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OPINION

COVID-19: Clouds Over the Antimicrobial Resistance Landscape

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In recent years, the increase in antimicrobial resistance (AMR) has been recognized as a real threat to human and animal health. It is a problem that has been given the highest priority, uniting nations in the fight against its causes and effects. Among the actions that have been implemented are: clinical and microbiological surveillance, promotion of rational and controlled use of antibiotics, AMR stewardship programs in hospitals, development of tools for rapid diagnosis of infectious diseases to establish prompt and adequate treatment, and radically improving vaccination strategies. The current COVID-19 pandemic has placed disproportionate demands on the healthcare infrastructure and economy worldwide, which will negatively impact on the availability of materials as well as the technical capacity for diagnosis, patient care, and treatment of both COVID-19 and non-COVID-19 patients. Disruptions to production and distribution chains will hamper the availability and usage of antibiotics, also interrupting several of the activities that have been implemented thus far to combat AMR, including detailed laboratory monitoring and reinforced vaccination programs. Here, we discuss the main aspects that should be considered with regard to AMR, that may be affected by the pandemic and propose some actions to counter them. © 2020 IMSS. Published by Elsevier Inc.

Key Words: Anti-bacterial agents, Antimicrobial stewardship, Coronavirus pandemic, Drug resistance, Microbial.

Introduction

Antimicrobial resistance (AMR) is currently one of the most pressing threats to human health and clear concerns and alarms have been raised by several institutions, governments, and international agencies. Calls to action against AMR by the United Nations (UN) (1), and the World Health Organization (WHO) (2) since 2014 have set in motion the development of national plans as well as the implementation of specific actions—from increased vigilance against AMR derived from the use and misuse of antibiotics, both in clinical contexts and within the agro-industrial complex, to the promotion of research that informs new and better approaches in combatting infectious diseases.

The current COVID-19 pandemic will certainly change the landscape of AMR by compromising many of the actions that have been implemented in recent years. At the time of writing, there are over 30 million confirmed cases across 188 countries and territories, and 940,000 deaths have occurred as a result of the disease (3). The situation changes by the minute, although we have chosen to use these numbers to illustrate the magnitude of the challenges that lie ahead.

Unexpected Overuse of Antibiotics

One of the first elements relevant to AMR derived from the COVID-19 pandemic is the high number of patients that require hospitalization. Depending on the series, the number oscillates between 41 and 100% (4). From this

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number−and under the assumption that approximately 50% of patients with COVID-19 will require hospitalization, and between 10 and 70% of those patients will require critical care that includes antimicrobial treatments (5) − an estimated of up to 10.5 million antibiotic treatments may have been administered so far for COVID-19 only in these patients, most of the times in schemes that include more than one drug and prolonged hospital stays.

Furthermore, if antibiotic prescriptions for outpatients who have mild COVID-19 symptoms follow the pattern usually described in the treatment of similar acute respiratory infections, in which an antibiotic is prescribed in up to 90% of cases despite a viral etiology (6) this would mean that in the current situation, approximately 10.8 million additional treatments will be prescribed for patients with COVID-19. This is in addition to the treatments for all other non-COVID-19 mild acute respiratory infections.

In our experience (data not published), in a COVID-19 diagnostic center for the university community in Mexico City, of 2,000 interviews carried out to people with uncomplicated acute respiratory disease looking for a molecular diagnosis of SARS-CoV-2 during April and May 2020, 1,600 (80.0%) reported having received antibiotic treatment.

A similar situation can occur with COVID-19 patients presenting with diarrhea. Antibiotics are often administered for uncomplicated, acute diarrhea with a marginal benefit, which can increase the risk of AMR (7). Strictly speaking, all these antibiotic prescriptions will be added to the total global usage and should be regarded as unnecessary and excessive.

Another important element related to the excessive consumption of antibiotics during this pandemic is related to the use of chloroquine (or hydroxychloroquine) plus azithromycin. This has been derived from a study with significant methodological limitations which received high media exposure and led to the unfounded assumption that it could effectively treat COVID-19 (8). In the United States (US) alone, the indiscriminate recommendation of the use of hydroxychloroquine caused an increase in the number of internet searches (9) as well as prescriptions for the drug. Initial journalistic estimates reported 32,000 prescriptions of this drug the days following President Trump's claim that it could cure COVID-19 (10); a more detailed analysis of prescriptions filled through Mar 31, 2020 at 48,900 pharmacies in the US documented an increase of 93,000 patients receiving hydroxychloroquine and azithromycin over the prior five month trend (11). This was despite hydroxychloroquine's well-known cardiovascular adverse effects, and the fact that preliminary evidence regarding its efficacy did not show utility for COVID-19 treatment (12), which was corroborated by later studies in both hospitalized (13) and outpatient patients (14).

The indiscriminate and excessive use of azithromycin could drive the appearance of resistant strains, not only because of its use within hospitals but also due to the spread of its unproven, panic-driven use as a prophylactic. Previous reports on the excessive use of azithromycin as a component of trachoma care programs have found that the appearance of *E. coli* and *S. pneumoniae* carriers can be favored, and the percentage of resistance to these bacteria increases (15). Additionally, the combined use of azithromycin plus chloroquine/hydroxychloroquine can potentially lead to adverse cardiovascular effects (16).

A relatively favorable aspect of the pandemic (if it were possible to say so) is that antibiotic use is currently falling in most hospitals due to significant numbers of certain routine procedures (surgical or otherwise) being postponed or cancelled in an attempt to minimize in-hospital COVID-19 infections.

Limited Access

Disruption of health services will certainly compromise the diagnosis and treatment of chronic infectious diseases such as HIV/AIDS and tuberculosis, both of which require long-term treatment and follow-ups. If partial interruptions due to the pandemic compromise treatment availability or access to laboratory supplies used for diagnostic and follow-up treatments, such patients will be at increased risk of opportunistic infections; or new, resistant strains of certain diseases could emerge due to interrupted treatment programs. A recently published survey from the WHO conducted in May and June 2020−105 countries assessed the impact of the COVID-19 pandemic on 25 essential health services (17). Eighteen percent of the surveyed countries reported some type of disruption in services related to the care of communicable diseases, and it is worth mentioning that there was interruption in services related to HIV, Malaria and Tuberculosis in 32, 46 and 42% of the countries responding those items, respectively; 76.2% of the surveyed countries indicated the need to strengthen infection prevention and control capacities as one of their priorities.

Research and Development

Research and development of new antibiotics has not been a priority issue in recent years for large pharmaceutical companies (18,19), and now there is a risk that finding a treatment for COVID-19 will become the priority, diverting resources from new antibiotic projects or their therapeutic applications. Clinical trials for antibiotics that are already running or are scheduled for the first half of 2020 might not achieve their goals due to the serious disruption brought on by the pandemic, as hospitals and research facilities reorganize to better suit the needs of COVID-19 patients and to prioritize a different research agenda.

Risks to Vaccination Efforts

As COVID-19 continues to spread around the globe, production chains for several industrial processes will be affected, including those related to the production, distribution, and delivery of vaccines. One critical concern raised by the WHO is the increased risk of a measles vaccine shortage, which would impact up to 117 million children worldwide (20). The example from Mexico is illustrative: while fighting the COVID-19 pandemic (the first case being reported on February 28th 2020) a measles outbreak of 196 cases of measles in four states (Mexico City, State of Mexico, Campeche and Tabasco) (21) between February and May, had to be contained with limited availability of a measles-containing vaccine, logistical challenges associated with confinement (started on March 23th in all the country) and field epidemiology services mainly focused on actions against COVID-19. This example illustrates perfectly the difficulties in containing outbreaks of a highly contagious and potentially lethal vaccine-preventable disease that primarily affects infants but also poses a risk to young adults and immunosuppressed patients protected by herd immunity.

Another equally serious concern brought on by the COVID-19 pandemic is the risk it poses to the availability of the influenza vaccine during the 2020−2021 flu season (for the Northern Hemisphere). The months from March−June are critical for seeding production laboratories with adequate numbers of viral strains. Production laboratories, in turn, must adapt their production and quality control processes in order to obtain testable vaccines between July and August. Once their safety and efficacy have been determined and regulatory requirements have been met, vaccines usually become available in October (22).

However, the COVID-19 pandemic might alter this delicate process in several ways. The availability of supplies could face disruption as resources are redirected towards fighting COVID-19. Personnel involved in the production of the influenza vaccine might also be redirected or could become ill and be unable to work for long periods during critical steps in vaccine production or testing. There are also many external points of failure: restrictions to air traffic, changes in maritime routes, border closures and protectionist policies, redirection of funding, maintenance of critical equipment, etc.

The possibility of influenza vaccine shortages for the next season is particularly worrisome. Vulnerable populations, particularly the elderly, would certainly find themselves at increased risk of respiratory infections, both mild and severe. An increased number of influenza cases presenting at the time of a possible second wave of the COVID-19 pandemic would prove fatal for many, and the strain on health services around the globe would be almost unimaginable. In terms of AMR, this scenario would prove to be disastrous as antibiotic use would certainly ramp up even more.

Small and medium-size production laboratories affected by shortages would almost certainly have to stop vaccine production (which is usually destined for local markets). As production halts, revenue streams will also cease, and the operation or survival of companies may be threatened. Without external financial help, many labs would have to close permanently. It is therefore imperative that production capacities at the local and national level are strengthened and that existing ones should not be allowed to weaken.

Protecting vaccine production capabilities should be a top priority for international health agencies and national governments. The proper planning and implementation of emergency funding or financial help directed towards this effort should begin immediately with the WHO, the United Nations International Children's Emergency Fund (UNICEF), Gavi, the Vaccine Alliance, government agencies and philanthropic associations coordinating their efforts, as they have done during previous complex scenarios.

Diminishing vaccine coverage would be catastrophic, particularly with regard to those diseases that appear in people at higher risk of COVID-19 complications, such as pneumococcal pneumonia and invasive *H. influenzae* disease. In addition, a low coverage of the tuberculosis vaccine (BCG) can lead to an increase in cases of severe forms of this disease in infants, which will lead to the use of antituberculous drugs with an inherent risk of resistance. Without vaccines, many preventable diseases would lead to large numbers of people requiring hospitalization, with a concurrent increase in the use of antibiotics and an increased risk of AMR.

Disruptions to the Agricultural Industry

The propagation of COVID-19 into rural areas will most likely endanger food production cycles and strategies. While disruption would mostly stem from sick individuals unable to tend to their animals or crops, additional pressure would come from interruptions to critical components within the food supply chain, such as feeding the animals. This new set of circumstances could push production towards adopting increasingly desperate measures to keep up with market demand. One possible solution might have to be the excessive use of antibiotics required to maintain healthy animals in overcrowded conditions, which would likely happen if animals are tended to by a diminished workforce. An increase in the use of antibiotics for food production raises the risk of AMR, not only through the development of resistance within the microbiota of treated animals but also by environmental leakage from animal excreta or waste waters.

Microbiological Surveillance and Monitoring

It is possible that during the COVID-19 pandemic, clinical, academic, and commercial laboratories will see a profound change in the scope and schedule of their usual activities. In

addition to the disruption of supply chains as previously discussed, other critical processes are bound to suffer as well. Environmental microbiological control will probably decrease and AMR monitoring in hospitals and clinics will also do so. The individuals in charge of implementing or supervising AMR-related programs might be relocated to projects with higher perceived priority as the pandemic progresses. Established surveillance networks will reduce data flow, and comparisons of previously registered AMR rates may no longer be possible in terms of expected trends.

Conclusion

There is no doubt that the COVID-19 pandemic is a clear and present danger in the fight against AMR. As such, it is of the utmost importance that urgent measures are implemented to counteract the risks brought on by the current situation. The commitment of multiple sectors will be crucial, and prominent roles will be played by health institutions, both human and veterinary, and by producers of vaccines and antibiotics as well as by governments and international agencies. However, the actions undertaken by individuals will also be paramount in controlling the pandemic and minimizing its impact on our day to day lives. Planning for contingencies, and avoiding infection by social distancing, adequate use of personal protection equipment and proper handwashing should be continued. The following months will be decisive in establishing actionable scenarios and preparing clear guidelines that will guarantee that our fight against AMR will continue.

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References

1. United Nations. Political Declaration of the high -level meeting of the General Assembly on antimicrobial resistance (A/71/L.2). 2016. https://digitallibrary.un.org/record/842813?ln=es. Accessed June 11, 2020.
2. World Health Organization (WHO). Resolution WHA67.25. Antimicrobial resistance. Sixty-seventh World Health Assembly 2014. http://apps.who.int/gb/ebwha/pdf_files/WHA67/A67_R25-en.pdf?ua=1&ua=1. Accessed June 11, 2020.
3. COVID-19 Dashboard by the Center for Systems Science and Engineering (CSSE) at Johns Hopkins University (JHU). https://www.arcgis.com/apps/opsdashboard/index.html#/bda7594740fd40299423467b48e9ecf6. Accessed June 11, 2020.
4. Sanders JM, Monogue ML, Jodlowski TZ, et al. Pharmacologic Treatments for Coronavirus Disease 2019 (COVID-19): A Review. JAMA, 2020.
5. Ferguson NM, Laydon D, Nedjati-Gilani G, et al. Report 9: Impact of non-pharmaceutical interventions (NPIs) to reduce COVID-19 mortality and healthcare demand 2020. https://www.imperial.ac.uk/media/imperial-college/medicine/sph/ide/gida-fellowships/Imperial-College-COVID19-NPI-modelling-16-03-2020.pdf. Accessed June 11, 2020.
6. Smith DRM, Dolk FCK, Pouwels KB, et al. Defining the appropriateness and inappropriateness of antibiotic prescribing in primary care. J Antimicrob Chemother 2018;73(suppl_2):ii1−ii8.
7. Malik OAA. Role of antimicrobials in the treatment of adult patients presenting to the emergency department with acute gastroenteritis - A mini review. Pak J Med Sci 2017;33:488−492.
8. Gautret P, Lagier JC, Parola P, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. Int J Antimicrob Agents 2020;56(1):105949.
9. Liu M, Caputi TL, Dredze M, et al. Internet Searches for Unproven COVID-19 Therapies in the United States. JAMA Intern Med 2020; 180(8):1116−1118.
10. Gabler E, Keller MH. Prescriptions Surged as Trump Praised Drugs in Coronavirus Fight. The New York Times. https://nyti.ms/2S9eqjf. Accessed June 11, 2020.
11. Shehab N, Lovegrove M, Budnitz DS. US Hydroxychloroquine, Chloroquine, and Azithromycin Outpatient Prescription Trends, October 2019 Through March. JAMA Intern Med, 2020.
12. Sarma P, Kaur H, Kumar H, et al. Virological and Clinical Cure in Covid-19 Patients Treated with Hydroxychloroquine: A Systematic Review and Meta-Analysis. J Med Virol, 2020.
13. Cavalcanti AB, Zampieri FG, Rosa RG, et al. Hydroxychloroquine with or without Azithromycin in Mild-to-Moderate Covid-19. N Engl J Med, 2020.
14. Skipper CP, Pastick KA, Engen NW, et al. Hydroxychloroquine in Nonhospitalized Adults With Early COVID-19: A Randomized Trial. Ann Intern Med, 2020M20.
15. O'Brien KS, Emerson P, Hooper PJ, et al. Antimicrobial resistance following mass azithromycin distribution for trachoma: a systematic review. Lancet Infect Dis 2019;19:e14−e25.
16. Naksuk N, Lazar S, Peeraphatdit TB. Cardiac safety of off-label COVID-19 drug therapy: a review and proposed monitoring protocol. Eur Heart J Acute Cardiovasc Care, 2020;. 2048872620922784.
17. World Health Organization (WHO). Pulse survey on continuity of essential health services during the COVID-19 pandemic: interim report. https://www.who.int/publications/i/item/WHO-2019-nCoV-EHS_continuity-survey-2020.1. Accessed September 1, 2020.
18. Ribeiro da Cunha B, Fonseca LP, Calado CRC. Antibiotic Discovery: Where Have We Come from, Where Do We Go? Antibiotics (Basel) 2019;8:45.
19. Nielsen TB, Brass EP, Gilbert DN, et al. Sustainable Discovery and Development of Antibiotics - Is a Nonprofit Approach the Future? N Engl J Med 2019;381:503−505.
20. World Health Organization. More than 117 million children at risk of missing out on measles vaccines, as COVID-19 surges. Statement by the Measles & Rubella Initiative: American Red Cross, U.S. CDC, UNICEF, UN Foundation and WHO. https://www.who.int/immunization/diseases/measles/statement_missing_measles_vaccines_covid-19/en/. Accessed June 11, 2020.
21. Subsecretaría de Prevención y Promoción de la Salud, Dirección General de Epidemiología. Casos confirmados por sarampión. https://www.gob.mx/salud/documentos/casos-confirmados-por-sarampion-2020. Accessed June 11, 2020.
22. Stohr K, Bucher D, Colgate T, et al. Influenza virus surveillance, vaccine strain selection, and manufacture. Methods Mol Biol 2012;865: 147−162.