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Perspective

Antimicrobial resistance: A challenge awaiting the post-COVID-19 era

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ABSTRACT

Microbe exposure to pharmaceutical and non-pharmaceutical agents plays a role in the development of antibiotic resistance. The risks and consequences associated with extensive disinfectant use during the COVID-19 pandemic remain unclear. Some disinfectants, like sanitizers, contain genotoxic chemicals that damage microbial DNA, like phenol and hydrogen peroxide. This damage activates error-prone DNA repair enzymes, which can lead to mutations that induce antimicrobial resistance. Public health priority programs that have faced drug-resistance challenges associated with diseases, such as tuberculosis, HIV, and malaria, have given less attention to risks attributable to the COVID-19 pandemic. Pathogen-specific programs, like the directly observed treatment strategy designed to fight resistance against anti-tuberculosis drugs, have become impractical because COVID-19 restrictions have limited in-person visits to health institutions. Here, we summarized the key findings of studies on the current state of antimicrobial resistance development from the perspective of current disinfectant use. Additionally, we provide a brief overview of the consequences of restricted access to health services due to COVID-19 precautions and their implications on drug resistance development.

Introduction

Antimicrobial resistance (AMR) is a global public health concern (Prestinaci, Pezzotti, & Pantosti, 2015). The main drivers of AMR include excess microbial exposure to antibiotic agents, mainly due to their overuse in agriculture and health facilities (Capozzi et al., 2013; Levy, 1998). On the other hand, progress in developing new antibiotics has remained stagnant due to scientific challenges, clinical hurdles, and low economic returns (Payne, Miller, Findlay, Anderson, & Marks, 2015). In addition to well-established factors that influence AMR, the overuse and misuse of existing antimicrobial agents have contributed to accelerating the spread of AMR during and beyond the COVID-19 pandemic (Fig. 1).

Recent findings have identified mechanisms that link antibiotic-resistance dissemination to the use of non-antibiotic pharmaceuticals (Wang et al., 2020). Those findings are essential for understanding AMR in the context of the SARS-COV-2 pandemic, which has led to extensive use of non-pharmaceuticals (e.g., alcohol-based sanitizers) as a measure to prevent infection (Hui et al., 2020). The marked increase in the use of hand sanitizers and environmental cleaners, without proof of their short and long-term side effects, is a potential concern for human, animal, and environmental health (Campos et al., 2017; Mantlo et al., 2020). Developing countries and regions with limited resources, a flawed pharmaceutical supply chain, and poor health service management systems might contribute most to AMR spread because the quality of pharmaceutical products remains questionable (CDC., 2020) (Chokshi, Sifri, Cennimo, & Horng, 2019). Here, we briefly provide insight into how COVID-19 preventive measures, such as the use of disinfectants and disruptions in treatment modalities of AMR-targeted diseases, could potentially lead to an increase in AMR beyond the pandemic.

Abbreviations: BAC, Benzalkonium chloride; DNA, Deoxyribonucleic Acid; DOTs, Directly Observed Treatment Strategy; HIV, Human Immunodeficiency Virus; NDM1, New Delhi Metallo-β-lactamase 1; SARS-COV2, Severe Acute Respiratory Syndrome Coronavirus 2; TB, Tuberculosis; TLS, Translesion Synthesis Polymerase; WHO, World Health Organization.

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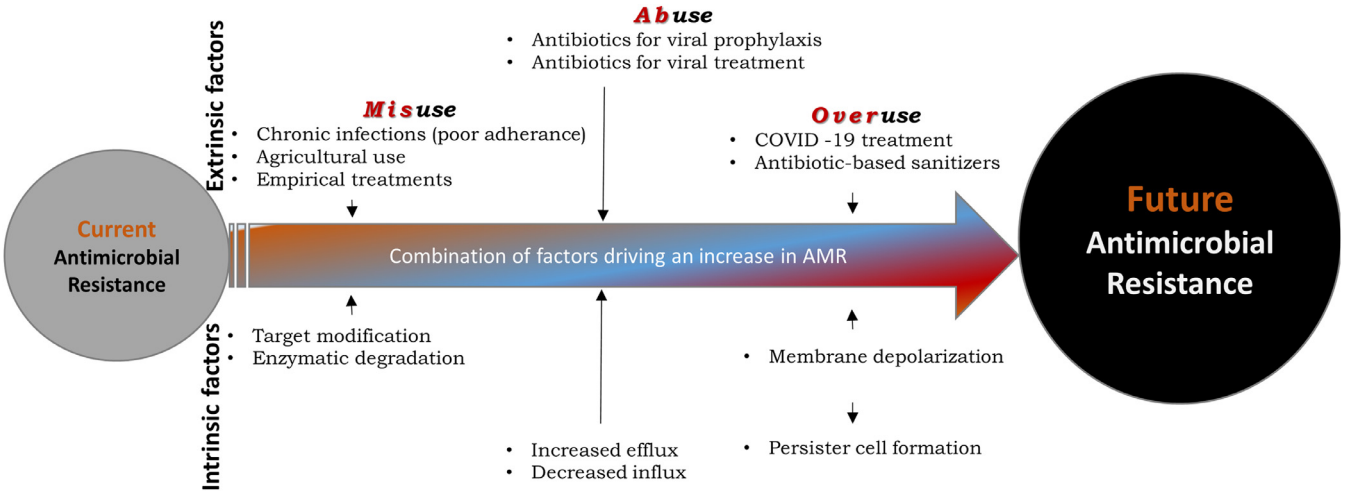

Figure 1. The main drivers of antimicrobial resistance. Inappropriate use of antimicrobial agents for clinical and non-clinical applications accelerates the rate at which drug resistance develops.

The current state of antimicrobial resistance

In 2017, the World Health Organization (WHO) released a report on drug-resistant bacterial pathogens that merit priority in research and development (WHO., 2017). Most pathogens on the list included bacteria that carry the enzyme New Delhi metallo-beta-lactamase 1 (NDM1), which confers resistance to a broader spectrum of mainstay antibiotics used for treating antibiotic-resistant bacteria (Kumarasamy et al., 2010; D. L. Paterson & Doi, 2007). Unfortunately, shortly after the release of the report, COVID-19 was recognized as a pandemic and required the full attention of the scientific community, which limited their capacity to fight AMR (Choudhury, Panda, & Singh, 2012; Ferri, Ranucci, Romagnoli, & Giaccone, 2017; Morehead & Scarbrough, 2018).

One of the WHO strategies for mitigating SARS-COV-2 infection was the use of hand sanitizers and disinfectants as frequently as, and whenever possible (CDC., 2020; Kratzel et al., 2020). As a result, the unseen microbial population is being continuously exposed to pharmaceutical and non-pharmaceutical agents at varying frequencies, concentrations, and doses (Haiderali, 2020). Regardless of composition, these products' long and short-term effects on microbial genetics and human health have apparently been overlooked; however, we believe that current practices may have a potential impact. Therefore, based on the lessons learned from biophysical and molecular responses of microbes to different stressors, we might infer that to the use of pharmaceutical and non-pharmaceutical agents may contribute to the emergence and spread of AMR via mutagenic mechanisms that introduce microbial genome instability (Booth et al., 2020; Cohen, Lobritz, & Collins, 2013; Dorr, Vulic, & Lewis, 2010; Gullberg et al., 2011; I. K. Paterson, Hoyle, Ochoa, Baker-Austin, & Taylor, 2016).

Mechanisms related to COVID-19 consequences that contribute to AMR

Previous studies have described the emergence of bacterial pathogens that became tolerant to alcohol-based sanitizers through unknown genetic and molecular mechanisms (Pidot et al., 2018). This tolerance could be induced by the constituents of sanitizers, such as alcohol, quaternary ammonium compounds, phenols, hydrogen peroxide, and surfactants, which cause microbial DNA damage, or benzalkonium chloride (BAC) and triclosan, which have antimicrobial properties (Carey & McNamara, 2015; McDonnell et al., 2013; Pereira & Tagkopoulos, 2019). BAC has a broad spectrum antimicrobial activity against bacteria, fungi, and viruses. It has been well documented that BACs create a selective environment that favors some microbial phenotypes, and thus, exposure to it can confer cross-resistance to various antimicrobial agents (Pereira & Tagkopoulos, 2019).

Most homemade and purchased cleaning and hand sanitizing products contain chemicals, such as phenol and hydrogen peroxides, that induce microbial DNA damage (da Silva, 2016; Akimitsu et al., 1999; WHO, 2010). The bacterial response to DNA damage by induction of translesion synthesis polymerases (TLS) tolerates and bypasses unrepaired DNA lesions creating mutations that contribute to the development of antimicrobial resistance (Choi, Kim, Motea, & Berdis, 2017; Fuchs & Fujii, 2013; Ghosal & Chen, 2013).

Upon exposure to antibiotic-based disinfectants, bacteria respond by forming a subpopulation that persists and can become highly tolerant to antibiotics. This "selected" subpopulation plays an essential role in the recalcitrance of biofilm infections (Fig. 2)(Dorr et al., 2010). Therefore, microbes can undergo both phenotypic and genotypic changes that can alter antibiotic targets (Lewis, 2007).

Moreover, the use of antibiotics has increased in current efforts to ameliorate COVID-19. Indeed, antibiotics were administered in nearly 70% of COVID-19 related hospital admissions and 80-100% of COVID-19 related intensive care unit admissions (Langford et al., 2020). For instance, individuals received antibiotics when they presented with either mild COVID-19 without pneumonia, or moderate COVID-19 with pneumonia (WHO., 2020a).

Health system challenges related to COVID-19

The pandemic has posed a challenge to the preventive and control programs for public health priority diseases, such as tuberculosis (TB), HIV, and malaria. For instance, fighting the notoriously drug-resistant bacterial infection, TB, with a directly observed treatment strategy (DOTs), has become practically impossible because COVID-19 related restrictions have prevented patients with TB from visiting health service centers (WHO., 2020b).

In developing countries, where infectious diseases and other chronic illnesses are prevalent, the WHO global strategy and the recommendation for digital health interventions have remained elusive due to low and limited internet coverage (Labrique, Agarwal, Tamrat, & Mehl, 2020). These countries are burdened with far worse illnesses than COVID-19; thus, perhaps in that context, the

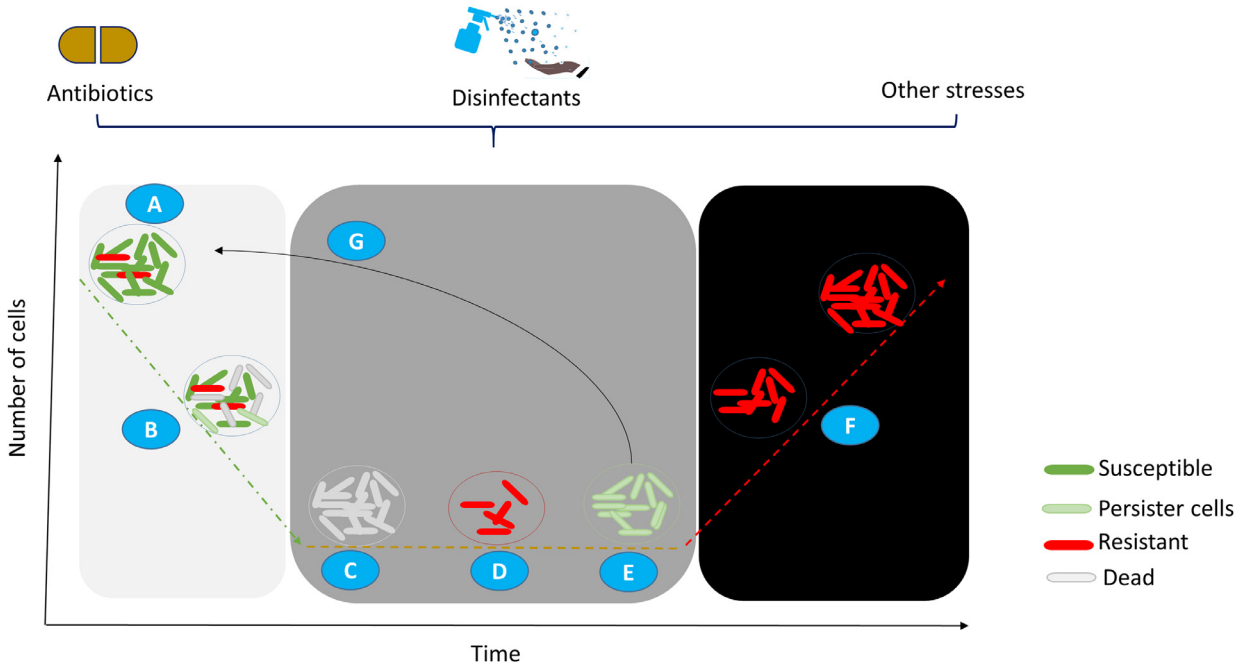

Figure 2. Classical curve showing biphasic killing by antibiotics that leaves a fraction of the bacterial subpopulation that enters into dormancy or becomes resistant. Pharmaceutical and non-pharmaceutical agents, such as antibiotics, sanitizers, and stress conditions, affect (A) actively replicating bacteria (green), which leads to (B and C) depletion of the sensitive clones (grey). A small proportion of surviving bacteria enters into (E) a dormant, persistent state (light green) or (D) a resistant state (red). The dormant, persistent fraction reactivates when antibacterial agents are removed (G), and become susceptible. The resistant subpopulation continues to multiply in the presence of the antimicrobial agent(s) that are designed to kill them (F).

COVID-19 measures are too strict compared to methods for managing other illnesses. Consequently, the number of empirical treatments has increased due to the lack of medical, physical, and laboratory examinations.

The consequences of undoing global efforts

Several global strategies have been established for combating AMR through the tremendous collaborative efforts of international agencies, including the US Center for Disease Control and Prevention, the European Center for Disease Prevention and Control, the WHO, the United Nations interagency coordination group on AMR, and the Global antibiotic resistance partnership (Chaudhary, 2016). If these achievements are undermined due to COVID-19 management strategies, we could experience even worse health, economic, social, and political crises.

Conclusions

Exposure of microbes to disinfectants and non-pharmaceutical agents contributes to the microbial ability to evolve mechanisms that increase AMR. Furthermore, the COVID-19 related restrictions to health services limited access for proper diagnosis, treatment, and management of patients with infectious diseases that need antibiotic-based interventions. Cognizance and actions are desperately needed to confront the existing and emerging public health threats from drug-resistant, multidrug-resistant, and total drug-resistant microbes.

Recommendations

Therefore, because the course of the COVID-19 pandemic remains enigmatic, we argue that the strategies for combating the emergence and spread of AMR should be incorporated into the pandemic response through different approaches.

A robust expert recommendation, as well as research on the formulations of disinfectants in current use, specifically for selecting, introducing, and regulating microbicides that have shown no or low selective pressure for inducing AMR, is critical. For example, investigations should focus on disinfectant constituents, mechanisms of action, genetic targets, and short and long-term effects on the environment, humans, and the microbial population. Furthermore, strategies should be designed and implemented to reach patients with chronic infections like TB that require antibiotic management. In this regard, it is indispensable to strengthen the capacity of community health care providers to follow and assist patients without compromising safety and infection prevention measures. In our opinion, alternatives to digital health (e-health) should be sought for areas with no or limited internet access. Here, we argue that internet expansion into remote areas is feasible provided there is an investment and political commitment.

The time is at hand to launch coordinated, collaborative measures to stem the further emergence and spread of untreatable infections and diseases, which could eventually lead to another public health emergency.

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Authors' contributions

TAL conceptualized, and TAL and AAR prepared the draft manuscripts. TAL wrote the mauscript. JAB, KIK, AA, KS, and MB contributed to revising the manuscript. All authors read and approved the final manuscript.

Ethics declarations

Ethical approval and consent to participate are not required and not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that there is no conflict of interest.

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