CASE STUDY   MAY 2021

AMR case study: the impact of COVID-19

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Applied Microbiology International is a global membership organization that seeks to bring the international microbiology community together to advance scientific impact. We are the oldest microbiology society in the UK and with more than half of our membership outside the UK, we are truly global, serving microbiologists based in universities, private industry and research institutes around the world.

Increased antibiotic prescribing as a result of increased telemedicine appointments has also been seen in general practice and dentistry.

Meta-analysis of COVID-19 papers suggests that a low proportion of hospitalised patients develop a secondary bacterial or fungal infection (7%–8%).[1, 2]

In spite of a low rate of secondary bacterial/fungal infections, antimicrobial use is common in COVID-19 patients. This includes common usage of broad-spectrum antibiotics.

Antimicrobial stewardship activities have been disrupted in the UK and globally.

AMR has also been affected in complex ways.

Both monitoring of this developing situation, and action of policymakers will be important if we are to avoid losing the gains in AMR management made in recent years.

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"COVID-19 is like a lobster dropped into boiling water, causing immediate suffering and noise. AMR is the lobster in cold water, slowly heating up and eventually leading to more devastation. COVID-19 has to be the world's wake-up call to take the AMR lobster out of the pot."

Professor Dame Sally Davies

INTRODUCTION

Antimicrobial resistance (AMR) is not a new problem; bacteria have been evolving resistance to these essential drugs since we first began using them. AMR has not paused during the COVID-19 pandemic, although it has been overshadowed, and there are many ways in which the pandemic could shape this problem now and in the future. Disruption of research activities has the potential to slow our understanding of AMR and the development of novel antibiotics to combat it, whilst the new pressures put on the healthcare sector mean that stewardship of the antibiotics we do have will be impaired as well. Understanding how the evolution, spread and management of AMR is changing and the challenges we face going forward will be essential for addressing this issue. International cooperation and strategy will be required to understand and mitigate the impact the COVID-19 pandemic has on AMR.

1   IMPACT OF COVID-19 ON AMR RESEARCH

Research funding

Restrictions put in place to control the pandemic had a significant impact on the access scientists had to research facilities where that research was not deemed essential to the pandemic. Laboratories employed a number of methods to mitigate this impact, including shifting to data analysis, computational work, or working on new or existing publications. However, some aspects of this disruption seem set to have long-term effects. Many labs were required to pause experiments that will take time to resume; cell lines and samples have been lost, and many researchers were required to cull laboratory animals, which will be expensive and

time-consuming to reacquire or reproduce. Many researchers, particularly women, have had the additional burden of increased caring responsibilities. Even with the easing of restrictions, access to laboratories is still restricted in many ways and this will have varying effects on individuals at different career stages. Social distancing in particular has restricted the number of researchers able to access laboratory facilities at one time, limiting the time individuals can spend on experiments, and shortages of materials required for COVID-19 testing (particularly PPE and consumables such as pipette tips) are further slowing progress for researchers.[3]

Funding was made rapidly available for research involving COVID-19 in response to the pandemic[4] and 43% of researchers surveyed by Springer Nature reported that they had already, or were likely to, repurpose existing grant funding for COVID-19 research.[5] This implies that there could be a shortfall in funding for projects not related to COVID-19; however, it is too early to say what impact changes in research funding will have in the field of AMR. Many researchers have shifted their focus to COVID-19 [4] and while this may mean that fewer researchers are investigating AMR overall, many have shifted their research topics to investigate COVID-19's intersection with AMR.

Applied Microbiology International conducted a membership survey and convened three Task and Finish Groups to investigate the impacts of COVID-19 on social equality, ensuring other areas of microbiology continue, and future preparedness for future public health emergencies. Survey participants raised concerns over research funding discrepancies, with fears that COVID-19 will continue to disproportionally attract funding as we emerge from the pandemic. The reduction

of funding and resources available to researchers investigating AMR limits our ability to understand and control this problem, and disruption to drug discovery and development places a further barrier in the challenging pathway to bringing new antibiotics to the public. We need to ensure that these research areas do not continue to be neglected as we emerge from the pandemic and support the generation of early career researchers who wish to progress in this field, particularly supporting those from backgrounds traditionally underrepresented in STEM to succeed in this increasingly competitive environment.

2   IMPACT OF AMR ON COVID-19 IN CLINICAL CARE

The healthcare systems across the world have had to adapt to treat not only existing patients, but also the influx of new COVID-19 cases under challenging circumstances, which have implications for AMR.

Intensive care units

COVID-19 patients, both in the NHS and globally, have a low rate (<10%) of secondary bacterial or fungal infections [1, 2, 6], although this is higher in ICU settings: meta-analysis by Lansbury et al.[2] puts this at 14%. Despite this low incidence of secondary infection, antibiotics are used frequently in this group; [7] 72% of patients in studies analysed by Rawson et al. in 2020[1] were treated with antibiotics, frequently broad-spectrum ones. Data from PHE's Fingertips also indicate that there is a trend in increased administration of antibiotics, including those in WHO 'watch' and 'reserve'* lists during the pandemic.[8] Most of the data estimating co-infection rates are from the USA, Europe

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and China. However, the incidence of co-infection may be different in other, particularly low/middle-income country (LMIC) healthcare systems, justifying a different approach to antibiotic use.[9]

There are a number of different factors contributing to increased antibiotic use in COVID-19 patients on critical care units.

- Microbiology testing capacity is reduced.

- Secondary bacterial infection is difficult to identify in COVID-19 patients, particularly pneumonia, as samples are harder to obtain, and there has been reluctance to perform aerosol-generating procedures on COVID-19 patients.

- Stress and high workloads of staff, with the mental health of many working in this environment suffering.[10] The emotional strain of caring for so many seriously ill patients may lead to increased prescriptions with the hope of improving survival over-riding rational stewardship protocols.

- Staff have been seconded to ICUs who have not previously worked in this environment.[11] This has also led to reduced staff levels in other healthcare areas; for example, 44% of antimicrobial pharmacists reported being seconded to the ICU during the first wave of the pandemic.[8]

- Interruption of routine antimicrobial stewardship (AMS) activities.[8]

Primary care

Face-to-face NHS GP/Practice Nurse appointments have declined by 50% since the pandemic began. These appointments are being replaced by telephone consultations, or patients are delaying booking appointments, with an overall decline of 20%, both of which have the potential to affect AMR.[12] Patients who delay seeking treatment during this period may also have worse outcomes later on, but it is unclear what the overall effects of these changes in general practice will have on AMR.[13]

Although there are mixed data on whether unnecessary antibiotic prescription is higher in telemedicine [14] it is certainly a concern given the sudden shift to remote appointments.[15] NHS prescription data shows an overall drop of 15% in antibiotic prescriptions during the pandemic but if the decrease in appointment numbers is accounted for, there has been a rise of 6.7%. The inability to assess patients in person may increase the uncertainty of the diagnosis; in place of empirical measurements (e.g. temperature and pulse), patients' self-reported symptoms must be relied upon; this is limited further if no video is available to make a visual assessment. In these circumstances the desire to prescribe antibiotics as a precaution is understandable.[12] Training is required to improve antibiotic stewardship in the case of remote prescription; there is evidence that where effective training and close adherence to AMS guidelines are in place, remote consultations can keep to appropriate antibiotic prescription rates.[16] It is also clear that there are many advantages to the implementation of telemedicine, especially in resource-limited settings, in reducing the risk of COVID-19 transmission and maintaining access to healthcare for rural or clinically vulnerable patients.[17, 18]

Dentistry

A similar trend in increased antibiotic prescribing can be seen in dentistry, again linked to remote prescribing.[19] A national increase of 25% of dental antibiotic prescription was seen in England in April–July 2020 compared with the same time last year. There was regional variation with prescriptions increasing in London by as much as 60%.[19] Although this prescription rate is set to drop back down as in-person appointments are allowed to continue, some areas did not see an immediate decrease.[19] This may be due to a backlog of patients limiting in-person appointments, or

conditions having worsened in patients who delayed seeking treatment during the lockdown.

Increased antibiotic use has been seen across the healthcare system during the COVID-19 pandemic, including increases in unnecessary prescriptions and broad-spectrum antibiotic use. The repercussions of this are yet to be seen; however, it is imperative that the situation is monitored, and actions taken to mitigate it. Whilst most research in this area focuses on the challenges facing western healthcare systems, other countries face different or amplified problems. International cooperation and support will be required not only to address the control of COVID-19 but also AMR.

PERSPECTIVE

DENTISTRY IN AUSTRALIA:
THE IMPACT OF COVID-19 ON AMR

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Australia declared COVID-19 as a pandemic on 27 February 2020 and by 21 March all non-essential services were closed for a month. This had a severe impact on dental services as 85% of dentistry is provided by the private sector.[20]

Acute odontogenic infections require surgical intervention with adjunctive use of antibiotics only if there is systemic involvement. During this pandemic, lack of access to dental services (practice closures), the rise of teledentistry (defensive prescribing) and seeking care from non-dental practitioners, i.e. provision of antibiotics from medical practitioners, may have resulted in an increase in antibiotic prescriptions with a commensurate rise in AMR.

Alternatively, it has been suggested that prescription rates decreased as no routine treatment was being undertaken so fewer prescriptions were written for prophylaxis for high-risk procedures. More broadly it is postulated that the spread of AMR should decrease due to improved infection control practices and the disruption to travel, specifically international travel as Australia's borders have been sealed since 20 March 2020.[21]

To better assess the impact of dental prescribing on AMR during this pandemic we need to analyse antibiotic prescription rates for dental complaints in Australia from 2020.

3   IMPACT OF COVID-19 ON AMR POLICY

Antimicrobial stewardship (AMS) policy in healthcare settings

AMS has been interrupted during the pandemic.[8] Whilst this is true globally, the public health challenges faced by high-income countries (HICs) differ from those in LMICs, as will the measures required to address them.[9] Where these have been neglected or disrupted, policymakers need to consider both how to take antimicrobial stewardship forward in the future and recover the lost gains resulting from the pandemic.

In a survey of the Pharmacy Infection Network of the United Kingdom Clinical Pharmacy Association (UKCPAPIN), during the first wave of the pandemic, most respondents (65%) reported that COVID-19 had an overall negative impact on AMS activities.[8] The areas reported as having been impacted the most were audit, quality improvement initiatives, education, training, AMS meetings and multidisciplinary working. Although this work was disrupted, this survey also found that hospital AMS teams were taking measures to mitigate this with new strategies. There was increased adoption of digital tools to manage AMS, including virtual meetings or ward rounds, and electronic prescription systems, and

increased use of new biomarkers such as procalcitonin to differentiate viral from bacterial infections. Guidelines on hospital- and community-acquired pneumonia and healthcare-acquired infections were also updated in line with National Institute for Health and Care Excellence (NICE) guidelines.[8]

There has been much interest in repurposing existing drugs, including antibiotics, to treat COVID-19. Antimicrobials including azithromycin in combination with the antimalarial hydroxychloroquine attracted much interest early in the pandemic. This led to increased usage, irrespective of data demonstrating their efficacy, resulting in shortages at the beginning of the pandemic.[22, 23] Drug shortages result in delays in treatment, use of suboptimal alternatives and ultimately lead to poorer patient outcomes.[23] The prolonged

hospitalisation and increased use of alternative antimicrobials are likely to have implications for AMR in the future. Whilst there is evidence that the azithromycin shortage in the USA is over, the implications of this event for AMR in the USA and globally are unclear.

LMICs face a number of different challenges in maintaining AMS. COVID-19 has put additional strain on already stressed health systems, limiting their infection prevention measures. A lack of microbial laboratory testing can lead to increased use of empiric therapies; [9] in South Africa the use of these facilities to test for COVID-19 has reduced the capacity for other clinical microbiology testing.[24] In many LMIC settings antibiotics are more readily available without a prescription,[25] raising concerns about inappropriate use of antibiotics for self-medication for COVID-19.[9, 26] Another issue results from the limited access to key resources for managing the pandemic and AMR, as LMICs can be outcompeted by HICs for materials required for testing, PPE[9] and now vaccines. While these challenges put these healthcare systems in a difficult position, now may be a good time to improve, implement and provide education in AMS.[9] Furthermore, it is clear that managing global health issues such as COVID-19 requires international cooperation, collaboration and support. Bacteria do not respect borders and so addressing AMR will require a similar global initiative. Understanding how the pandemic is affecting the spread of AMR and measures designed to control it across the world will be vital in allowing us to tackle this problem in the future.

Healthcare policy outside AMS

Other diseases such as TB, which present a key challenge in AMR, have been exacerbated [27] and initiatives designed to manage them must adapt.

However, as TB is an airborne pathogen, the measures designed to prevent COVID–19 transmission may also mitigate its spread during this time.[13] The Stop TB Partnership predicted a 5–8 year setback in TB control and treatment at the start of the pandemic in May 2020.[28] However, their recent analysis of data gathered during the pandemic suggests that the setback is closer to 12 years.[29] In India, decisive efforts were taken to successfully start to tackle this, with TB screening combined with COVID–19 testing initiatives, and contact tracing for both diseases.[29] They recommend an approach that focuses on: (1) the implementation of widespread testing for both COVID–19 and TB, given their similar symptoms; (2) the creation of support networks and communities; (3) infection prevention against airborne diseases in healthcare and community settings; and (4) the use of real–time data to inform public health decision–making. Healthcare workers in LMICs report that COVID–19 has made it challenging for many patients with HIV or TB to access healthcare as normal.[18] Measures that enable patients to travel to access healthcare where necessary, or the implementation of schemes allowing for supply of drugs within their local area, and telemedicine to reduce in–person appointments were identified as key steps for mitigating the disruption.[18] Other vaccine–preventable diseases are likely to see a rise in cases as vaccination programmes are disrupted [30] which will impact healthcare systems and AMR into the future.[13] This disruption of vaccination programmes can be seen internationally, although LMICs will feel the greatest impact in the wake of COVID–19.[30]

The WHO issued advice to temporarily suspend vaccination programmes where there was not an active outbreak of that disease.[31] Whilst this measure is important for the prevention of spread of COVID–19, protecting both healthcare professionals and patients, a major effort is required to ensure that when it is possible these programmes are resumed, ensuring that the populations who have missed out get the protection they need.[31] Polio and measles vaccination programmes have also been substantially impacted.[32] Understanding the global implications of disrupted AMS activities and other health policies including vaccination programmes on AMR will be important in formulating a strategy going forward. Addressing the shortfalls in the treatment and diagnosis of other bacterial diseases such as TB resulting from pandemic disruption will be essential in managing increased resistance to antimicrobials.

PERSPECTIVE

LEARNING FROM COVID–19 TO TACKLE AMR

Professor Laura Piddock
Scientific Director, GARDP

The COVID–19 pandemic has exposed weaknesses in health systems across the world. However, from this immense global tragedy, we are also learning valuable lessons that can be used to tackle the silent pandemic of antimicrobial drug–resistant infections.

We have seen how investments in preparedness, including the research and development of new diagnostics, treatments and vaccines, are necessary and cost–effective in tackling a pandemic. These have not been equitably available during COVID–19 because traditional market incentives are neither sufficient nor appropriate to ensure they are developed in a timely manner and on a global scale. It has also become clear how this can undermine the trust many countries have in the international system.

COVID–19 has clearly shown that a single country cannot solve the challenges of a fast–moving pandemic on its own. Collaboration and international coordination are vital.

Clinical trials in both developed and developing countries, as well as equitable and affordable access to diagnostics and treatments, are essential for a comprehensive and effective pandemic response.

Out of the global tragedy of COVID-19, we can mobilise and take collective responsibility to prevent a health catastrophe fuelled by the silent pandemic of AMR.

GARDP is working to develop five new treatments by 2025 to fight drug-resistant infections that pose the greatest threat to health (**www.gardp.org**).

4   PUBLIC ATTITUDES TO AMR IN LIGHT OF COVID-19

Increased interest and awareness of public health in the general population could be harnessed to communicate AMR issues. The pandemic may have led to a new level of understanding surrounding situations where antibiotics can and cannot be used.[7] However, there are currently no studies investigating how the pandemic has impacted public scientific literacy surrounding AMR. Using the COVID-19 pandemic as a tool to demonstrate the importance of the 'slow-moving pandemic' of AMR may be a useful communication strategy going forward.

New behaviours have also been an aspect of managing the pandemic. Measures such as mask-wearing, increased handwashing, social distancing and uptake of the flu jab are now established as effective methods of managing infection spread.

Impact of public behaviours on AMR during COVID-19

Increased use of antimicrobials or biocides in domestic cleaning and handwashing may have an effect on AMR going forward. It is difficult to say yet whether this will

have a net positive or negative effect; on one hand, increased hand hygiene and decontamination of surfaces will prevent the spread of AMR organisms (AROs); however, the increased use of biocides may lead to resistance developing, particularly in the environment (see section 5).[7]

Social distancing and stay-at-home orders, including school closures, have led to decreased interactions in the community but increased contact time with other members of a household. This may impact patterns of transmission of AROs with transmission within the community decreasing, but with greater incidence of household transmission.[13] Other interventions such as mask-wearing and travel restrictions may reduce the spread of AROs on both a local and global scale.[13, 7]

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5 INCREASED RISK OF AMR EVOLUTION IN THE ENVIRONMENT

> **PERSPECTIVE**
>
> ### INCREASED RISK OF AMR IN THE ENVIRONMENT AS A RESULT OF THE COVID-19 PANDEMIC
>
> **Dr Aimee Kaye Murray**
> *University of Exeter*

In 'Tackling antimicrobial resistance: the UK's five-year national action plan', the UK Government included 'minimising the spread of AMR in the environment' as one of the key priority areas. In this document, it was recognised that 'it is clear that reducing antimicrobial contamination is an important consideration in tackling the spread of AMR' and further research is needed in this area.[33]

Natural environments (soils, freshwater and marine environments) are contaminated daily with antimicrobials. These include antibiotics excreted by humans and antimicrobials used for disinfection, such as biocides and alcohols. Wastewater treatment is not designed to remove antibiotics or antimicrobials, so these enter rivers and streams via wastewater effluent and are applied to agricultural soils via sewage sludge used as fertiliser. Indirect sources of pollution, such as surface run off, can also contribute to levels of antimicrobials in natural systems.[34]

Numerous studies have demonstrated that even very low concentrations of antimicrobials, similar to those found in the environment, can increase levels of AMR in bacteria.[35, 36, 37] One study even found low concentrations can, in some cases, elevate AMR levels in communities of bacteria just as much as high, clinical concentrations.[37] However, research suggests there is some variability across antibiotics in terms of the concentration that selects for AMR, with some antibiotics having much higher selective concentrations than others.[38] Considerably less work has determined selective concentrations of antimicrobials, such as biocides. However, there is some evidence to suggest selection for AMR can occur at environmentally relevant biocide concentrations.[39, 40]

Antibiotic prescriptions have likely increased during the pandemic (see section 2, Impact of AMR on COVID-19 in clinical care), which could lead to greater proliferation of AMR in the environment. To estimate potential environmental risks of increased prescribing, a recent study modelled the environmental impact of several potential COVID-19 treatments, including the antibiotic azithromycin. It was estimated that only a 0.016% increase in azithromycin usage in the human population would equate to an environmental risk, including increased AMR.[41]

Use of disinfectants has undoubtedly increased as a result of the pandemic, through increased handwashing and surface disinfection. Importantly, surface disinfection now occurs routinely in not only clinical settings, but also in community settings (e.g. public transportation and workplaces).[42] Although it is unclear whether these practices will be sustained in the long term, the global disinfectant market is predicted to grow significantly over the coming years.[43] One group of biocidal compounds of key concern are quaternary ammonium compounds (QACs). These are found in many of the disinfectants recommended for use during the pandemic by the US Environment Protection Agency and the Association for Applied Hygiene in Germany.[43] Exposure of bacteria to QACs can lead to increased AMR, including antibiotic resistance through a process called co-selection. Limited evidence also suggests that prolonged exposure to certain alcohols, found in hand
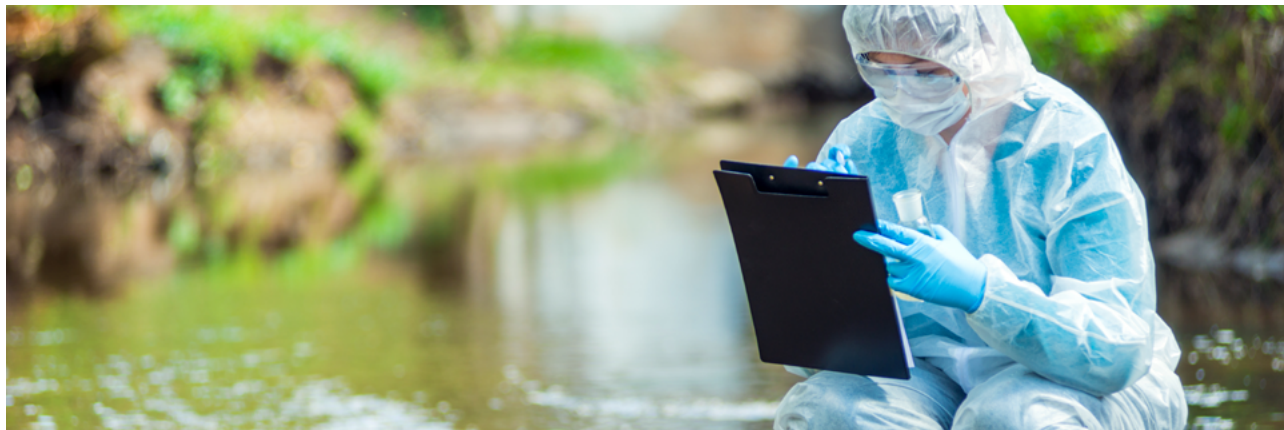
sanitiser, may result in increased alcohol tolerance,[44] but whether this could be a novel mechanism of antibiotic resistance co-selection is a novel research area.

Elevated concentrations of antimicrobials in the environment could result in greater selection of AMR, to a point. Very high concentrations of disinfectants are expected to completely kill bacteria, which would also prevent AMR emergence. However, complete inhibition of microbes would have important implications for wastewater treatment, which relies on microbial activity. Potential effects on microbial communities in the environment that perform key ecosystem roles are also not understood.[7]

Systematic and routine environmental surveillance of antibiotic and antimicrobial concentrations and AMR in the environment is required to determine whether the risk of selection for AMR is greater during and following the COVID-19 pandemic. The availability of pre-pandemic data is limited, highlighting the importance of consistent environmental monitoring both now and in future. Modelled estimates, as highlighted previously,[41] can also be used to plug missing data gaps using antibiotic prescription or antimicrobial usage data. Further research studying the conditions and antimicrobial concentrations under which AMR emerges is also required in order to fully understand the extent to which COVID-19 may have increased risk of AMR in the environment.

PERSPECTIVE

TOOLS FOR UNDERSTANDING AMR IN THE ENVIRONMENT

Professor Mathew Upton
University of Plymouth

Predicting antibiotic use in hospitals was difficult due to hospitalised patients being discharged more rapidly and because many patients with severe illness, who in pre-COVID times would have been admitted to hospital due to their severity of illness, were managed in their places of residence or community hospitals. In addition, the majority of elective surgery was cancelled, and it was also unclear how many patients would be admitted to hospitals during Spring 2020. By focusing on one of

the proposed Nightingale hospitals, we were able to accurately predict the impact of the facility at maximum capacity, using NICE prescribing guidelines and data for the sewage treatment plant that would receive human waste. We predicted an impact on AMR in the environment and demonstrated that the tools used could help inform future placement of emergency hospitals in order to mitigate the risks of environmental contamination. Combined with retrospective data on prescribing, these tools provide valuable insights into the geographical hotspots where there has been a high risk of selection for AMR in the environment.[45]

6   THE FUTURE OF AMR IN LIGHT OF COVID-19

The COVID-19 pandemic has affected many different aspects of society and our daily lives. Changes across healthcare, research, public attitudes, existing and new health policies, and the environment have the potential to alter AMR in many different ways. As we emerge from the pandemic, we must investigate how AMR has been affected and what that means for the future. We must assess whether or not current policies are still functioning or whether additional action needs to be taken.

PERSPECTIVE

FIVE WAYS TO STRENGTHEN THE INTERNATIONAL RESPONSE TO AMR

Professor Laura Piddock
Scientific Director, GARDP

COVID-19 has presented a turning point to improve the response to pandemics. GARDP recommends five ways to strengthen the international response to the pandemic of drug-resistant infections in its report: 'Learning from COVID-19 to tackle antibiotic resistance'.[46]

The first is to recognise and urgently address the silent pandemic of antimicrobial drug-resistant infections. Unlike COVID-19, where much is still to be learnt about the virus and how the body reacts to infection by SARS-CoV-2, with AMR, the drug-resistant microbes are known.

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Following decades of underinvestment, far more investment is needed. Now is the time to step up efforts to prepare and respond to AMR. This includes health and surveillance systems to prevent, detect and treat emerging drug-resistant infections.

We need to ensure that access to diagnostics, treatments and vaccines for all people in all countries is a cornerstone of pandemic preparedness and response.

Expanding global cooperation across geographies and sectors and within a One Health framework is key. This will ensure we recognise the importance of connecting the health of people to both the health of animals and our shared environment.

It is vital that LMICs are seen as equal partners in a comprehensive global response and for governments and partners to find a collective approach that is fair to all.

because it enables us to work collaboratively, across borders and languages.

Globally, nationally and locally, we need to strengthen surveillance of antimicrobial use, and resistance rates and prevalence. With real-time data, the public and policymakers could monitor, understand and change this for the better. This would also empower clinicians and patients to conserve antimicrobials.

Global collaboration is the best way to tackle global health challenges. In light of COVID-19, we have a challenge and an opportunity to put sustainability at the heart of our health, social, food and economic systems. As patients and as prescribers, and across public and private sectors and academia, we have to step this up – keeping AMR on the agenda and pushing for action.

PERSPECTIVE

THE FUTURE OF AMR

Professor Dame Sally Davies
UK Special Envoy on AMR

We must use COVID-19 as an opportunity to make progress on infection prevention and control, including handwashing. However, over 3 billion people across the world lack access to soap and water at home. We need infrastructure and then behavioural change to ensure that everyone can access this most basic of measures to protect against infections.

Like with COVID-19 vaccines, treatments must be accessible to all who need them. The world is now appreciating vaccines are powerful health tools, including to minimise antibiotic usage. We also need collaboration between scientists and the media to share evidenced information, starting with the fact that antibiotics do not treat viruses.

COVID-19 is the first pandemic that we are facing in the digital age, so using technology and data to overcome it – and to strengthen our health systems in doing so – is an opportunity that we should not pass up. Not least

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