Collateral damage of the COVID-19 pandemic: Exacerbation of antimicrobial resistance and disruptions to antimicrobial stewardship programmes?

Termed an 'invisible pandemic' by the World Health Organization (WHO), antimicrobial resistance (AMR) could result in 10 million deaths per year by 2050 if unchecked.[1] The World Bank has reported that AMR could also result in increased deaths during pandemics of bacterial and viral diseases.[2] In the midst of the current COVID-19 pandemic, there are significant concerns that the pandemic itself will result in increased numbers of deaths associated with secondary bacterial and fungal infections caused by organisms that frequently harbour antimicrobial resistance genes. This commentary is intended to promote the first strategic objective of the WHO's global action plan on AMR, which is to improve awareness and understanding of AMR.[3]

There is sufficient historical evidence demonstrating that respiratory viral infections frequently precede and predispose to superimposed bacterial infections. This was demonstrated in the 1918 H1N1 influenza pandemic, the severe acute respiratory syndrome coronavirus (SARS)-CoV-1 outbreak, and the 2009 influenza pandemic, where mortality was frequently due to secondary bacterial pathogens.[4,5]

Notably, pandemic viral pneumonias have demonstrated clinical and radiological presentations similar to other pneumonias such as those caused by *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Klebsiella pneumoniae*, *Staphylococcus aureus*, *Mycobacterium tuberculosis*, other seasonal respiratory viruses, and fungi such as *Pneumocystis jirovecii*. With South Africa (SA)'s concurrent HIV and tuberculosis epidemics, teasing out SARS-CoV-2 from other aetiological agents is already proving to be a challenge. Empirical antimicrobial treatment of all possible causes in the severely and critically ill patient is therefore the default option.

Published data so far indicate that the primary use of antimicrobials for patients admitted with COVID-19 is high. Large published case series have revealed prescription rates ranging from 56% in the International Severe Acute Respiratory and emerging Infection Consortium (ISARIC) series to 95% as reported by Zhou *et al*.[6-8] Equally concerning, however, are large case series that omit data on antimicrobial prescribing altogether.[9,10]

There is evidence of antimicrobial use for healthcare-associated infections, as the length of hospital stay in severely ill COVID-19 patients is reported to be 10 - 14 days, with duration of intensive care admission ranging from 4 to 8 days.[7,9] Secondary infections have been reported in 15% of all patients, and in 50% of those who died,[7] whereas a multicentre study by Feng *et al*.[11] demonstrated a rate of 35% in the critically ill, with a higher likelihood of death in those receiving antibiotics. Both Guan *et al*.[12] and Feng *et al*.[11] also report that ~8% of critically ill patients received antifungal agents.

Antimicrobial stewardship (AMS) is defined as a co-ordinated approach to ensure appropriate antimicrobial use to improve patient outcomes, limit the emergence of resistant pathogens and safeguard antimicrobials for the future.[13] In SA, AMS programmes have been hampered by periodic lack of access to antimicrobials and suboptimal infection prevention and control measures. However, despite significant challenges in implementation and maintenance of robust AMS programmes, some progress has been made towards improving AMS, including formation of provincial and hospital AMS committees and AMR surveillance and reporting.

The SARS-CoV-2 pandemic has, however, shifted even the marginal AMS resources towards the pandemic response. Infectious diseases physicians, already a critically scarce resource in SA,[14] are now in the frontline of the fight against COVID-19, and this is significantly impacting on AMS-related activities in hospitals. Furthermore, most public sector hospitals do not have enough pharmacists to dedicate any of them exclusively to AMS; this was the case even prior to the pandemic.

The extent of the involvement, if any, of AMS teams in pandemic planning at hospital level in SA is unknown. An informal Twitter poll conducted by Stevens *et al*.[15] in the USA found that only 30% of respondents reported direct involvement in SARS-CoV-2 planning at their institutions.

The promotion of telemedicine consultations to reduce contact with potentially infected patients may have an additional effect on AMS.[16,17] In the absence of broadly available, cost-effective, rapid syndromic diagnostic panels, both general and specialist practitioners now face the additional challenge of determining the nature of the illness. Telehealth in the SA private sector, as described by Ray *et al*.,[18] could potentially cause a spike in inappropriate prescriptions and AMR.

There are additional effects in terms of the 'One Health' approach to AMS. With the economic impact of the pandemic on agriculture and agricultural activities, an increase in use of antibiotics as growth promoters to sustain production may occur. Measures to monitor agricultural antimicrobial use require strengthening to avoid a spike in AMR related to animal agriculture use.[19]

The intensity of the COVID-19 pandemic, with high volumes of patients presenting over short periods of time, could result in a spike in antimicrobial consumption with increased AMR development in wastewater.[20]

Traditional AMS principles apply to the use of antibiotics for suspected and confirmed COVID-19 patients. Prior to initiation of antimicrobials, suitable specimen collection and utilisation of available diagnostics to exclude other causes of pneumonia are crucial. If possible, antibiotics should be reserved for cases where it is not possible to differentiate between bacterial and viral causes of pneumonia. Antimicrobial therapy must be reviewed 48 - 72 hours after initiation, once microbiological test results are available. Treatment duration must be short and a switch from IV to oral therapy should occur where possible.

Regarding AMS activities, where not already the case, AMS teams should be involved in development of COVID-19 management protocols. Regular online multidisciplinary AMS meetings/ward rounds are a possible approach for discussions around antimicrobial management and interpretation of microbiology results. It is also vital during this time that AMS activities in non-COVID-19 sections of healthcare facilities continue.

In the private sector outpatient setting, enhanced ordering of rapid multiplex or syndrome-based diagnostic assays during telemedicine visits may reduce inappropriate antimicrobial prescribing, as well as allay anxiety among patients.

Regarding diagnostics during the pandemic, it is important for accurate, sensitive and specific rapid point-of-care tests to

be available in consistent and steady supply. Appropriate patient management is reliant on a SARS-CoV-2 result obtained soon after hospital admission. In addition, rapid assays and reliable diagnostics for other pathogens causing pneumonia and healthcare-associated infections should be more accessible, particularly in the public sector, to reduce prolonged use of broad-spectrum antimicrobials.

Diagnostics have been deemed a 'critical enabler of health for all' by the WHO's Tedros Adhanom Ghebreyesus, but the focus on diagnostics seems to be highlighted only during pandemics. Once media interest wanes, it is hoped that interest in diagnostics will not once more disappear.[21]

It must be noted that the current intense focus on SARS-CoV-2 testing in these relatively early stages of the SA epidemic has, at least in the public sector, been to the detriment of microbiological sample collection and analysis of patients with other conditions.

Finally, the issue of lasting protective immunity against SARS-CoV-2 remains as yet undefined. Answering this question will require that patients be followed up for a minimum of 1 year, with the added possibility that recurrent seasonal epidemics may occur over the next few years. Lack of protective immunity may be exacerbated by the current lack of effective treatments and vaccines.[22]

If antimicrobial use is not adequately addressed early in the pandemic, continued excessive antibiotic prescribing will add an additional burden to already strained AMS programmes.[14] With implementation of SA's National Strategic Framework on AMR still in its infancy, it is imperative that this be addressed sooner rather than later.

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