Key considerations on the potential impacts of the COVID-19 pandemic on antimicrobial resistance research and surveillance

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Antibiotic use in severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) patients during the COVID-19 pandemic has exceeded the incidence of bacterial coinfections and secondary infections, suggesting inappropriate and excessive prescribing. Even in settings with established antimicrobial stewardship (AMS) programmes, there were weaknesses exposed regarding appropriate antibiotic use in the context of the pandemic. Moreover, antimicrobial resistance (AMR) surveillance and AMS have been deprioritised with diversion of health system resources to the pandemic response. This experience highlights deficiencies in AMR containment and mitigation strategies that require urgent attention from clinical and scientific communities. These include the need to implement diagnostic stewardship to assess the global incidence of coinfections and secondary infections in COVID-19 patients, including those by multidrug-resistant pathogens, to identify patients most likely to benefit from antibiotic treatment and identify when antibiotics can be safely withheld, de-escalated or discontinued. Long-term global surveillance of clinical and societal antibiotic use and resistance trends is required to prepare for subsequent changes in AMR epidemiology, while ensuring uninterrupted supply chains and preventing drug shortages and stock outs. These interventions present implementation challenges in resource-constrained settings, making a case for implementation research on AMR. Knowledge and support for these practices will come from internationally coordinated, targeted research on AMR, supporting the

preparation for future challenges from emerging AMR in the context of the current COVID-19 pandemic or future pandemics.

Keywords: antimicrobial resistance, COVID-19, stewardship, surveillance, public health

Introduction

The COVID-19 pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has affected all aspects of society, including actions to address antimicrobial resistance (AMR). The pandemic has revealed that increased strain on healthcare systems can lead to increased, often inappropriate antibiotic use[1–4] and deprioritisation of AMR surveillance and antimicrobial stewardship (AMS).[5]

Widespread broad spectrum antibiotic use in patients with COVID-19 has been reported.[4] Detailed data are lacking but preliminary data (reviewed below) suggest that outpatient antibiotic use may have decreased in certain settings. This may be due to diminished access to healthcare because of lockdowns and physical distancing, or to decreased community spread of other infections in some settings, or a combination of both. However, treatment of the majority of hospitalised COVID-19 patients with antibiotics early in the COVID-19 pandemic increased antibiotic use compared with the prepandemic period.[3,6–8]

Globally, there has been a diverse response to SARS-CoV-2 due to differences in the severity of the outbreaks, local and national policies, available resources, cultural aspects and social awareness. However, most countries tried to ensure that their healthcare systems were able to cope with a high predicted number of severe cases but many different practices were employed, ranging from strict, enforced lockdowns to vague and suggestive physical distancing recommendations. Some of the most prominent epicentres were in places where AMR is a challenge[9,10] and where many of the factors that are associated with severe SARS-CoV-2 infection, including underlying conditions, advanced age, group housing and residence in a living facility for older people, are also linked to an increased risk of multidrug-resistant infections.[11,12]

We provide an overview of factors during the pandemic that may influence AMR and provide recommendations for antibiotic use, data collection, surveillance and stewardship, research and policy.

Excessive hospital use of antibiotics did not align with microbiological investigation

The interplay of inappropriate and excessive antibiotic use and (lack of) access to appropriate treatment was challenging in the initial stage of the pandemic. Coinfections are infections caused by pathogens presenting concurrently with COVID-19 upon hospital admission or upon COVID-19 diagnosis, while secondary infections are infections occurring after the start of COVID-19 disease and are usually healthcare-associated and exacerbated by invasive procedures and the use of immunosuppressant drugs.[13,14] Suspected coinfections drive empirical therapy at hospital admission, while secondary infections drive antibiotic use after hospital admission and are potentially more preventable through adequate infection prevention and control measures.

Meta-analyses revealed that 7–8% of admitted COVID-19 patients were diagnosed with a bacterial or fungal infection[2,15,16]; these were more frequent in intensive care unit (ICU) patients (8–14%) than in patients in other wards (4–6%). Coinfections occurred in only 3.5% of patients (95% CI 0.4 to 6.7%), while secondary infections occurred in 14.3% (95% CI 9.6 to 18.9%).[16,17] The most commonly reported bacterial co-pathogens were *Mycoplasma* species, *Haemophilus influenzae* and *Pseudomonas aeruginosa*.[15,16] In these studies, the criteria for coinfections and sampling for co-pathogens were heterogeneous, and prospective, well-designed studies using appropriate definitions are needed.

Despite low reported levels of bacterial infections, antibiotic use in COVID-19 patients was considerably high: 71.9% (95% CI 56.1 to 87.7%) of COVID-19 patients received antibiotics.[16] Importantly, 74% of the antibiotics reportedly prescribed were fluoroquinolones and third-generation cephalosporins. Studies showed an increase in the consumption of amoxicillin-clavulanic acid during the first weeks of the pandemic, mostly to empirically cover coinfections, and a later increase in the consumption of broader spectrum drugs, mostly to cover secondary infections.[3,17] At a hospital outside of a COVID-19 epicentre in the USA, antibiotic days of therapy per 1000 bed days of care significantly increased from March to June 2020. Increases were most significant for macrolides and non-antipseudomonal penicillins, agents recommended at the hospital as first-line treatment for community-acquired pneumonia.[8] Paradoxically, the empirical and wide-scale antibiotic use in COVID-19 patients may have led to an underestimation of coinfections.[18] Data from low- and middle-income countries (LMICs) reporting differences in antibiotic use and the presence of coinfections are currently lacking. The need to conduct studies on the worldwide evolution of AMR during the COVID-19 pandemic with a focus on the challenges of LMICs was recently reviewed by Lucien et al.[19]

The discrepancy between the proportion of patients with bacterial coinfections or secondary infections and those receiving antibacterial agents has several hypothetical explanations, including the reaction to the medical uncertainties in the best management of COVID-19 patients during the first weeks of the pandemic. The risk of contracting SARS-CoV-2 by medical staff, the strained health resource and supply chain challenges also reduced the collection of samples for microbiological evaluations,[20] reducing the opportunities for informed therapy instead of empirical antibiotics. Reduction in antibiotic stewardship activities[2,21] is likely related to the redirection of healthcare resources and specialists to the COVID-19 response.

To evaluate the appropriateness of antibiotic use in the first stage of the COVID-19 pandemic it is important to consider specific criteria for different patient populations, such as ventilated critically ill patients, hospitalised but non-ventilated patients, outpatients and the COVID-19-naïve population. Although the inci-

dence of bacterial coinfections in critically ill COVID-19 patients is low, the infections tended to present during the later stages of hospitalisation, and these infections result from microbiota of the respiratory tract or from the nosocomial environment.[22] The diagnosis of ventilator-associated pneumonia (VAP) is complex, both from clinical and aetiological perspectives. Starting early treatment with antibiotics after obtaining adequate samples has been recommended in patients with haemodynamic instability or severe hypoxemia, and patients with a high pretest probability of VAP according to clinical criteria.[23] However, treatment can be delayed if these criteria are not present.

Further studies using molecular techniques on samples from ventilated and non-ventilated COVID-19 patients are needed, with current experience suggesting that coinfections and secondary infections are likely to reflect local microbiology and resistance patterns.[24,25] However, limitations in safe sampling methods on patients with severe COVID-19 inhibit the possibility of diagnosing respiratory infections, which is difficult without pulmonary lavage.

It is currently unknown whether new or evolving antibiotic resistance in areas with low previous rates will emerge in COVID-19 patients, but this should be examined in retrospective and prospective clinical and microbiology studies.

Community consumption of antibiotics is likely to have significantly changed during the pandemic

The vast majority of COVID-19 patients (80%) have uncomplicated illness and are managed on an outpatient basis. Although there is minimal literature on the management of COVID-19 cases in the community, there exists well-documented inappropriate antibiotic use in self-limiting, viral upper respiratory tract infections in non-hospitalised settings.[26,27] Inappropriate antibiotic use is thus equally, if not more likely, in community settings, especially where antibiotics are accessible online, without prescription and from informal drug sellers.

Studies have reported decreased antibiotic use in COVID-19 outpatients[28] and in hospitals outside of COVID-19 epicentres.[29] There is a need to monitor the relationship between changes in antibiotic use in the community and potential future adverse effects. Removal of physical distancing and lockdowns could lead to an increase in the overall incidence of infections and the number of individuals seeking healthcare, which would likely result in an increase in antibiotic prescriptions. An increase in levels of seasonal influenza and other respiratory viruses would further accentuate this. The use of surveillance systems and differential diagnostics that are simple, affordable and timely, combined with support for research projects, would determine where antibiotics are overused and the impact of antibiotic use on the epidemiology of drug-resistant infections. This is particularly needed in LMICs, where existing data on antibiotic use and resistance are limited.

Factors affecting the spread of bacterial pathogens and AMR

The impact of the COVID-19 pandemic on AMR is unknown.[21,26–32] An overview of factors, including changes in infection control practices that could affect AMR, are summarised in Table 1. The focus on the importance of hand hygiene and the correct use of personal protective equipment (PPE) would likely have positive impacts, while cohorting due to high patient numbers[33] and shortages in the availability of PPE[34] probably promote the transmission of multidrug-resistant bacteria. Existing data already available should be used to better inform antibiotic prescription in the COVID-19 pandemic. In a recent bulletin, the WHO recommended that AMS activities should be integrated as a component of the COVID-19 pandemic response across the broader health system through five measures, including implementation of a research agenda to stem the emergence of AMR infections and diseases.[35]

Disruption of surveillance of AMR in hospitals during the COVID-19 pandemic

Personnel, resources and attention were redirected from AMR surveillance to COVID-19 diagnosis, tracking and tracing. The sharing of raw data from surveillance efforts, including by companies, such as GSK's SOAR programme, Merck & Co, Inc.'s SMART programme, Shionogi's SIDERO-WT and the Shionogi Japanese Surveillance Studies Programme, would enable open research and analysis pertaining to global AMR surveillance. These data could help researchers better understand potential disruptions in surveillance efforts, and highlight and analyse any potential resistance patterns that might have emerged because of inappropriate use of antibiotics linked to COVID-19 and secondary infections. While the WHO's Global Antimicrobial Resistance Surveillance System (GLASS) helps to analyse and report global data, the Access to Medicine Foundation's AMR Benchmark found that companies included in its scope of research had data from 38 countries not covered by GLASS, at the time of publication an essential piece of the global AMR surveillance puzzle and important for understanding the impact of COVID-19 on AMR.[36]

Disruption of research during the COVID-19 pandemic

Research in non-COVID-19 fields including AMR has been deprioritised, delayed and even halted. Delays in research projects limit the ability of scientists to meet contractual grant deadlines and targets within projects. Limitations on international travel have halted the sharing of information at workshops and conferences, and created delays in international networking activities. There have been disruptions in the review, processing and proofing of non-COVID 19 manuscripts. Many funding agencies across the globe have given research grant extensions; however, the long-term impact of the pandemic on AMR research has yet to be understood and factors such as the effect on early-career researchers may take years to manifest. To ensure that AMR research continues to be adequately prioritised and financially supported, it is important to prioritise funds for AMR research at both national and international scales, and it may be necessary to implement targeted AMR fellowship schemes, and new research support mechanisms, to ensure career entry in the field.

The LMICs and resource-constrained settings

COVID-19 has illustrated how vulnerable our healthcare systems are. This is even more noticeable in LMICs and in resource-constrained settings that lack infrastructure and personnel and

Table 1. Interventions implemented for COVID-19 likely to have an impact on antimicrobial resistance (AMR) in the future

	Patient-related factors	COVID-19 management-related factors	Health-system related factors
Positive impact	• Personal hygiene/hand and respiratory hygiene • Environmental cleaning • Physical distancing • Altered health-seeking behaviour • Decreased travel	• Hand hygiene by HCW • Use of PPE • Physical distancing • Environmental cleaning • Universal masking	• Implementation of IPC policies • Implementation of AMS policies • Microbiology and pathology laboratory infrastructure with EQA • Isolation wards • Training of personnel on IPC measures
Negative impact	• Increased susceptibility to bacterial and fungal infections	• Increased antibiotic exposure, specifically broad-spectrum drugs • Increased risk of HAI due to invasive interventions and use of immunosuppressive agents • Reuse of PPE • Lack of isolation wards • Biocide use	• Non-compliance/breakdown of IPC and AMS policies • Deprioritisation of antimicrobial use and resistance surveillance • Overcrowding of patients • Absence of clear guidelines • Increase in telemedicine • Decreased laboratory capacity on AMR (antimicrobial susceptibility testing, surveillance cultures…) • Excess stress of healthcare providers

Abbreviations: AMS, antimicrobial stewardship; EQA, external quality assessment; HAI, healthcare-associated infections; HCW, healthcare workers; IPC, infection prevention control; PPE, personal protective equipment.

are not well prepared to deal with pandemics or other emergencies.[36–38] In many of these settings, infection rates, antibiotic use and consequent increase or decrease in antibiotic resistance may be very different. In addition, laboratory infrastructure, surveillance and diagnostic capacity for both COVID-19 and AMR are unreliable, and at times are unavailable in many LMIC settings. In addition, infection prevention and control policies, practice and personnel are noticeably suboptimal and, in many instances, unsustainable.[39] Expectations for regulated antibiotic use are difficult to enforce in those settings where there is poor access to antibiotics without prescription and substandard and counterfeit medicines are frequently available. Adding to this, sociobehavioural interventions such as physical distancing and hand hygiene are limited, and large proportions of the population are living hand to mouth, especially in areas with high population densities, such as informal settlements, where there is suboptimal access to clean water and sanitation services. In addition, co-managing multiple infectious disease threats simultaneously is a further challenge for LMICs. Initial reports show a more severe disease and higher death rate in patients coinfected with TB and COVID-19.[40] Unless current trends are reversed, the increasing levels of MDR TB will likely have a similar impact on LMICs in the future, with estimates suggesting that by 2050 drug-resistant TB will be responsible for 2.6 million of the total 10 million annual deaths associated with AMR.[40,41] An exit strategy from COVID-19 for many LMICs may not be pharmacologically based in the short term and more community-based strategies are currently being explored.[42]

Key recommendations for the future

The COVID-19 pandemic has magnified weaknesses in fighting AMR and there are many lessons that can be learnt from the current situation that will affect the ways in which AMR can be addressed. Knight et al. recently published an overview of the impact of the COVID-19 pandemic on AMR and made a call for action for the AMR community to consider the global perspective when dealing with this global health challenge.[43] Below, we describe recommendations to define a strong research agenda to facilitate this knowledge and enhance the understanding of beneficial and detrimental practices that drive or limit the spread of AMR. These recommendations are summarised in Figure 1.

Microbiological diagnosis of coinfections and secondary infections

To study the impact of the COVID-19 pandemic on AMR, it is critical to maintain existing screening and diagnostic systems, and to ensure appropriate collection of microbiological samples for guiding the individual management of patients. Research and innovation focused on developing diagnostic tests differentiating between bacterial infection and SARS-CoV-2 infection, or the use of multiplex diagnostic tests targeting viruses and bacterial pathogens, would prevent the overuse of antibiotics.

Collection of microbiological samples should be guided by clinical presentation and microbiological diagnostics. Practices to collect samples should guarantee the safety of healthcare
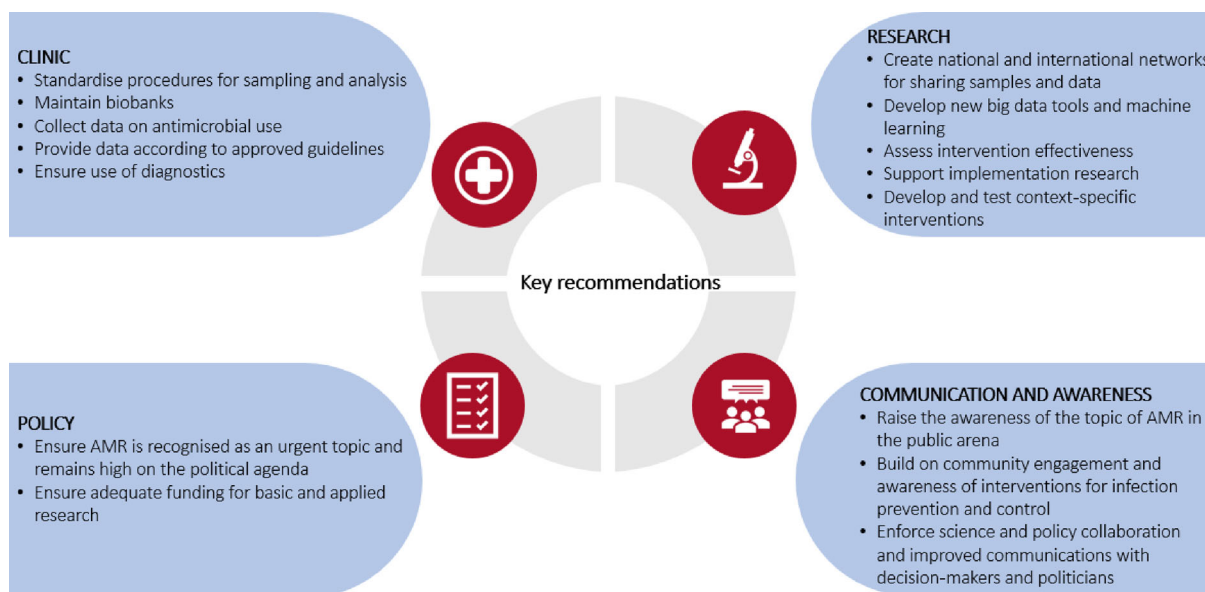
Figure 1. Key recommendations for continued support for antimicrobial resistance (AMR) research for clinical, research and policy stakeholders.

workers to the best degree possible. An important limitation of the available data is the heterogeneity in microbiological sampling, laboratory microbiological procedures and interpretation of results. Specifically, designed studies with routine collection of samples, appropriate microbiological procedures and adequate criteria for aetiological diagnosis should be performed. The development of standardised protocols by the WHO or a network of interested investigators for microbiological diagnosis of COVID-19-associated coinfections and secondary infections would be useful to ensure data integrity and comparability across study centres.

Samples for biobanks should be collected, using the appropriate informed consent, and many institutions are already collecting samples from COVID-19 patients for future studies. Networking will be important for the greater good of AMR research, with high quality data needed to link clinical case data to microbiology and ensure comparability between hospitals within and between countries.

Early in the COVID-19 pandemic, autopsies were infrequently conducted in patients who died with COVID-19 due to the risk of infection to pathologists and ancillary personnel.[44] As a result, limited microbiological information is available in individual hospitals. A minority of autopsies showed inflammatory changes using histopathology that is potentially consistent with bacterial or fungal bronchopneumonia,[45] but in the absence of microbiological studies, it is impossible to interpret these findings. Pooling of data and samples is needed to draw accurate conclusions regarding the ultimate causes of death, and to the role of bacterial coinfections.

Predictors (clinical, biomarkers) for bacterial coinfection and secondary infections

Research on the predictive ability of diverse clinical and laboratory investigations at hospital admission for coinfections is needed. Collection of comprehensive data must be standardised in prospective studies and in different profiles of patients, in association with appropriate microbiological sampling. This is critical for any retrospective research, including big data analysis; however, prospective collection of data with the objective of development and validation of predictive scores for bacterial coinfections is needed. Such scores might be useful in deciding which patients might be considered for antibacterial use at admission. Biomarkers such as C-reactive protein and procalcitonin (PCT) that have been used by clinicians to help in diagnosing bacterial infections may be elevated in severe COVID-19 patients,[31] which limits their use in defining the proper use and duration of antibiotic therapy. The clinical usefulness of PCT alone or in combination with other biomarkers should be optimised in prospective studies to develop protocols guiding antibiotic treatment of COVID-19 patients. For secondary infections, the usual protocols for nosocomial infections may be used. In addition, studies addressing the impact on outcome of empirical antibacterial coverage in different groups of patients must be designed and performed, as not all patients with coinfection need empirical antibacterial treatment.

Collection and analysis of global data on the use of antibiotics during the COVID-19 pandemic

Collection of antibiotic use data in COVID-19 and non-COVID-19 wards, as well as in the community, is needed. Recommended methods and indicators, as well as stratification for specific families and drugs, and for type of wards, are to be followed.[46–52] Analysis according to the AWaRE categorisation of antibiotics would provide invaluable information on whether the choice and/or quantities of antibiotics prescribed could potentially escalate antibiotic resistance. To detect variations in the consumption of some antimicrobials, monthly consumption comparisons with data from preceding years is needed.

When analysing changes in antimicrobial use, the confounding effect of changes in the case-mix occurring in hospitals, particularly during periods of high rates of COVID-19, must be considered. Therefore, collection of data allowing the control of confounders is also needed. Adequate statistical management of the data including the use of time series analyses is required to understand changes in antibiotic consumption among different healthcare and industrial sectors.

Data on the appropriateness of prescribing practices must also be considered, both in the context of treatment guidelines and stewardship principles. To evaluate the quality of prescription, national, regional or local guidelines must exist as a reference. Such guidelines would be subject to change as new evidence becomes available. In terms of AMS, diagnosis confirming non-viral aetiology, antibiotic choice, dose, dosing frequency, route, duration and de-escalation are important considerations.

Surveillance of AMR

Surveillance of resistance must continue and be reinforced, in both COVID-19 and non-COVID-19 patients. The key bacteria, resistance and specific mechanisms of resistance must be recorded with appropriate indicators (incidence density) on a regular basis.[48–52] Epidemiological data from patients colonised or infected with high-risk or emerging multidrug-resistant bacteria must be collected. Active surveillance for colonisation must be continued in high-risk areas (ICUs, haematological wards) and in high-risk patients, particularly when cohorting is used for COVID-19 patients.

Investigating the correlation between changes in antibiotic use during the pandemic and evolution and/or escalation of antibiotic resistance must be conducted considering information on hospital structural changes, variations in the composition of the case-mix of the wards, and adjusted by changes in diagnostic procedures and clinical algorithms. Carefully analysing global AMR surveillance data, particularly from surveillance programmes in LMICs where national efforts to monitor resistance may be limited, will be critical to understanding potential emerging patterns of resistance and the contributing factors behind them. All partners collecting data, including pharmaceutical companies, should be encouraged to share the raw data of their programmes on open data platforms.

AMS interventions

It is critical to ensure that AMS programmes remain active. Due to the multidisciplinary approach implemented in many hospitals for the management of COVID-19 patients, stewardship programmes should be reinforced, with activities directed to non-infectious disease physicians, including educational activities, prospective audits of prescriptions and feedback of data.

Of particular importance is diagnostic stewardship of community-acquired pneumonia by general practitioners to control inappropriate usage of antibiotics, not only in patients not infected by SARS-CoV-2, but even more importantly in those suffering from mild COVID-19 and treated at home. Measuring the impact of the interventions should be performed using suitable methods.[53] The endpoints may be antibiotic consumption, appropriateness of use, rates of adverse events of antibiotics, overall mortality, duration of hospital stay, rates of antibiotic resistance and need for readmission after discharge. It would be most suitable to design multicentre, cluster randomised trials or well-executed quasi-experimental designs with time series analyses.

Using a multidisciplinary approach to support AMR stewardship and surveillance

Sharing of data and samples is strained by the academically driven weakness of 'publish or perish'. Although there might have been a disruption to some AMR surveillance activities, the new multidisciplinary networks of infectious disease clinicians, microbiologists and other healthcare workers, formed to attend to COVID-19 patients, have the potential to continue working together to address AMR in the future. Large multinational registries that have been built to support COVID-19 research could be leveraged for AMR research.

Continuing public and political engagement on infectious diseases and promotion of research

Communication between governments, healthcare professionals, scientists, the media and the public has been a key component in the pandemic response.[54] The AMR research community is in an ideal position to work with the media and policymakers to raise awareness of the topic of AMR in the public arena and build on community engagement and awareness of the importance of interventions in sanitary infrastructures,[55] handwashing, disinfection, social distancing when ill or avoiding unnecessary use of antibiotics. Harnessing the public understanding of the relevance of infectious diseases towards the long-term pandemic of AMR could have major implications for promoting good practices about AMR and the control of transmission.

A critical lesson from the COVID-19 pandemic is the importance of embedding research in the response, which is particularly challenging to perform in the pandemic situation. Supporting good quality implementation research could help to understand how and why an intervention has been successful. As global solidarity efforts and pledges emerge to address COVID-19, so too must efforts to openly share research and data. Cooperation and coordination on behalf of the private sector could contribute to a more fulsome picture of potential changes in antibiotic use in all corners of the world. When it comes to AMR, a research agenda that can generate context-specific solutions for decision-makers will be key to successful preparedness.

Conclusions

The COVID-19 pandemic has demonstrated the economic and societal impact of an uncontrolled infectious disease, an impact that is similar to what has been predicted for AMR in multiple reports. Among the many consequences of the COVID-19 pandemic, there is the important potential impact on AMR through the change in antibiotic use and health-seeking behaviour, as well as infection prevention and control practices. Determining these effects on AMR is critical for both promoting

good practices and prioritising research. Being proactive, in the context of predictable AMR, will allow us the luxury of not having to be reactive in the future, as we currently have to be with COVID-19. However, if not addressed, AMR will likely have similar consequences but over a longer timescale.

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