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Evolution of Antimicrobial Resistance in the Era of COVID-19

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Authors' contributions

This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.

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Review Article

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ABSTRACT

Antimicrobial resistance is a slow-growing phenomenon that could even be a reason for a future pandemic. Due to inappropriate diagnosis and consumption of antibiotics, the bacteria have become resistant to the antibiotics used. In the era of COVID-19, this blind consumption of antibiotics has rapidly increased due to the period of quarantine and fear of the disease. Ligue to the fear of the pandemic, especially in ru, rural areas, many patients avoid going to the hospital and consuming antibiotics without any prescription. Various retrospective studies have shown a relationship between bacterial co-infection and AMR, which is increased in the era of COVID-19. Also, the secondary bacterial infections associated with the pandemic of COVID-19 have added to the risk of antimicrobial resistance. The viral effect on the respiratory system is favorable for bacterial infection, as in the case of COVID-19 affecting the respiratory tract followed by co-bacterial infection in some cases. COVID-19 has affected AMR in many aspects. Proper antibiotic resistance tests should be performed before prescribing any antibiotics to the patient to reduce the chances of AMR, especially in such an obnoxious situation of COVID-19. This crucially calls for a brand new and effective plan of action to attenuate the influence of the pandemic on antimicrobial resistance. Statistics of various countries in matters of antimicrobial resistance have shown an increase in AMR due to the concentration of health workers, researchers, and population on the

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pandemic associated with COVID-19. This calls for the necessity to aware the population worldwide about antimicrobial resistance and how it could be a hidden menace in the future and could probably prove to be a matter of concern as it would worsen the condition of the patients in a particular disease and would decrease the various possible aspects of the treatment especially in case of treatment based on antibiotics.

Keywords: Antimicrobial resistance; antibiotics; co-bacterial infection; COVID-19.

1. INTRODUCTION

Antimicrobial resistance(AMR) is seen to be emerging as a threat to effective prevention and treatment in the 21st century [1]. AMR can be explained in regards to antibiotic resistance developed over decades in the bacteria causing infections resulting in the ineffectiveness of any new antibiotic in the market on the resistant bacteria [1]. Accurate secondary bacterial infection characterization is critical in the clinical management of the most severe COVID-19 cases, might save lives, and enhance patient outcomes a commitment to antimicrobial stewardship across the pandemic's progress [2]. In patients of covid 19, bacterial co-infections associated with COVID-19 have been reported, which will ultimately add up to the possibility of increased antimicrobial resistance [3].

The obnoxious situation that we are hit with, the COVID-19 is reported to be contributing to the risk of antimicrobial resistance through medical management (i.e., by reported cases of bacterial co-infections), although the reported cases of secondary bacterial infections associated with COVID-19 are less as compared to the reports of usage of the antibiotics when treating COVID -19 patient [4]. Bacterial and fungal infections of various types have been reported in patients of COVID-19, along with resistance to antimicrobials leading to worse outcomes and even death [5].

2. RETROSPECTIVE STUDIES, FACTS, AND FINDINGS OF BACTERIAL CO-INFECTION AND AMR IN DIFFERENT COUNTRIES

According to a retrospective study done at Wuhan Union Hospital, it was found that bacterial co-infections were associated with the severity in the case of patients hospitalized. It is also evident that the gram-negative bacteria, most commonly A. bau,mannii, and K. pneumonia, were the cause of oco-infection-infections and were also highly resistant to antimicrobials [6]. A retrospective cohort analysis conducted at a Barcelona hospital proved to be crucial in determining the role of empiric antimicrobial therapy and stewardship efforts [7]. Another retrospective case series of confirCOVID-positive time patients at the UK furthering the first wave of COVID-19 reports low levels of secondary bacterial infection in preliminary COVID-19 hospital presentations [8].

Every year at least 2 million people in the U.S. have been reported wisevereous bacterial infections to which they are resistant. Among these, an unignorable figure of 23,000 patients died antibiotic-resistant instant infections, and this figure increased when further complications were added to the picture [9]. Approx. Four hundred thousand infections and 25,000 deaths are estimated yearly in Europe because of the multi-resistant bacteria like S. aureus, Escherichia coli, Enterococcus faecium, Streptococcus pneumonia, Klebsiella pneumonia, and Pseudomonas aeruginosa [10]. A study survey among the European citizens reported that the percentage of the participants in the survey involved in the usage of antibiotics in the treatment of flu-like symptoms and known that antibiotics do not act against viral infections was found to be 20%. On the other hand, 14% of the participants admitted that they took antibiotics to treat acute rhinitis or cold [11]. A study survey in the UK amidst the adults reported that the percentage of participants of the survey that didn’t know that antibiotics do not act against cold and cough was 38% [12]. According to a survey, Sweden’s comprehension of anti and the possibility of AMR is good and homogenous. Only one-fifth of the participants were assured with the myth that antibiotics treat the common cold more effectively [12].

3. ANTIMICROBIAL-RESISTANT ORGANISMS

3.1 *Staphylococcus aureus*

MRSA is the name given to the strain of Staphylococcus aureus resistant to anti-staphylococcal penicillin [13].

In the U.S., in 2011, there was an estimation of about 80,000 MRSA cases. Only 14,000 cases out of these were reported in hospitals [14,15].

Between 2010 and 2013, there was a considerable decline in the rate and ratio from presumptuous infections in Europe [16].

3.2 *NTS- non-typhoidal salmonella*

In the usage of antimicrobial agents such as ampicillin, chloramphenicol, sulphonamides, and tetracycline, the cases of multi-drug resistance are frequent in Non-typhoidal Salmonella [17,18].

3.3 *Klebsiella pneumoniae*

ESBLs, i.e., extended-spectrum beta-lactamases mediated resistance, include all penicillin, cephalosporins, and aztreonam [19].

3.4 Various Aspects in which COVID-19 Impacts AMR

Secondary bacterial infections have long been thought to be a significant cause of illness and death in viral infections, and they have also been documented in COVID-19 patients, but only a tiny percentage [20]. Antibiotics are misused during the pandemic to self-limit the upper respiratory tract infection in non-hospitalized settings [21,22]. AMR is expected to cause 1,30,000 more fatalities by the end of 2020 owing to the present state of the COVID-19 epidemic [20].

Due to the lack of beds in hospitals and the weakened immune systems of the COVID-infected patients, they are more prone to secondary bacterial infections or co-infections [23,24,25]. Multidrug resistance is reported as using inappropriate antibiotics in COVID-19 patients [23,26].

Even though antibiotic prescribing practices differ by region, enlarged work pressure and psychological stress on medical practitioners make adhering to community hospital antimicrobial stewardship policies more complex. Despite the reality that empiric antibiotics hurt later clinical output, the research suggests that secondary bacterial infections influence only a tiny chunk of COVID-19 victims [27]. Finally, the increased hospital utilization of antibiotics in the case of COVID-19 victims throughout the preliminary phases of the COVID-19 pandemic may impact the total antimicrobial resistance, influencing the load of diseases for later generations. Moreover, the pandemic of COVID-19 has created a severe and extensive global economic crisis, with the potential to fuel a substantial increase in global poverty levels. Lower- and middle-income countries (LMICs) are projected to agonize disproportionately, with many people who are already poor being driven further into poverty [27].

Despite the difficulty in distinguishing pneumonia caused by bacterial infection from pneumonia caused by COVID-19 infection and the lack of antiviral therapy with proven efficacy in treating COVID-19 patients, particularly the critically ill patients, antibiotics must be utilized as a part of an empirical strategy. To avoid considerably more difficult repercussions, it is critical to take antibiotics responsibly even during the pandemic. However, due to antibiotic usage and the increasing percentage of antimicrobial resistance, this concept raises worries about the effects [28].

3.5 Antibiotic Selection Difficulties for COVID-19 Victims in LMI

Suppose the danger of necessitating invasive mechanical ventilation justifies the usage of antibiotics to cure hospital acquhospital-acquired infections. In that case, the scarcity of ventilators in LMICs reduces this probability and should thus considerably decrease unwanted antimicrobial usage. Even though temporary peripheral venous catheters are associated with frequent numb with an f case of infections of bloodstream infection tions in LMICs, risk the s involved in case of the rising figures of COVID-19-infected patients who are hospitalized, which will result in a greater dependence on antibiotics to combat hospital-acquired infections associated with the catheter. Antimicrobial use, along with infection-control strategies, could assist in reducing this risk. Research findings indicate that, in the case of similar pathogenic bacterias, disparities occur among HIC and LMIC in terms of communities at risk, associated symptoms, the prevalence of spread of pathogenic bacteria, and drug sensitivity. The potential danger of COVID-19 may provide chances for LMICs to enforce antimicrobial stewardship programs by WHO guidelines, such as antimicrobial stewardship team education and training, advances in medical guidelines, resistance monitoring, and antibiotic use monitoring [29].

Table 1. Percentage of patients receiving antibiotics and percentage of confirmed secondary infections

%Covid-19 patients treated with antibiotics	Confirmed secondary bacterial infection	Infecting agent	Geographical location
41/41 (100%)	4/41 (10%)	-	Wuhan, China
49/52 (94%)	1/94 (1%)	K. pneumoniae	Wuhan, China
26/53 (49%)	16/53 (30%)	*A. Baumannii, Haemophilusinfluenza, P. aeruginosa, S. aureus, S. pneumoniae*	Milan,Italy
39/92 (42%)	26/92 (28%)	*A. baumannii, H. influenza, Moraxella catarrhalis, P. aeruginosa, S. aureus, S. pneumoniae*	France
181/191 (95%)	28/191 (15%)	-	Wuhan, China
143/150 (95%)	12/150 (8%)	-	Wuhan, China
42/48 (88%)	6/48 (13%)	*E. faecium, H. influenza, P. aeruginosa*	Vitoria, Spain
37/298 (12%)	30/298 (10%)	-	Shenzhen City, China
319/476 (67%)	35/410 (9%)	-	Wuhan, Shanghai, and Anhui (China)
49/49 (100%)	2/49 (4%)	Serratia sp., Enterobacter sp.	Hong Kong, China
6/11 (55%)	6/11 (55%)	H. influenza, K. pneumoniae	Bangkok, Thailand
66/67 (99%)	3/28 (11%)	A. baumannii, Enterobacter cloacae	Wuhan, China

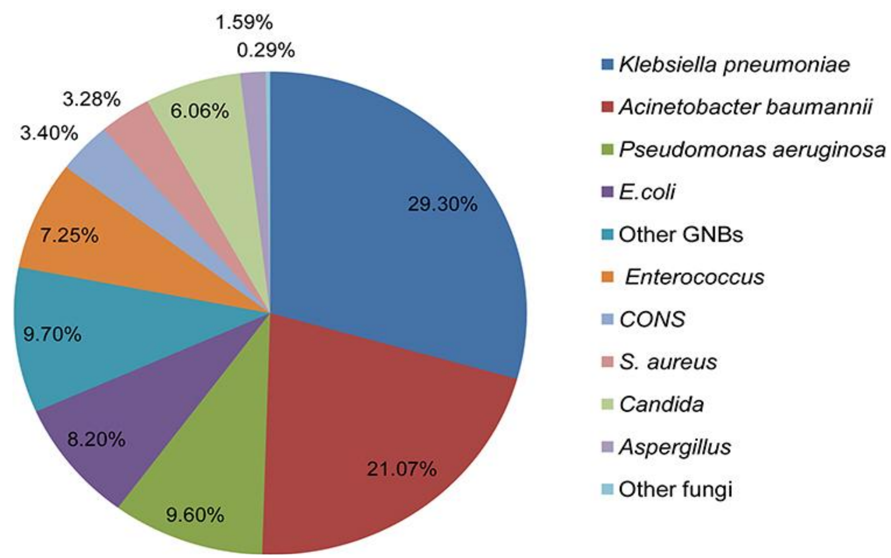

Fig. 1. Isolated bacterial and fungal pathogens from Covid-19 patients with their distribution [32]

3.6 Strategies to Attenuate Consequence of COVID-19 on AMR

The health care system needs to balance the imbalance in antibiotics and microbial investigations [30]. Assessment of the articles, reports, and studies about the enlarged possibility of AMR due to the pandemic of COVID-19 plays an essential role in the development of attenuation strategies [31]. AMR should be made as an essential basic in clinical practices [32].

Diagnostics should be more appropriate in this challenging time of the pandemic of COVID-19 in terms of identifying the proper organism involved as the cause of the secondary bacterial infection (30). A support system must be built to support the researchers and their confidence, encouraging them to carry on with the AMR research and monitoring [33]. The formation and appearance of networks of collaborators coming up in the covid 19 era should be encouraged to help us with their motive to handle issues regarding the covid 19 pandemic [33].

International campaigns like the biennial World Antibiotic Awareness Week raise awareness of AMR and the importance of antibiotic stewardship More regularly washing hands (e.g., through Hand Hygiene Day) appears to pay off when hygiene practices are prioritized. Usage of antibiotics should be with caution and care, in case of empirical therapy in advance for occurrence with a strong possibility of microbial co-infection and the statistics of resistance taken into consideration. In reaction to microbiological discoveries, empirical prescriptions should be rapidly re-evaluated and changed. [27].

3.7 Antimicrobial Stewardship Program and COVID-19

Antimicrobial stewardship denotes collaborative, integrated programs and initiatives to promote appropriate antimicrobial treatment regimens, including dose, length of treatment, and other factors [28]. Antimicrobial stewardship programs can observe and improve compliance with the help of treatment guidelines during pandemics of respiratory viruses accompanied by bacterial co-infections and diseases such as pneumonia and ARDS. Severe COVID-19 instances have been treated with broad-spectrum antibiotics. Despite the complexity of distinguishing COVID-19 from bacteria associated pneumonia, the uncertainty about bacterial superinfections, the lack of precise antiviral treatment for the prevailing pandemic, and the high death rates, antibiotics should be considered to be part of the empirical therapy for the most severe suspected or confirmed COVID-19 cases (e.g., patients necessitating mechanical ventilation). Antibiotics should, however, be administered with caution and caution during such a pandemic [28].

3.8 Monitoring AMR in the Era of Covid-19: A Challenge

Due to lack of time and increase of burden and responsibilities on health care professionals and population, the whole attention is being shifted towards working on Covid-19. This has affected the participation and involvement in AMR research and has also led to the discontinuation in maintaining the accounts of and monitoring AMR. Recently developed and implemented systems of monitoring for Covid-19 can be utilized to fortify environmental monitoring of antimicrobial resistance [33].

3.9 Statistics and Facts

- In Wuhan, antibiotics were preferred for treatment in 95% of patients, and antivirals were given to 21% [34].
- As per the fourth GLASS report, the 2019 data collection regarding AMR by WHO estimates 3 106 602 laboratories confirmed cases of infections in 70 countries [35].
- Another data collected by GLASS in 2019 presents the percentage resistance to ciprofloxacin for UTI to be 8.4% - 92.9% with the involved bacteria as E. coli, and in the case of Klebsiella pneumonia, it ranges from 4.1% - 79.4% [29].
- As a result of a study, it was found and admitted by 41% of the participants that during the treatment of COVID, 19 frequently prescribed drug of choice was azithromycin. [28]
- COVID-19, due to the SARS coronavirus 2 (SARS Cov2), caused 119.2 million illnesses and 2.64 million deaths worldwide as of 14 March 2021.
  India had 11.35 million illnesses and 0.15 million fatalities as of March 14, 2021 [32].
- In 2020, AMR is expected to have killed one-third of the total people killed due to COVID-19 [33]

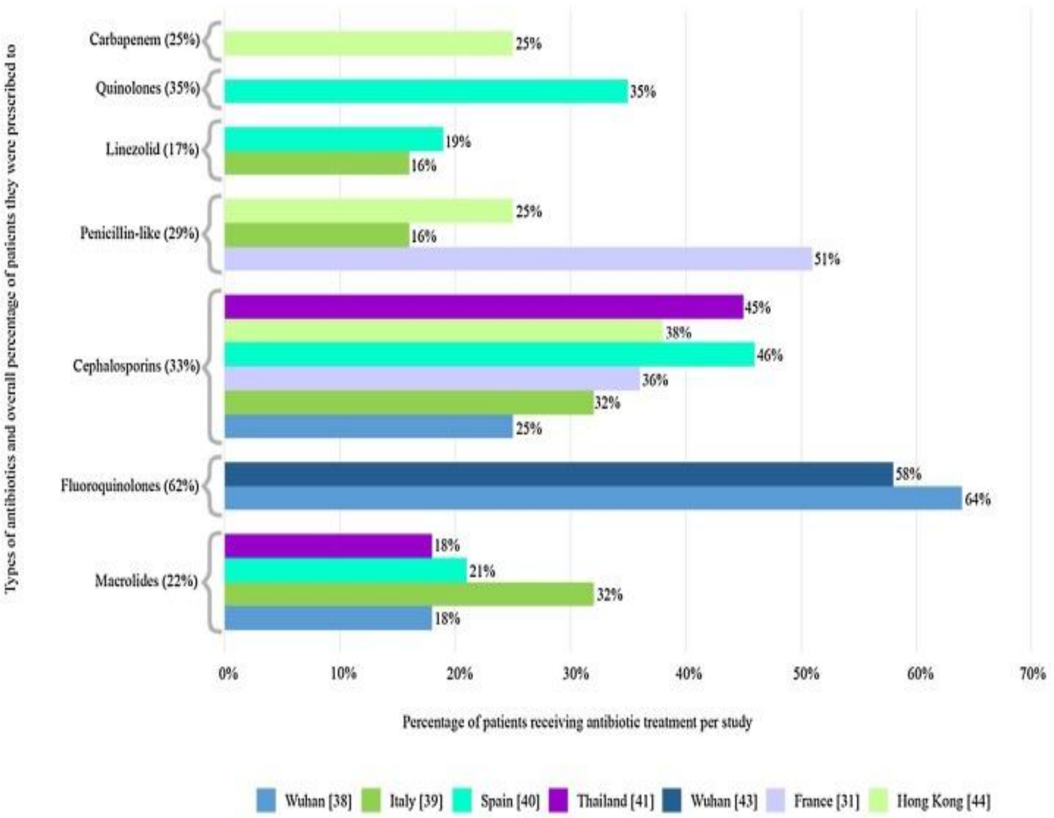

Fig. 2. Rate of patients with particular antibiotics received and Rate of patients with prescribed antibiotics [28]

4. COMBINED EFFECTS OF BACTERIAL AND VIRAL PATHOGENS

It is evident that viral infection like COVID-19 affecting the respiratory tract also promotes bacterial growth by altering the function of the innate immune system [29]. It is also evident that due to the impact of immune response throughout a viral infection like covid, there is a modification in the anatomy of the respiratory tract, which has been known to sabotage the immune system's defenses against the pathogenic virus or bacteria [29].In the case of infected SARS-CoV-2 subjects, the pulmonary alveoli filled with puss and fluid favors and provide the suitable medium for the growth of P. aeruginosa and S. aureus-like bacteria [29].

4.1 Bacterial Coinfection and Subsequent Infections Predictors (Clinical, Biomarkers)

There is a need for more research into the predictive ability of various clinical or laboratory investigations during the patient's hospitalization for coinfections. Complete data collection must be harmonized across randomized trials, studies, and varied patient profiles, along with adequate microbiological investigations [20]. Clinicians have employed biomarkers such as C-reactive protein (CRP) and procalcitonin (PCT) to aid in diagnosing infections associated with bacteria. In severe cases, it may be high. COVID-19 patients have a limited lifespan due to the virus. Use in determining how long and how often antibiotics should be given [36].

4.2 Access of Antimicrobials

COVID-19 has impacted antibiotic availability by altering supply chains and worldwide antimicrobial manufacture, resulting in modifications in consumption levels.

The vulnerability of the network of antibiotics was emphasized not so long ago when a single Chinese manufacturer was shut down, resulting in a worldwide scarcity of piperacillin-tazobactam. Fears of scarcity have prompted the European Medicines Agency to take "urgent and synchronized measures to stop and reduce medicine deficits inside the EU."As a result of COVID-19, nations that produce and trade antibiotics are increasingly facing domestic demand, leading to a drop in shipments, as observed in India. This may result in a request for expanded antibiotic production beyond the production hubs of India and China. COVID-19 is supposed to be leading to modifications in antibiotic use, which would have a parallel impact on supply chain shortfalls; eleven producers have claimed azithromycin scarcity to the United States Food And drug, possibly due to its use for COVID-19 medication [33].

4.3 Antimicrobial use in COVID-19 Patients

Antimicrobials are administered to up to 70% of COVID-19 patients in either an inpatient facility or outpatient care setting, which will support AMR [33]. Antimicrobials are being used because they are thought to influence SARS-CoV-2 negatively. This could lead to resistance in pathogenic microbes that co-infect or co-colonize(37). Cheap, quick diagnostics in community settings may detect infections like SARS-CoV-2 earlier, mainly in the face of imprecise symptomatology, and hence reduce antibiotic use. This will be especially relevant in low- and middle-income countries where antibiotics are available without a prescription and testing is emphasized, whereas vaccinations may take more time to become more widely utilized [33-45].

5. CONCLUSION

This review demonstrates the effect of the covid 19 pandemic on antimicrobial resistance and vice-versa. AMR, which has been a hidden menace, is discussed covid 19 to create awareness regarding future risks with AMR. The importance of correct diagnosis about the secondary bacterial infections is mentioned, as it was found to be out of focus in the covid 19 era due to the burden on health care professionals. We are realizing the fact that covid 19 has piqued our curiosity leading to unbalanced monitoring of the AMR, which will now be encouraged. An account of bacterial and fungal co-infection in covid 19 patients along with retrospective studies from different countries are discussed in this review to draw knowledge about the link between AMR and COVID-19.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

DISCLAIMER

The products used for this research are commonly and predominantly used in our research area and country. There is no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Dixit A, Kumar N, Kumar S, Trigun V. Antimicrobial resistance: progress in the decade since emergence of New Delhi metallo-β-lactamase in India. Indian journal of community medicine: official publication of Indian Association of Preventive & Social Medicine. 2019;44(1):4.
2. Cox MJ, et al. Co-infections: potentially lethal and unexplored in COVID-19. Lancet Microbe. 2020;1:E11.
3. Rezasoltani S, Yadegar A, Hatami B, Aghdaei HA, Zali MR. Antimicrobial resistance as a hidden menace lurking behind the COVID-19 outbreak: the global impacts of too much hygiene on AMR. Frontiers in Microbiology. 2020;11.
4. Murray AK. The novel coronavirus COVID-19 outbreak: global implications for antimicrobial resistance. Frontiers in microbiology. 2020;11:1020.
5. Rodríguez-Álvarez M, López-Vidal Y, Soto-Hernández JL, Miranda-Novales MG, Flores-Moreno K, de León-Rosales SP. COVID-19: Clouds Over the Antimicrobial Resistance Landscape. Archives of Medical Research. 2021;52(1):123-6.
6. Li J, Wang J, Yang Y, Cai P, Cao J, Cai X, Zhang Y. Etiology and antimicrobial resistance of secondary bacterial infections in patients hospitalized with COVID-19 in Wuhan, China: a retrospective analysis. Antimicrobial Resistance & Infection Control. 2020;9(1):1-7.

7. Rawson TM, Moore LS, Castro-Sanchez E, Charani E, Davies F, Satta G, Ellington MJ, Holmes AH. COVID-19 and the potential long-term impact on antimicrobial resistance. Journal of antimicrobial chemotherapy. 2020;75(7):1681-4.
8. Hughes S, Troise O, Donaldson H, Mughal N, Moore LS. Bacterial and fungal coinfection among hospitalized patients with COVID-19: a retrospective cohort study in a UK secondary-care setting. Clinical Microbiology and Infection. 2020;26(10):1395-9
9. US Department of Health and Human Services. Antibiotic resistance threats in the United States, 2013. Centers for Disease Control and Prevention. 2013:1-13.
10. ECDC E. The bacterial challenge–time to react a call to narrow the gap between multidrug-resistant bacteria in the EU and development of new antibacterial agents. Solna: ECDC & EMEA Joint Press Release;2009.
11. Eurobarometer S. Antimicrobial resistance, November-December 2009. Brussels: TNS Opinion & Social. 2010;338.
12. André M, Vernby Å, Berg J, Lundborg CS. A survey of public knowledge and awareness related to antibiotic use and resistance in Sweden. Journal of Antimicrobial Chemotherapy. 2010;65 (6):1292-6.
13. Ofori-Asenso R. “When the Bug Cannot Be Killed”—The Rising Challenge of Antimicrobial Resistance. Medicines. 2017;4(2):40.
14. Centers for Disease Control and Prevention. Active Bacterial Core Surveillance Report, Emerging Infections Program Network, Neisseria meningitidis, 2010. Top of Page View Page In: pdf icon PDF [52K] Page last reviewed: April. 2011;6:2012.
15. Dantes R, Mu Y, Belflower R, Aragon D, Dumyati G, Harrison LH, Lessa FC, Lynfield R, Nadle J, Petit S, Ray SM. National burden of invasive methicillin-resistant Staphylococcus aureus infections, United States, 2011. JAMA internal medicine. 2013;173(21):1970-8.
16. European Centre for Disease Prevention and Control (ECDC) Antimicrobial resistance surveillance in Europe 2013. Annual Report of the European Antimicrobial Resistance Surveillance Network (EARS-Net). Stockholm: ECDC; 2014.
17. Mather AE, Reid SW, Maskell DJ, Parkhill J, Fookes MC, Harris SR, Brown DJ, Coia JE, Mulvey MR, Gilmour MW, Petrovska L. Distinguishable epidemics of multidrug-resistant Salmonella Typhimurium DT104 in different hosts. Science. 2013;341(6153):1514-7.
18. Li Y, Xie X, Xu X, Wang X, Chang H, Wang C, Wang A, He Y, Yu H, Wang X, Zeng M. Nontyphoidal salmonella infection in children with acute gastroenteritis: prevalence, serotypes, and antimicrobial resistance in Shanghai, China. Foodborne pathogens and disease. 2014;11(3):200-6
19. Delgado-Valverde M, Sojo-Dorado J, Pascual Á, Rodríguez-Baño J. Clinical management of infections caused by multidrug-resistant Enterobacteriaceae. Therapeutic advances in infectious disease. 2013;1(2):49-69.
20. Sama Rezasoltani,Abbas yadegar et al. Antimicrobial Resistance as a Hidden Menace Lurking Behind the COVID-19 Outbreak: The Global Impacts of Too Much Hygiene on AMR;2020.
21. Dekker AR, Verheij TJ, van der Velden AW. Inappropriate antibiotic prescription for respiratory tract indications: most prominent in adult patients. Family practice. 2015;32(4):401-7.
22. Gulliford MC, Dregan A, Moore MV, Ashworth M, Van Staa T, McCann G, Charlton J, Yardley L, Little P, McDermott L. Continued high rates of antibiotic prescribing to adults with respiratory tract infection: survey of 568 UK general practices. BMJ open. 2014;4(10):e006245.
23. Afshinnekoo E, Bhattacharya C, Burguete-García A, Castro-Nallar E, Deng Y, Desnues C, Dias-Neto E, Elhaik E, Iraola G, Jang S, Łabaj PP. COVID-19 drug practices risk antimicrobial resistance evolution. The Lancet Microbe. 2021;2(4):e135-6.
24. Cox MJ, Loman N, Bogaert D, O'Grady J. Co-infections: potentially lethal and unexplored in COVID-19. The Lancet Microbe. 2020;1(1):e11.
25. Sterenczak KA, Barrantes I, Stahnke T, Stachs O, Fuellen G, Undre N. Co-infections: testing macrolides for added benefit in patients with COVID-19. The Lancet Microbe. 2020;1(8):e313.
26. Moreno-Gamez S, Hill AL, Rosenbloom DI, Petrov DA, Nowak MA, Pennings PS.

Imperfect drug penetration leads to spatial monotherapy and rapid evolution of multidrug resistance. Proceedings of the National Academy of Sciences. 2015; 112(22):E2874-83..

27. Pelfrene E, Botgros R, Cavaleri M. Antimicrobial multidrug resistance in the era of COVID-19: a forgotten plight?. Antimicrobial Resistance & Infection Control. 2021;10(1):1-6.
28. Soumya Ghosha, Charné Bornmana, Mai M. Zafer b. Journal of Infection and Public Health. Antimicrobial Resistance Threats in the emerging COVID-19 pandemic: Where do we stand?. 2021;14:555–560.
29. Lucien MA, Canarie MF, Kilgore PE, Jean-Denis G, Fénélon N, Pierre M, Cerpa M, Joseph GA, Maki G, Zervos MJ, Dely P. Antibiotics and antimicrobial resistance in the COVID-19 era: Perspective from resource-limited settings. International Journal of Infectious Diseases. 2021;104:250-4.
30. Rawson TM, Ming D, Ahmad R, Moore LS, Holmes AH. Antimicrobial use, drug-resistant infections and COVID-19. Nature Reviews Microbiology. 2020;18(8):409-10.
31. Sharland M, Pulcini C, Harbarth S, Zeng M, Gandra S, Mathur S, Magrini N. Classifying antibiotics in the WHO Essential Medicines List for optimal use—be AWaRe. The Lancet Infectious Diseases. 2018;18(1):18-20.
32. Vijay S, Bansal N, Rao BK, Veeraraghavan B, Rodrigues C, Wattal C, Goyal JP, Tadepalli K, Mathur P, Venkateswaran R, Venkatasubramanian R. Secondary Infections in Hospitalized COVID-19 Patients: Indian Experience. Infection and drug resistance. 2021;14:1893.
33. Rezasoltani S, Yadegar A, Hatami B, Aghdaei HA, Zali MR. Antimicrobial resistance as a hidden menace lurking behind the COVID-19 outbreak: the global impacts of too much hygiene on AMR. Frontiers in Microbiology. 2020;11.
34. Zhou, F. et al., Clinical course and risk factor of mortality of adult inpatients with COVID-19 in Wuhan, China. 2020; Lancet 395:1054-1062
35. Patil D, Overland M, Stoller M, Chatterjee K. Bioinspired nanostructured bactericidal surfaces. Current Opinion in Chemical Engineering. 2021;34:100741.
36. Rawson TM, Moore LS, Castro-Sanchez E, Charani E, Davies F, Satta G, Ellington MJ, Holmes AH. COVID-19 and the potential long-term impact on antimicrobial resistance. Journal of Antimicrobial Chemotherapy. 2020;75(7):1681-4.
37. Tedijanto C, Olesen SW, Grad YH, Lipsitch M. Estimating the proportion of bystander selection for antibiotic resistance among potentially pathogenic bacterial flora. Proceedings of the National Academy of Sciences. 2018;115(51):E11988-95.
38. Acharya, Sourya, Samarth Shukla, and Neema Acharya. “Gospels of a Pandemic- A Metaphysical Commentary on the Current COVID-19 Crisis.” Journal of Clinical and Diagnostic Research. 2020;14(6):OA01–2.
Available:https://doi.org/10.7860/JCDR/2020/44627.13774.
39. Arora, Devamsh, Muskan Sharma, Sourya Acharya, Samarth Shukla, and Neema Acharya. “India in ‘Flattening the Curve’ of COVID-19 Pandemic - Triumphs and Challenges Thereof.” Journal of Evolution of Medical and Dental Sciences-Jemds. 2020;9(43):3252–55.
Available:https://doi.org/10.14260/jemds/2020/713
40. Bawiskar, Nipun, Amol Andhale, Vidyashree Hulkoti, Sourya Acharya, and Samarth Shukla. “Haematological Manifestations of Covid-19 and Emerging Immunohaematological Therapeutic Strategies.” Journal of Evolution of Medical and Dental Sciences-Jemds. 2020;9 (46):3489–94.
Available:https://doi.org/10.14260/jemds/2020/763.
41. Burhani, Tasneem Sajjad, and Waqar M. Naqvi. “Telehealth - A Boon in the Time of COVID 19 Outbreak.” Journal of Evolution of Medical and Dental Sciences-Jemds. 2020;9(29):2081–84.
Available:https://doi.org/10.14260/jemds/2020/454.
42. Butola, Lata Kanyal, Ranjit Ambad, Prakash Keshaorao Kute, Roshan Kumar Jha, and Amol Dattaroa Shinde. “The Pandemic of 21st Century - COVID-19.” Journal of Evolution of Medical and Dental Sciences-Jemds. 2020;9(39):2913–18.
Available:https://doi.org/10.14260/jemds/2020/637.

43. Dasari, Venkatesh, and Kiran Dasari. “Nutraceuticals to Support Immunity: COVID-19 Pandemic- A Wake-up Call.” Journal of Clinical and Diagnostic Research. 2020;14(7):OE05–9. Available:https://doi.org/10.7860/JCDR/2020/44898.13843.
44. Dhok, Archana, Lata Kanyal Butola, Ashish Anjankar, Amol Datta Rao Shinde, Prakash Kesharao Kute, and Roshan Kumar Jha. “Role of Vitamins and Minerals in Improving Immunity during Covid-19 Pandemic - A Review.” Journal of Evolution of Medical and Dental Sciences-Jemds. 2020;9(32):2296–2300. Available:https://doi.org/10.14260/jemds/2020/497.
45. Gawai, Jaya Pranoykumar, Seema Singh, Vaishali Deoraoji Taksande, Tessy Sebastian, Pooja Kasturkar, and Ruchira Shrikant Ankar. “Critical Review on Impact of COVID 19 and Mental Health.” Journal of Evolution of Medical and Dental Sciences-Jemds. 2020;9(30):2158–63. Available:https://doi.org/10.14260/jemds/2020/470.

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