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Review

A parallel and silent emerging pandemic: Antimicrobial resistance (AMR) amid COVID-19 pandemic



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ABSTRACT

World is in the middle of the pandemic (COVID-19), caused by SARS-COV-2 virus, which is a significant global health crisis after Spanish influenza in the beginning of 20th century. Progressive drastic steps have been enforced to minimize the transmission of the disease. Likewise, in the current years, antimicrobial resistance (AMR) has been referred as one of the potential perils to the global economy and health; however, it is now veiled under the present pandemic. During the current pandemic, AMR to available frontline antibiotics may prove fatal and life threatening to bacterial and fungal infections during routine procedures like elective surgery, C-sections, etc. Currently, a swift elevation in multidrug-resistant organisms (MDROs), like carbapenem-resistant New Delhi metallo- β -lactamase (NDM)-producing *Acinetobacter baumannii*, Enterobacterales, extended-spectrum β -lactamase (ESBL)-producing *Klebsiella pneumoniae*, methicillin-resistant *Staphylococcus aureus* (MRSA), multi-triazole-resistant *Aspergillus fumigatus* and pan-echinocandin-resistant *Candida glabrata* has been seen. Thereupon, the global outbreak of COVID-19 also offers some important ramification for developing antimicrobial drug resistance. This article aims to highlights episodes and aspects of AMR prevalence, impact of management and mismanagement of COVID-19 crisis, hospital settings, community, environment, and travel on the AMR during the current pandemic. © 2023 The Author. Published by Elsevier Ltd on behalf of King Saud Bin Abdulaziz University for Health Sciences. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>).

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Introduction

The ongoing pandemic has overwhelmed healthcare systems globally and at the same time, increase in AMR and MDR (multi-drug

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resistant) pathogens maintains to risk the world health through momentous morbidity, mortality, and economic loss [1]. AMR can be defined as an increasing resistance to frontline lifesaving antibiotics that undermines the ability to treat common and serious infectious diseases. A recent study reports, owing to the (COVID-19) pandemic, higher number of patients have been admitted in hospitals for pragmatic antimicrobial treatment that might not be applicable [2,3], potentially leading to resistant infections worldwide. Although the COVID-19 treatment with antimicrobial therapy is non effective, there are other various reasons for prescribing the antimicrobials: the presence of clinical manifestation that are similar to bacterial or other pneumonias, the possibility of secondary infections, and protocols of healthcare functioning, that might recommend the antimicrobial usage [4]. Though, the antimicrobial treatment in COVID-19 patients could be justifiable in case of bacterial or fungal secondary infection, while for AMR, optimal therapies and appropriate reduction of dose or withdrawal of antimicrobial treatment, and antimicrobial stewardship directed on promoting the line of empirical treatment when a co-infection is present would be of paramount importance [4].

An increasing number of studies indicates that AMR has been growing, after the antibiotic treatment for COVID-19 patients, however, the analysis of existing AMR and comparative range of the related pathogens is still unclear. Studying the occurrence of AMR in COVID-19 patients is of paramount importance. There is a clear indication that over consumption of antimicrobial in humans has led to resistant pathogens that adversely affects the human health, perhaps, among the top ten list, AMR is considered as the potential global threats to human health, food security, and development [5–7]. A crucial information divergent exists about the occurrence, and characteristics of secondary infections with bacteria and fungi, including AMR among the COVID-19 patients.

As per the World health organization, as on 10th November 2022, **6,583,163** lives are lost due to COVID-19 globally since the outbreak and AMR is currently estimated to kill approximately 700,000 people, annually. Assuming that the given data for both are accurate, a rough comparison evaluates that death rates for COVID-19 will stay fixed for the remaining year, however, AMR will kill over 130,000 people annually alone [8]. Moreover, AMR deaths are expected to rise to 10 million deaths every year by 2050, whereas COVID-19 may hopefully be controlled in a much briefer period [1]. This article discusses the impact of various factors on AMR prevalence during the current pandemic, for example, prevalence of bacterial and fungal secondary infections, incoherent use of antimicrobial in covid-19 patients, impact of the management of COVID-19 in hospital settings, community, environment, and travel (Fig. 1) [9].

Secondary infections during the pandemic

Bacterial infections

One of the important issues is the secondary bacterial infections among COVID-19 patients. Until now 1–10% of cases have been recorded to have secondary infections. However, regardless of the proportionality of low recognition of secondary infections, relatively more usage of antibiotics has been recorded during the treatment of COVID-19 patients. This is being practiced even after the WHO recommendation, that is contrary to the consumption of antimicrobials for COVID-19 patients. There are various studies which reports an elevation in MDR bugs during the ongoing pandemic (Table 1). One of the retrospective studies reported, that the colonization of carbapenem-resistant Enterobacterales has raised from 6.7% to 50% from 2019 to 2020. In China, Li et al. presented the study reported the isolation of 159 bacterial strains from 102 COVID-19 patients having secondary infections, among them, the most common was *Acinetobacter baumannii* (35.8%; $n = 57$), that was

followed by *Klebsiella pneumoniae* and *Stenotrophomonas maltophilia* with (30.8%; $n = 49$) (6.3%; $n = 10$), respectively. Additionally, the rate of carbapenem resistance for *A. baumannii* was 91.2% and *K. pneumoniae* 75.5%. Another study in France, found that 26 COVID-19 patients in ICU with severe respiratory disease were having a bacterial co-infection, among which five isolates were resistant to third generation cephalosporins and two for amoxicillin/clavulanate. Likewise, another study of 19 COVID-19 patients who were admitted to ICU had a coinfection with 17 MDR- *A. baumannii* and a MRSA. Fu et al. reported five cases of ICU COVID-19 patients with co-infections of MDRs like, extended-spectrum β -lactamase (ESBL)-producing *K. pneumoniae*, *Burkholderia cepacian*, *P. aeruginosa* and *S. maltophilia*. Additionally, New Delhi metallo- β -lactamase (NDM)-producing *Enterobacter cloacae* was reported to be a causative agent for secondary infection in five COVID-19 patients in New York (USA). A retrospective study reported 1959 rare isolates with 29% (569) resistant pathogens while as secondary infection with resistant pathogens ranged from 0.2% to 100%. Multi-drug resistant organisms, MRSA, carbapenem-resistant *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae* and *Candida auris* were among the commonly isolated organisms. This study also reported higher prevalence of AMR outside of Europe and in ICU settings [10–18].

A bacterium is considered as resistant to any specific antimicrobial agent when the drug substance – after a recommended dose – does not effectively kill or inhibit the multiplication of the bacterium. Even though, many bacteria are characteristically resistant to antimicrobials, however, others can develop resistance via gene mutations (for example insertions and deletions) and horizontal gene transfer through conjugation, transformation, or transduction by temperate phages (Fig. 2) [36,37]. The mechanism of antimicrobial resistance in bacteria can be summarized into different categories: (1) restrictive uptake of a drug; (2) altering a drug target; (3) drug inactivation; (4) efflux pump (Fig. 2). The restrictive drug uptake, inactivation of drug, and active drug efflux are considered as the mechanism of intrinsic resistance while acquired resistance may be modification of the drug target of the microbial cell, inactivation of drug molecule, as well as drug efflux pump [38]. Gram negative and gram-positive bacteria varies in the mode of mechanism due to the differences in their cellular structure. Gram negative bacteria may opt all the four main mechanisms, however gram-positive bacteria mostly adopt the restrictive drug uptake as it lacks an LPS outer membrane, hence having limited capacity for specific drug efflux mechanisms [39,40]. In gram negative bacteria, the LPS layer offers a barrier to various types of drug molecules imparting them with innate resistance to several groups of antimicrobial drugs [41]. Fig. 2 demonstrates the general antimicrobial resistance mechanisms.

Fungal infections

Though not recognized well, but fungal infections constitute greatly to human mortality. The unwarranted usage of antifungals has raised the prevalence of invasive mycoses, that have resistance to many antifungals [42] (Fig. 2). In China and worldwide a study on SARS and influenza virus suggests an increased threat of invasive mycoses in COVID-19 immuno-compromised patients. Life-saving surgeries and treatments needs appropriate diagnosis and appropriate treatment for the co-fungal infections [43]. In a study by Posteraro et al., 53-day clinical course of a COVID-19 patient having type 2 diabetes mellitus, was found to have bloodstream infection by three different organisms, *Morganella morganii*, MRSA, and *Candida glabrata* [44]. After the 13 days treatment with caspofungin, *C. glabrata* was found to have FKS-associated pan-echinocandin resistance. In New Delhi (India), candidaemia was found in 15 COVID-19 critical patients, among them 10 cases were MDR *Candida auris* which accounted for 6 deaths [45]. Mohamed et al. observed a severe

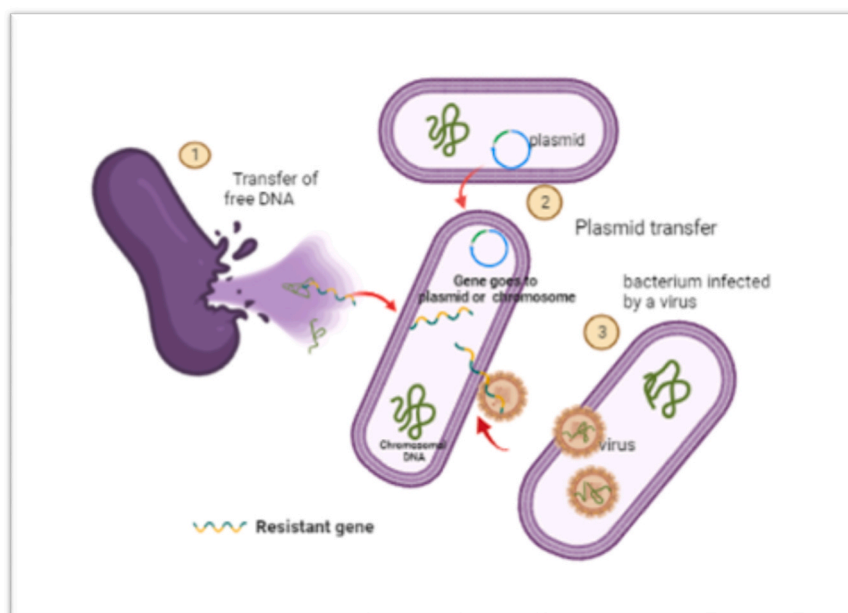


Fig. 1. AMR by bacteria is acquired through mutated “resistance genes” via vertical transfer; gene intake from lysed bacteria, that can also occur between different strains; plasmids as carrier of genes as a horizontal transfer between one bacterium to the other and viruses transporting the genes.

Table 1

Some of the AMR studies from different nations during the COVID-19 pandemic.

Secondary Infection	Country of study	Year	Settings	Number of patients	Resistance	Ref.
<i>E. coli</i> , <i>Klebsiella</i> , <i>S. aureus</i> (MSSA), <i>S. aureus</i> (MRSA), <i>P. aeruginosa</i> . and <i>Enterobacter</i> species	Iran	2020	Outpatients/ inpatients	340	Cotrimoxazole, piperacillin, ceftazidime, and cefepime	[9]
<i>A. baumannii</i> , <i>K. pneumoniae</i> , and <i>S. maltophilia</i> .	China	2020	ICU	102	Carbapenem- and Methicillin	[19]
<i>K. pneumoniae</i> , <i>A. baumannii</i> , <i>S. maltophilia</i> , <i>C. albicans</i> , and <i>Pseudomonas spp.</i>	China	2020	ICU	190	Carbapenem	[20]
<i>A. baumannii</i> .	Iran	2020	ICU	19	colistin	[14]
<i>K. pneumoniae</i> and 4 <i>Enterobacter cloacae</i>	USA	2020	ICU	13	ceftazidime/avibactam	[21]
<i>A. baumannii</i> , and <i>K. pneumoniae</i> .	India	2021	ICU	750	MDR, Carbapenem 47 %	[22]
<i>Acinetobacter spp.</i>	Serbia	2021	ICU	611	imipenem, meropenem, and ciprofloxacin	[23]
<i>K. pneumoniae</i> , and <i>A. baumannii</i> .	Egypt	2021	ICU	197	(PDR) <i>K. pneumoniae</i> , and (MDR) <i>A. baumannii</i>	[24]
<i>E. coli</i> and <i>K. pneumoniae</i>	Pakistan	2021	ICU	856	<i>E. coli</i> to ciprofloxacin and ampicillin. <i>K. pneumoniae</i> to ampicillin and amoxicillin	[25]
<i>S. aureus</i> , and <i>P. aeruginosa</i>	Italy	2021	Outpatients/ inpatients	255	oxacillin, vancomycin, carbapenems, colistin, third- and fourth-generation cephalosporins.	[26]
<i>A. baumannii</i> and <i>E. coli</i>	India	2021	ICU	7309	MDR	[27]
<i>E. coli</i>	Indonesia	2021	Outpatients/ inpatients	148	ofloxacin, aztreonam, Fosfomycin, piperacillin, amoxicillin, cefadroxil, and ampicillin	[28]
<i>E. coli</i> , <i>K. pneumoniae</i> , and <i>P. aeruginosa</i> .	Turkey	2021	Outpatients/ inpatients	3532	SBL producing <i>Enterobacterales</i> MDR	[29]
<i>E. coli</i> , <i>A. baumannii</i> , <i>K. pneumoniae</i> , <i>S. aureus</i> and <i>E. faecalis</i> .	Italy	2021	ICU	89	MDR	[30]
<i>A. baumannii</i> , <i>K. pneumoniae</i> .	Saudi Arabia	2022	Outpatients/ inpatients	108	piperacillin/tazobactam and trimethoprim/sulfamethoxazole.	[31]
<i>E. coli</i> and <i>P. aeruginosa</i>	Iran	2022	ICU	553	carbapenem-resistant	[32]
<i>K. pneumoniae</i> and <i>A. baumannii</i>	Iran	2022	ICU	38	amikacin, gentamycin, imipenem, and cefixime.	[33]
<i>Acinetobacter spa</i>	Iran	2022	ICU	38	amikacin, gentamycin, imipenem, and cefixime.	[33]
<i>A. baumannii</i> , <i>K. pneumoniae</i> , <i>P. aeruginosa</i> , and <i>E. faecium</i>	Turkey	2022	ICU	119	tigecycline.	[34]
<i>K. pneumoniae</i> and <i>A. baumannii</i> .	India	2022	inpatients	122	Carbapenem	[35]

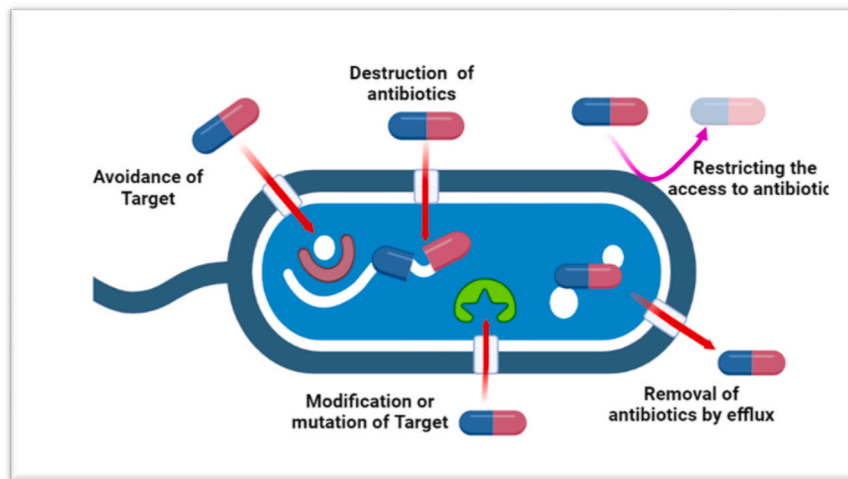


Fig. 2. Antimicrobial resistance in bacterial co-infections. Bacteria can develop the mechanism that avoid the target either by producing enzymes capable of destroying the drug or modifying their structure. Bacteria use efflux pumps to remove the antimicrobial or reduce the affinity by mutating the target.

COVID-19 pneumonia with a co-infection of *Aspergillus fumigatus*, a multi-triazole-resistant strain [46]. A cohort of 31 subjects found, 19.4% were having aspergillosis and other studies done in Indian hospitals during the COVID-19 treatment, were detected with candidemia in 2.5% critical patients, among which 53% died. Moreover, 66% of them were suffering from a persistent fungemia despite the treatment with antifungal therapy [47,48]. For many years, azole group has been established as the gold standard treatment against fungal infections. However, Denning et al. in a study demonstrated a greater occurrence of resistance to triazole by *Aspergillus fumigatus* among the patients with chronic fungal diseases. Therefore, fungal infections among the COVID-19 patients bear a constant treatment challenge that demands examining the non-traditional solutions to combat the drug resistance menace post COVID-19.

One of the mechanisms for the resistance is fungi tend to produce elevated amount of enzymes that are the main target for azole group and other antifungal drugs, hence preventing the suppression of metabolic reactions. Another mechanism used is the modification of the arrangement of targeted enzyme that minimize the attachment efficacy of azole significantly [49]. Additionally fungal cells can actively pump out the antifungal drugs by using the efflux pumps. Moreover, cell can also bypass the metabolic cascades that the drug is known to target. The fungi have the ability to produce extracellular enzymes that can dissociate the antifungal compounds [50–52] (Fig. 3).

Perspective

Instead, great discretion is needed for the fact that improper use or abuse of antimicrobials is recognized to be one of a potential operator for the occurrence of AMR. Significant approach on AMR focusses on minimizing the inappropriate utilization of antimicrobials by clinicians and health practitioners. Several nations, which have relatively made advancement in this field, may easily confront reduced AMR infections compared to the nations who have achieved little or no success in minimizing the antibiotic consumption. The antibiotics by clinicians should be considered very critically and carefully, as frequent antibiotic prescription of antibiotics makes public believe that all antibiotics are effective for the treatment of viral infections in general and SARS-CoV-2 in particular.

Incoherent application of disinfectants

Beyond the clinics, almost all the nations have been exercising measures, intended at reducing the spread of SARS-CoV-2, that

varied from physical distancing to complete lock down. However, the constant instructions from the beginning have been regular hand washing with soaps and/or the use of sanitizers Nevertheless, the use of disinfectants and antimicrobial soaps has exponentially increased over the period of this pandemic and is likely to continue [1,53]. Undoubtedly such practices may help in combating the spread of virus; however, it has an adverse effect that could emerge from increased usage of products that are mainly microbiocidal (Fig. 3). Ultimately, these microbiocidal found in most of the disinfectants and surface cleaners may also lead to development of AMR, as these increased concentrations of biocides usually find their way into wastewater treatments plants and other water bodies [54,55]. Most importantly if the concentration of biocide is very high, possibly the maximum inhibition of bacteria will take place, however, if the concentration increases but does not reach the minimum inhibitory concentration required for varying microbial flora, this would in turn offer an opportunity to the emergence of AMR. Moreover, preventive treatment for bacterial secondary infection among COVID-19 patients could be also responsible to elevated levels of antibiotics in the water bodies and the receiving environments which may result in the evolution of AMR [56,57] (Fig. 4).

Hospital settings

The health management system throughout the globe has been under immense burden which led towards several modifications in clinical practice that may have an impact on AMR. Regarding the COVID-19 management in health care settings, most of the world governments have recommended some measures for the prevention and control of infection through droplets, aerosols and direct contact with potentially contaminated surfaces. These strategies like extra vigilance of hygiene, sterilization techniques may lower down the circulation of AMR bacteria within clinical settings. However, it would be of paramount importance to collect the information on the prevalence of prior and post AMR infections during the current pandemic, to evaluate and contain the AMR menace at local and thereby at global level. Clinicians and researchers need to work hand in hand for the study and correlation of whole genome sequences of clinical isolates, prior, during and post COVID-19 pandemic, which is one of the promising technique to interpret the changes in the transition of AMR mechanisms [58–61].

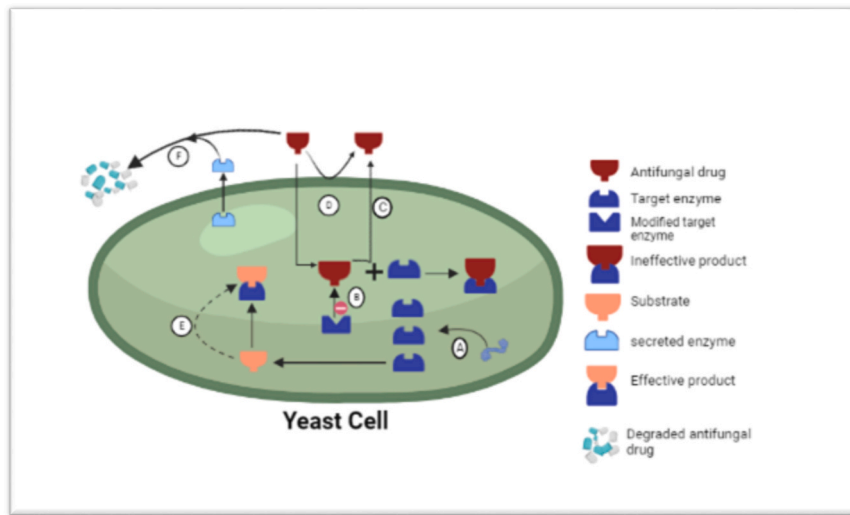


Fig. 3. Fungal resistance against antifungal compounds. (A) Fungi likely increase the production of enzymes that are main targets for the drugs. This counters the inhibition of metabolic activities. (B) Modifying the spatial structure of target enzyme minimizes the drug binding efficiency. (C) Efflux pumps efficiently pumps out the antifungal drugs out of the cell. (D) fungal cell wall/membrane blocks the penetration of antifungals. (E) The fungal cell escapes the routine pathway that the drug recognizes to target. (E) The secretion of extracellular enzymes having the ability to degrade the antifungal drug.

Travel and AMR

Travel has been also seen to have impact on the transmission of AMR. Transfer of important AMR genes between nations is inarguable. Among the primary genes responsible for resistance to last option antibiotic carbapenem was initially identified in India [62], and thereafter isolated throughout the world [63]. Moreover, inception of the *mcr1* gene responsible for conferring resistance to colistin an important antibiotic, was initially isolated in China, however now found to exist worldwide [64,65]. First time, the emergence of tigecycline resistance gene *tet* (X4), has recently found in China. One of the “pandemic” labeled gene i.e., CTX-M genes emerged among environmental bacteria is found worldwide Nevertheless, a viral pandemic has even more rapid effect of infection, usually with symptoms, hence transmission of AMR may lead to colonization and shedding [66–69]. Restrictions of travel during

the pandemic on a massive scale may have a huge impact on slowing the spread of AMR.

Conclusion and outlook

The current pandemic will be remembered as a momentous event in the history of humankind. Eventually, COVID-19 would be an important comparison for defining the development of AMR and illustrating the challenges to contain it, once it has evolved. Unfortunately, a widespread misconception seen among the common masses is that antibiotics like azithromycin, amoxicillin, amoxiclav etc., are effective in treating COVID-19. Additionally, suspected cases that are self-isolating and confirmed asymptomatic COVID-19 cases are reported to use antibiotics. Therefore, it is pertinent to create greater awareness in the public about the consequences of overuse and misuse of antibiotics. The reasonable

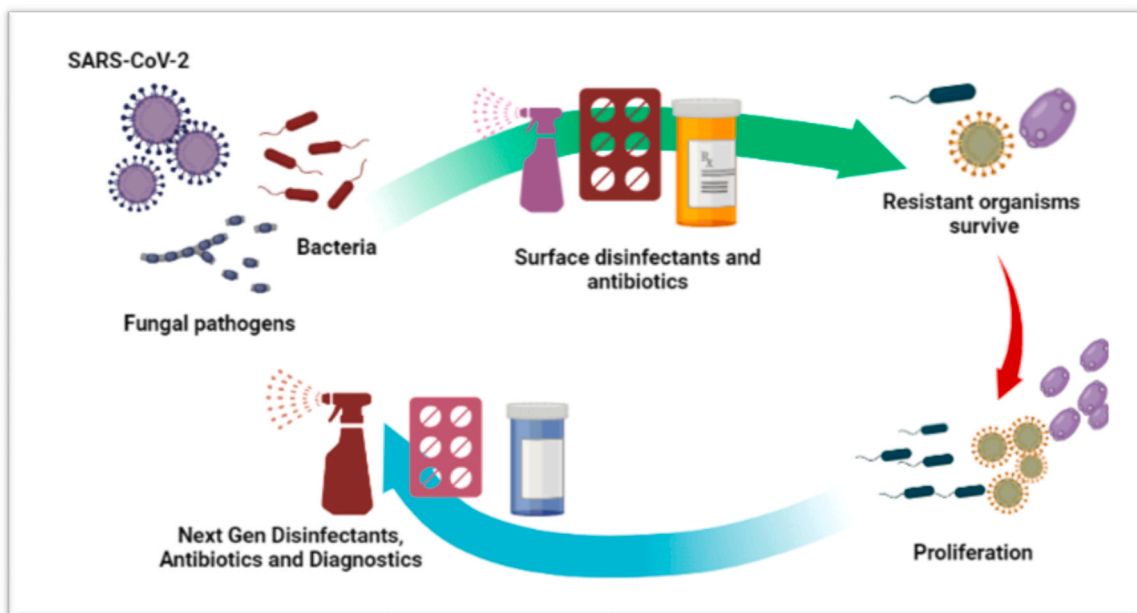


Fig. 4. Incoherent usage of disinfectants leading to proliferation of resistant microbes that would be needing next generation antibiotics.

understanding of appropriate usage of antibiotic would be instrumental in preventing the occurrence of AMR. However, among the emerging infectious diseases, AMR will persist over and above the COVID-19 pandemic. Likewise, the current and other pandemics, AMR too are a problem that “knows no borders” and is considered as more intriguing problem. Undoubtedly, AMR presents lesser immediate impact on everyday life, though potentially greater and far-reaching adverse effects on humankind. Therefore, management strategies to reduce the emergence of AMR should be investigated and implemented at local and global level.

Remarks

Apart from current pandemic, the clinicians in developing countries have been heavily prescribing antibiotics even for the common cold where they are least or not effective at all. Furthermore, other factors which are considered as a criminal offense in the developed parts of the world, for example, over the counter usage of antibiotics and their prophylactic consumption, are a normal practice in developing regions. This abuse of antibiotics is an additional challenge that needs action from policy makers at national and international institutional level.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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