or past infection.⁵⁻⁷</p>	<p>Antibody neutralization assays correlate moderately well with protection from infection, but not protection from severe disease. T-cell assays do not correlate well with severe disease protection.⁸</p>

The indicators of disease burden should be stratified by age and geographic level, in order to optimally define the characteristics of the outbreak. An increase in caseload should be communicated as not being a concern unless there are also indications of increased severity.

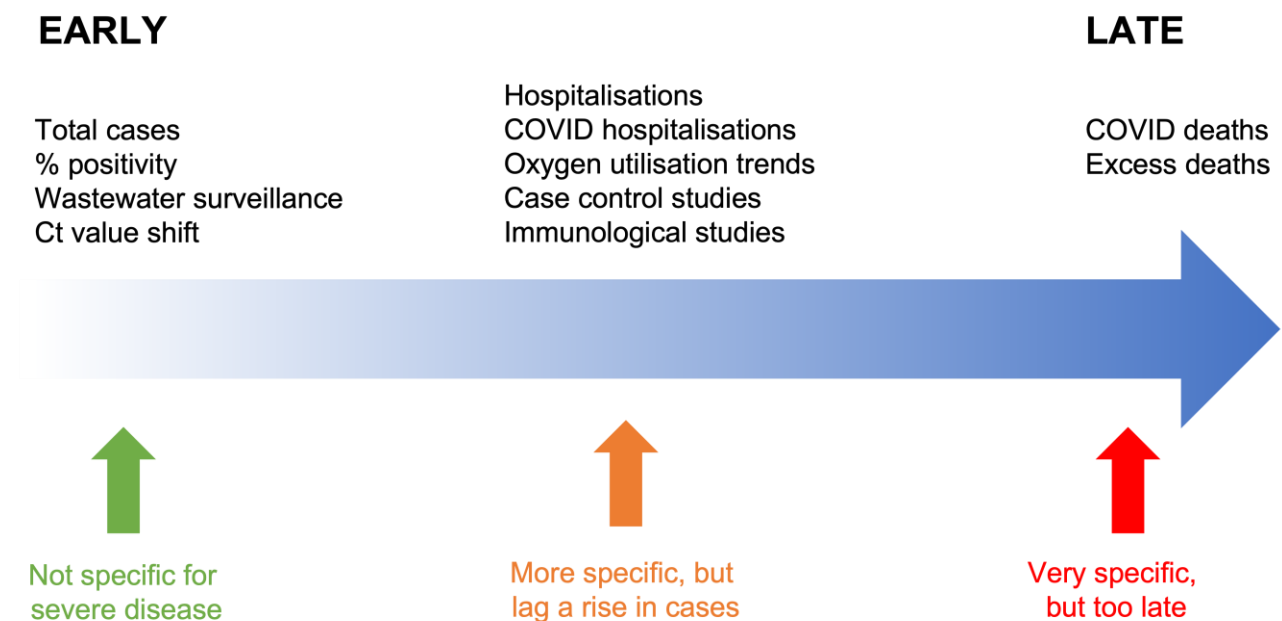


Figure 1 – Range of indicators

QUESTION 2: What response is needed if an acute outbreak is thought to be likely?

The priority at this stage would be to determine the likely burden of severe disease as rapidly as possible. Some indications may be gleaned from national and international data:

1. **National** – COVID hospitalisations, total hospitalisations, oxygen utilisation trends, deaths.
2. **International** – where a variant has first been described in another part of the world, data on severity may already be available, and should be used.

If the available national and international data are deemed insufficient, a rapid **case-control study** can be considered to establish disease severity and potential immune escape of the new variant compared to the previous one. Linkage between national databases of tests, hospitalisations and vaccinations is essential for this task.

Another key aspect of the acute response should be to **rapidly scale up the volume and speed of SARS-CoV-2 genomic surveillance**, targeting the geographical areas where the caseload is rising. Although a new variant or sublineage's arrival does not necessarily portend a substantial burden of severe disease, understanding whether a change in genomics is driving the acute outbreak is important for many reasons. These include allowing for speculative extrapolations from genotype to phenotype and indicating the need to perform immunological studies on the new variant (e.g. antibody neutralization assays). Sustainable funding needs to be provided to maintain the capacity to do genomic sequencing on sufficient numbers of COVID-19 cases within a timeframe that is likely to be useful in an acute outbreak (ideally less than 1 week from the time of testing).

COVID-19 surveillance should be incorporated in a sustainable way into routine respiratory pathogen surveillance systems (e.g. SARI surveillance, currently conducted by NICD) to provide unbiased data that is not vulnerable to changes in testing volumes, strategies and practices. If the SARI network is used, sustainable funding should be provided to expand this surveillance system to all provinces.

Furthermore, if a new variant is detected, it is vital to **establish whether the sensitivity of the RT-PCR and rapid antigen tests is impaired**, if this is not already known.

QUESTION 3: What mitigation strategies are recommended if a high burden of severe disease is thought to be likely?

A rising caseload alone (as evidenced by total cases, percentage positivity, rising wastewater viral burden, or falling cycle threshold values) does NOT warrant further action in and of itself. However, more intensive restrictions and enhanced mitigation efforts can be justified if a high burden of severe disease is shown to be likely. Should it be deemed likely that the integrity of the healthcare system is under threat, the following measures can be considered:

- 1. Vaccination booster drive according to immunisation guidelines** –primarily targeting those individuals at the highest risk of severe disease (age >50 and/or comorbidities). Given that it may take ~2 weeks for a protective effect to be seen, this should occur as soon as possible, and can be promoted as soon as an acute outbreak is thought to be likely, even before the clinical effects on severe disease are known.
- 2. Linkage between vaccination coverage data (EVDS), testing data (as reported to NICD) and hospital admission data (DATCOV)** should be strengthened so that the designated agency has access to all components in an acute COVID-19 outbreak to rapidly assess the likely severity of disease and the likely importance of a new outbreak.
- 3. Securing of adequate quantities of essential medicines** – as identified by National Essential Medicines List MAC on COVID-19 Therapeutics. Currently, the key medicines for severe cases would be systemic corticosteroids, low-molecular weight heparins and baricitinib, but other medicines may be considered (e.g. tocilizumab, antivirals).
- 4. Strengthening of oxygen supplies and oxygen supply chain** – maintaining an effective oxygen supply monitoring system and close liaison with suppliers is also key.
- 5. Ordering of sufficient consumables required for a severe COVID-19 outbreak** – e.g. personal protective equipment (PPE), oxygen delivery tubing and masks.
- 6. Putting surge capacity strategies on standby** – e.g. additional beds, redeployment of staff, reduction of elective surgeries, public-private partnerships to alleviate bed capacity shortfalls.
- 7. Efficient public communication about mask wearing, avoidance of large gatherings, and ventilation and spacing in indoor venues.** The focus should primarily be on high risk individuals, with recommendations being favoured over mandates – e.g. high risk individuals to consider a mask in public (preferably a surgical or N95 mask), and to avoid large public gatherings and public transport if possible. If the severity of the acute outbreak is thought sufficient to justify additional measures, the above advice can be extended to all members of the public, and/or be made mandatory.
- 8. Restrictions on the sale of alcoholic beverages** – this should ONLY be considered to rapidly decongest the ICU/high care beds available if these are becoming overwhelmed during an acute COVID outbreak.
- 9. New restrictions on school attendance** - should be introduced as an intervention of last resort, noting the negative impact of such restrictions on children’s education, development and mental health.

Can the actions listed be implemented without declaring a national state of disaster?

Draft Regulations issued in terms of the National Health Act and International Health Regulations Act are currently awaiting public comment. Where possible, restrictions and responses should be enabled without the declaration of a state of disaster. However, that option of reinstatement remains available, if needed. A state of disaster can also be declared at a district or provincial, rather than a national level, although this introduces new complexities. Restrictions on the sale of alcoholic beverages and significant restrictions on business and educational activities, or mandatory interventions at a population-wide level require intergovernmental action and co-ordination, and would seem to warrant invocation of the Disaster Management Act. Any restrictions in citizen’s rights need to pass the test posed by section 36 of the Constitution.

Rationale for recommendations

- Although the emergence of a new variant of SARS-CoV-2 cannot be ruled out, COVID-19 is expected to become endemic. Endemicity implies continued transmission of the virus, possibly with seasonal or other acute outbreaks.
- In the face of considerable population immunity, a rising caseload by itself does not necessarily indicate that an outbreak will lead to a substantial amount of severe disease (hospitalisations and deaths - i.e. to an “acute outbreak of national importance”). The primary focus for any public health measures should be to mitigate the burden of severe disease due to COVID.
- Early warning of the possibility of an acute outbreak of national importance is crucial, but no single indicator suffices in this regard. Combining information from a range of indicators can help to identify an acute outbreak of national importance, and to respond in a timely and effective manner.
- Maintaining the capacity to provide timely indicators of severe disease is crucial, as is the ability to rapidly activate additional resources to manage an acute outbreak of national importance.

Thank you for consideration of this advisory.

Kind regards



PROF KOLEKA MLISANA

CO-CHAIRPERSONS: MINISTERIAL ADVISORY COMMITTEE ON COVID-19

DATE: 22 April 2022

CC:

- » **Dr SSS Buthelezi (Director-General: Health)**
- » **Dr N Crisp (Deputy Director-General: National Health Insurance)**



PROF MARIAN JACOBS

Disclaimer: As stipulated in its Terms of Reference, the MAC on COVID-19 is an advisory Committee to the Minister of Health and does not have any delegated powers to act on behalf of, or to commit, the Minister or Government to any actions. Recommendations offered by the MAC on COVID-19 constitute evidence-informed advice only and do not represent final decisions of the Minister of Health or government.

REFERENCES

1. Davies M-A, Kassanje R, Rosseau P, et al. Outcomes of laboratory-confirmed SARS-CoV-2 infection in the Omicron-driven fourth wave compared with previous waves in the Western Cape Province, South Africa. *medRxiv* 2022: 2022.01.12.22269148.
2. Wang L, Berger NA, Kaelber DC, Davis PB, Volkow ND, Xu R. COVID infection severity in children under 5 years old before and after Omicron emergence in the US. *medRxiv* 2022: 2022.01.12.22269179.
3. Ferguson N, Ghani A, Hinsley W, Volz E. Report 50: Hospitalisation risk for Omicron cases in England. *DOI* 2021; **10**: 93035.
4. Pillay L, Amoah ID, Deepnarain N, et al. Monitoring changes in COVID-19 infection using wastewater-based epidemiology: A South African perspective. *Sci Total Environ* 2021; **786**: 147273.
5. Moyo-Gwete T, Madzivhandila M, Makhado Z, et al. Cross-Reactive Neutralizing Antibody Responses Elicited by SARS-CoV-2 501Y.V2 (B.1.351). *New England Journal of Medicine* 2021; **384**(22): 2161-3.
6. Wibmer CK, Ayres F, Hermanus T, et al. SARS-CoV-2 501Y.V2 escapes neutralization by South African COVID-19 donor plasma. *Nature Medicine* 2021; **27**(4): 622-5.
7. Khan K, Karim F, Cele S, et al. Omicron infection of vaccinated individuals enhances neutralizing immunity against the Delta variant. *medRxiv* 2022: 2021.12.27.21268439.
8. Keeton R, Tincho MB, Ngomti A, et al. T cell responses to SARS-CoV-2 spike cross-recognize Omicron. *Nature* 2022; **603**(7901): 488-92.