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Review Article

Antibiotics- Access or excess? Reviewing alternative targets for antibacterial activity

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ABSTRACT

Antimicrobial resistance is a condition in which microorganisms no longer respond to medications that were previously effective against them. This makes infections more difficult to cure, necessitating greater doses, and leads to increase morbidity and mortality. Antimicrobial therapy failure is frequently caused by the spread of resistant infections, which eventually replace susceptible pathogens. Antibiotics are a type of medicine employed for a limited time and for specific indications. As a result, there isn't much incentive to research and development of newer antibiotics. The temporal utility of antibiotics keeps decreasing as we use them. Hence it is a continuous ordeal, and we need new agents to fight the war against infection. This article attempts to summarize the newer anti-bacterials and some alternative approaches.

1. Introduction

The advent of the germ theory of disease created a revolution in understanding the nature of diseases and their pathogenesis, following which several microbes were identified and characterized. Antimicrobials are agents that kill microorganisms or stop their growth.[1] They are grouped according to the microorganisms they act against, say anti-bacterials against bacteria, antifungals against fungi, and so on. The terms antibiotic and antimicrobial have often been used interchangeably but the term 'antimicrobial' is considered more encompassing and inclusive.

The discovery of penicillin in 1928, changed the course of medicine. Penicillin helped reduce the morbidity and mortality amongst troops during World War II and laid the foundation of the antibiotic era. However, the first sign of antibiotic resistance to penicillin became apparent soon. By 1942, four *Staphylococcus aureus* strains in hospitalized patients were found to be resistant to the action of penicillin.[2] The next few years saw a rapid rise in the proportion of infections caused by penicillin-resistant S. aureus, spreading quickly from hospitals to communities. By the late 1960s, more than 80 percent of both community and hospital-acquired strains of S. aureus were penicillin-resistant.[3] There has been a roughly similar course with antibiotics discovered later, the reason being antimicrobial resistance.

Antimicrobial resistance (AMR) is a phenomenon where microorganisms including bacteria, viruses, fungi, and parasites no longer respond to drugs they were previously susceptible. This makes infections increasingly difficult to treat, often requiring higher doses, leading to toxic effects. Treatment failure in antimicrobial therapy is often the result of the multiplication of resistant pathogens which ultimately replace susceptible bacteria.

Two major factors associated with the emergence of antibiotic resistance are evolution and practices. When subjected to an existential threat, microbial species select mutations in the genome that support their survival. This evolution is hastened by poor therapeutic practices by

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healthcare workers and poor environmental practices such as the indiscriminate use of antibiotics in agriculture and animal husbandry. The extent of the use of antibiotics has a bearing on the emergence of resistance against them.

Antimicrobial resistance (AMR) has devastating consequences on healthcare, increasing morbidity and mortality. Patients due to AMR, require treatment for prolonged periods, usually with costly reserve antibiotics which adds up to the economic burden. More than 35000 people die every year due to antibiotic-resistant infections in the US.[4] A report projected that with the current trend global mortality would touch 10 million by the year 2050.[5] Such figures predict a dire situation in the upcoming future. With the antibiotic development pipeline drying up, the world is in search of newer sources and alternative strategies. Although the phenomenon of antibiotic resistance applies to different classes of drugs including antibacterials, antivirals, and antifungals, in this article, we focus on newer anti-bacterials and some alternative approaches.

Antibiotics are 'time warped' medicines. They are used for a short duration and in restricted indications. Hence the development incentive is not much. The temporal utility of antibiotics keeps decreasing as we use them. Hence it is a continuous ordeal, and we need new agents to fight the war against infection.

2. Recently Approved Antibiotics

With the emergence and rapid spread of multi and pan-resistant bacteria, in 2017 WHO published a list of 12 families of bacteria for which new antibiotics are needed urgently, a list of 'priority pathogens.[6] The list was created to identify, guide, and promote the research and development of newer antibiotics and to address urgent healthcare needs. The WHO priority pathogens are classified as critical, high, and medium priority pathogens. The critical priority pathogens are carbapenem-resistant *Acinetobacter baumannii* (CRAB), carbapenem-resistant *Pseudomonas aeruginosa* (CRPA), and Enterobacteriaceae resistant to 3rd gen cephalosporins and carbapenems (CRE). In 2019, WHO identified 50 antibiotics and combinations and 10 biologicals in clinical development, of which 26 are active against the WHO list of priority pathogens. Out of the 26, only seven were considered to be innovative due to fulfilment of at least one of the innovation criteria.[7] These include two beta-lactamase inhibitor combinations (taniborbactam + cefepime and VNRX-7145 + ceftibuten), two topoisomerase inhibitors (zoliflodacin and gepotidacin), a new enoyl-acyl carrier protein reductase (FabI) inhibitor Afabicin, a filamenting temperature sensitive Z (FtsZ) inhibitor (TXA709) and a cationic peptide (PLG0206). Taniborbactam, zoliflodacin, and gepotidacin are in Phase 3 clinical trials, Afabicin is in Phase 2, whereas TXA-709 and PLG0206 are in Phase 1. Only two of the seven innovative antibiotics, taniborbactam in combination with cefepime and VNRX-7145 in combination with ceftibuten target at least one of the critical Gram-negative bacteria. Two antibacterials, Solithromycin, and contezolid have moved to the New Drug Application (NDA) filing stage.

A major gap is in the development of antibiotics are agents that meet at least one of the WHO innovation criteria and target the critical Gram-negative bacteria. Of the 26 antibiotics targeting the WHO priority pathogens, two agents, zidebactam + lascufloxacin and SPR-206, have activity against all three critical priority pathogens. They are both are in Phase 1 trials. Antibacterial agents currently in clinical development do not address the problem of extensively or pan-drug-resistant Gram-negative bacteria. Novel antibiotics targeting carbapenem-resistant *A. baumannii* and *P. aeruginosa* are still lacking. There is also a gap of oral antibiotic treatment options for ESBLs and CRE that could allow treatment outpatient treatment or shorten the duration of treatment in the healthcare facility. A major gap in the treatment options is for agents that are effective against carbapenem-resistant *Acinetobacter baumannii* and/or *Pseudomonas aeruginosa*.

The timeline of FDA approval of antibiotics in the past 10 years is depicted in Figure 1. The antibacterial agents approved in the past 10 years have been summarised in Table 1.

3. Future or the Path Ahead

Conventional antibiotics target cell wall synthesis or protein synthesis or RNA synthesis. Instead of focusing on developing newer conventional antibacterials, one can consider other options that may be equally or more effective. This includes the use of bacteriophages, anti-quorum sensing agents, RNA decay, toxins, microbiome modulation, and biofilm adhesion.[8] Recently, there has been focus on the development of strategies alternative to conventional antibacterials.[9] Methods developed under these alternative strategies are collectively known as non-traditional antibacterials. Most of these non-traditional products are being tested with an intension to use them in combination with standard antibiotics. Non-traditional antibacterials may be classified broadly into four categories namely, antibodies, bacteriophages/phage-derived enzymes, microbiome-modulating agents and immunomodulating agents.

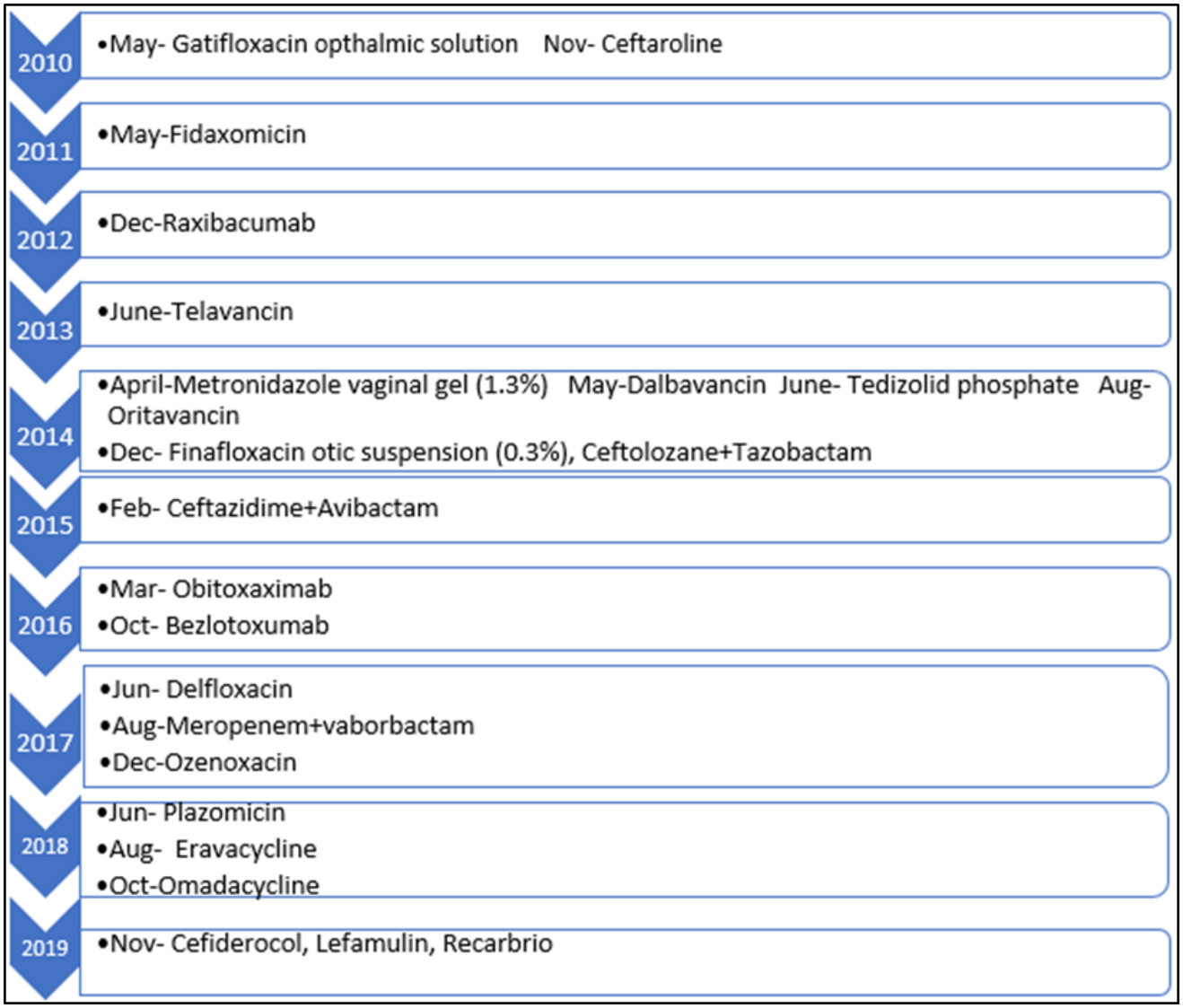

Fig. 1: Timeline of FDA approval of antibiotics in the past 10 years

Table 1: Antibacterial agents approved by FDA in the past 10 years.

S.No.	Name of the drug	Target/MOA/Class	Coverage	Approved use	Part of NLEM/ WHO EML	Effective against WHO critical priority pathogens (Yes/No)
1	Ceftaroline	5th gen Cephalosporin or anti methicillin resistant Staph aureus (MRSA) cephalosporin	G +ve & G -ve	• Acute bacterial skin and skin structure infections (ABSSSI)• Community-acquired bacterial pneumonia caused by susceptible isolates·	WHO EML Reserve category	No
2	Gatifloxacin 0.5% ophthalmic solution	2nd gen fluoroquinolone	Gram +ve & Gram -ve	Bacterial conjunctivitis caused by susceptible strains.	No	No
3	Finafloxacin 0.3% Otic suspension	Fluoroquinolone	Gram +ve & Gram -ve	Acute otitis externa.	No	No
4	Ceftolozane + Tazobactam	Cephalosporin+ beta lactamase inhibitor	Gram +ve & Gram -ve	Combination with metronidazole for complicated intra-abdominal infections and for hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia.	WHO EML Reserve category	Yes (CRPA)
5	Ceftazidime+ Avibactam	Cephalosporin+beta-lactamase inhibitor	Gram +ve & Gram -ve	Combination with metronidazole for complicated intra-abdominal infections and urinary tract infections.	WHO EML Reserve category	Yes (CRE)
6	Meropenem + Vaborbactam	Carbapenem + beta-lactamase inhibitor	Gram +ve & Gram -ve	Complicated urinary tract infections.	WHO EML Reserve category	Yes (CRE)
7	Delafloxacin	Fluoroquinolone	Gram +ve & Gram -ve	Acute bacterial skin and skin structure infections.	WHO EML Watch category	OPP
8	Ozenoxacin	Fluoroquinolone	Gram +ve & Gram -ve	Impetigo (ointment for topical administration)	No	Yes (High priority, MRSA)

Continued on next page

Table 1 continued

9	Erevacycline	Tetracycline	Gram +ve & Gram -ve	Complicated intra-abdominal infections	WHO EML Reserve category	Yes (CRE)
10	Omadacycline	Tetracycline	Gram +ve & Gram -ve	Community-acquired bacterial pneumonia and bacterial skin infections.	WHO EML Reserve category	OPP
11	RECARBRIO	Carbapenem + beta-lactamase inhibitor (Imipenem+cilastatin+ relebactam)	Gram +ve & Gram -ve	Complicated urinary tract infections/intra-abdominal infections.	No	Yes (CRE)
12	Fidaxomicin	Macrocyclic antibiotic	G +ve	*Clostridium difficile* associated diarrhoea.	No	No
13	Raxibacumab	Monoclonal antibody	G +ve	Treatment and prevention of inhalational anthrax.	No	No
14	Telavancin	Semi synthetic lipoglycopeptide antibiotic	G +ve	Hospital-acquired and ventilator-associated bacterial pneumonia	No	Yes (High priority, MRSA)
15	Dalbavancin	Lipoglycopeptide	G +ve	Bacterial skin and skin structure infections	No	Yes (High priority, MRSA)
16	Tedizolid	Oxazolidinone	G +ve	Bacterial skin and skin structure infections	No	Yes (High priority, MRSA)
17	Oritavancin	Lipoglycopeptide antibiotic	G +ve	Bacterial skin and skin structure infections	No	No
18	Obiltoxaximab	Monoclonal antibody	G +ve	Inhalational anthrax (combination with appropriate antibacterial drugs)	No	No
19	Bezlotoxumab	Human monoclonal antibody	G +ve	Recurrent *Clostridium difficile* infection	No	No
20	Lefamulin	Pleuromutilin	G +ve	Community acquired bacterial pneumonia	No	OPP
21	Plazomicin	Aminoglycoside	G -ve	Complicated urinary tract infections	WHO EML Reserve category	Yes (CRE)
22	Cefiderocol	Cephalosporin	G -ve	Complicated urinary tract infections	No	Yes (CRE, CRAB, CRPA)

3.1. Bacteriophage

Bacteriophages are viral agents that infect and replicate in bacteria. Phages have been explored as means to treat infections since the early 20^{th} century.[10] They are easy to identify and isolate and are highly specific, hence less likely to affect the normal flora of the host. They do not affect human cells. They are less likely to develop resistance since their mechanism of action is different from other antibiotics. Also, they can be modified to overcome bacterial resistance. Phages are used for direct lysis of a target bacteria or as nano-delivery vehicles.

They can be useful even in biofilm generating microbes. However, being highly specific, they can be used only if we know the strain of bacteria i.e. only definitive treatment is possible. A possible strategy to overcome this is using a cocktail of different types of bacteriophages to cover likely organisms, however, it can be difficult to get approval for the same. There is also the concern of by-products and toxins released on killing bacterial cells. The phage may introduce resistance to the bacteria by incorporating resistance genes, by itself. Hence there is a need to screen for the presence of resistance genes. So far, with bacteriophages, the results have been inconsistent. The PhagoBurn study was conducted in the European Union between 2013-2017 to evaluate phage therapy in burns infected with Ps.aeruginosa and *E.coli*.[11] This resulted in the large-scale production of GMP phage. The findings of the study suggested that the cocktail of phages decreased bacterial burden in burn wounds, but at a slower pace than standard of care and recommended further studies with higher concentrations and phagograms and a larger sample size. Subsequently, new regulations were created specifically for phage therapy. It is also under consideration as a food additive to prevent contamination.

3.2. Anti- Quorum sensing agents

Quorum sensing is a bacterial cell-to-cell signaling system that plays a vital role in the regulation of virulence in many pathogens. Anti-quorum sensing agents are designed to abolish cell-to-cell communication and prevent the expression of virulence factors. They cause disruption by receptor inactivation and signal degradation. However, there is insufficient data on the stability of these agents in vivo. Also, blocking amino acid and fatty acid synthesis by bacteria can lead to selection pressure, especially with synthesis inhibitors. So far, flavonoids, N decanoyl benzyl ester (a structural analogue of N-Acyl homoserine lactones signals), meta-bromo-thiolactone, and triclosan are some of the agents being explored for their anti-quorum sensing activity. Medical devices are being coated with acylase and oxidoreductase to prevent the colonization of biofilm-producing organisms.[12] Workers are also considering using nonpathogenic bacteria such as *Pectobacterium carotovorum* to degrade the QS signals instead of enzymes.

3.3. RNA decay via degradosome

Degradosomes are multiprotein complexes involved in the processing of ribosomal RNA and degradation of mRNA. They are present in most bacteria. Mutation in the RNA can lead to a reduction in virulence and cytotoxicity like the OMP in *E.Coli.* Inhibition of RnpA of *S.aureus*, has been found to be effective in biofilms, with a broad spectrum of activity against G+ve organisms. RNA Inhibitors have a narrow spectrum, hence preserving the host's normal flora and less chance of developing resistance. RNA decay, however, contributes to the infectivity of only some bacteria. Also, the inactivation of RNA decay can increase the virulence in some bacteria such as *Salmonella*. This mechanism only affects the pathogenesis of the disease and does not kill the bacteria directly. Hence, we cannot use this in immunocompromised patients. The bacterial RNA degradation machinery is structurally homologous to human RNA degradation machinery. Hence there is a probability of human cells being affected. It is also difficult to assess the MIC or the potential of the agent. Researchers are currently searching for RNAase with less homology to human RNA degrading machinery e.g., RNase Y.[13]

3.4. Toxins (Monoclonal antibodies and chemical inhibitors

Monoclonal antibodies are antibodies produced by a single clone of plasma B cells and interact with one specific epitope on an antigen. Their homogeneity, selectivity, and lower potential for cross-reactivity make them ideal candidates for the treatment of bacterial infections.

Monoclonal antibodies may be synthesized to target bacterial epitopes and virulence factors. Targets include surface proteins, bacterial toxins, and polysaccharides. The logic behind targeting toxins is that inhibition at the toxin level prevents the development of resistance. The bacterial machinery of toxin production or introduction can be targeted.

However, there are developmental challenges such as identifying optimal bacterial targets and designing the clinical trials for such agents, the risk of allergic reactions, and the cost of production. This is one target against which a lot of agents have been approved recently, such as Raxibacumab (2012) for inhalational anthrax, Obitoxaximab (2016) for *B.anthracis* (binds to protective antigen), Bezoltoxumab (2016)- for *Cl.difficile* (toxin B).

3.5. Microbiome modulation

In recent times, there has been considerable interest in investigating the composition and role that the human gut microbiome in health.[14,15] The gut microbiome has been

found to have a role in the modulation of immune responses and the gut-brain axis. Similarly, alteration of the gut microbiome can lead to illness where pathogens, such as C. difficile, become dominant and cause harm. The idea is to modify the microbiome to eliminate or prevent the carriage of resistant or pathogenic bacteria.

These agents are expected to cause less harm since they modulate the immunity and defences naturally present within the host. However, there is a lack of data on how the donor's microbiota would affect the recipient's health. Researchers are still trying to determine whether to use a standard mixture of microbiota or to use a customized regimen according to the patient. This method has been explored in the treatment of recurrent *Clostridium difficile* infection with faecal microbiota transplant (FMT) and in post hematopoietic stem cell transplant to protect against gastrointestinal colonization of *Enterococci* and *Klebsiella*, using *Barnesiella*.

3.6. Agents targeting biofilm and adhesion

Biofilm is a syntrophic consortium of microorganisms by which cells stick to each other and surfaces. Adherence is the first step in biofilm formation hence agents which target adhesion can be used on devices such as catheters, as a preventive measure. They are unlikely to develop resistance. Catheters coated with zwitterionic sulfobetaine (reduced *S.aureus* and *E.coli* adhesion) are being tested in clinical trials.[16] Methylcellulose-coated implants are being tested in the pre-clinical stage, as anti-adhesive.[17] Small molecules are being developed against adhesins such as the lectin type fimbriae in *E.coli* to prevent attachment to the urogenital epithelium.

4. Conclusion

The immediate future looks bleak with very few antibiotics in the pipeline. Hence there is even more reason to conserve what limited drugs we have in our arsenal. From a policymaker's point of view, the drug approval process of antibiotics may be subsidized in terms of time and money, or a longer patent may be provided to the innovator to encourage the research and development of new antibiotics. The approval process may be fast-tracked to bring out these drugs into the market in a shorter time frame. Any new antibacterial drug introduced in the market remains effective only for a short while since resistance develops to it soon. Take the example of Ceftaroline which was approved in 2010 for MRSA and has already started showing resistance among clinical isolates.[18,19]

This hardly gives the manufacturer any time to recover the expenses which have gone into the development and marketing of the drug. Judicious use of these drugs would ensure that their effectiveness is preserved. The inclusion of such drugs in the national list of essential medicines (NLEM), needs more frequent review. Inclusion in the NLEM would lead to an increase in accessibility and as discussed earlier, it would speed up the development of resistance. From a clinician's point of view, it must be ensured that the newly approved agents are used only in cases where existing drugs have failed to produce the expected results. Otherwise, these new agents will meet the same fate as their predecessors. It is highly advisable to set up drug review committees to ensure that such agents are used only where they are warranted. Access to such drugs must be restricted. The focus should be directed at preserving the efficacy of the few antibiotics that are currently effective. This calls for the rational use of antibiotics. This includes using them only when indicated, and for the appropriate duration. Timely de-escalation of antibiotics and changing the agent based on clinical sample sensitivity results are also to be emphasized. Another strategy that can be adopted is real-time monitoring of minimum inhibitory concentration (MIC). Regional data, national systems, and global alliances would go a long way to help preserve antibiotics by sharing antimicrobial resistance (AMR) data including MIC values. This can help us formulate different MIC cut-off values where an antibiotic must be stopped, restricting its further use with the idea of preserving the effectiveness of the drug. This can ensure that the drug remains effective for a much longer time, increasing the number of treatment options at our disposal. Such 'drug holidays' are effective such as in the case of drugs that have not been used in a long time due to resistance. It has been observed that microorganisms have started showing sensitivity to them. Colistin is an example of an old drug that was successfully redeveloped for use in multi-drug resistant microorganisms.[20] One of the methods to enforce drug holidays is removing the drug from the national list of essential medicines (NLEM). A national list of essential antibiotics may be formulated where the list is revised more frequently say every two years or so. One of the challenges when it comes to using old antibiotics is the knowledge gap from the period between their discovery and the present. Also, many of these antibiotics were not subjected to the trials and procedures which are currently mandated by the drug regulatory authorities. Rigorous testing is essential to ensure that these drugs do not end up doing more harm than good. Modern-day analytical, microbiological, pharmacokinetic, and pharmacodynamic methods can help optimize the use of 'old' antibiotics. Such methods have been applied to fosfomycin, fusidic acid, nitrofurantoin, and chloramphenicol in an attempt to redevelop them for modern-day use.[21] To check the alarming state of AMR, WHO in its global action plan for 2015 had identified an antimicrobial stewardship programme. The Indian Council of Medical Research (ICMR) has been conducting workshops for the implementation of the same

in India. ICMR has also initiated Antimicrobial Resistance Surveillance & Research Network (AMRSN) in 2013 to understand the degree and recognize the patterns of AMR.[22]

The 20th edition of the WHO essential medicines list (EML) has grouped antibiotics into three categories- 'Access', 'Watch' and 'Reserve', collectively known as the 'AWaRe' categories.[23]The list comes with recommendations on where each category should be used.It is considered a major revision in the history of EML and it aims to ensure the availability of antibiotics when they are needed and that appropriate antibiotics are prescribed for infections. This is expected to improve treatment outcomes, reduce the development of antimicrobial resistance amongst bacteria, and preserve the effectiveness of "high end/last resort" antibiotics that are needed when all others fail. WHO experts have added 10 antibiotics to the list for adults, and 12 for children.

The logic behind this system is to preserve the effective drugs in our armamentarium. The shelf life of antibacterial drugs is limited, and accessibility is a double-edged sword. Though the availability of drugs at medical care facilities can often save lives, better accessibility leads to more widespread use of these drugs and widespread use accelerates the development of resistance to the same. Hence there is a need to restrict the availability of higher-end drugs, especially in smaller settings.

One of the factors leading to AMR is the lack of access to antibiotics, which is quite prevalent in India. This often leads to the use of inappropriate drugs and delayed treatment.[24] Substandard drug quality is another issue that our country is dealing with. It is estimated that lack of access to antibiotics leads to a greater number of deaths than AMR.

Despite the efforts to raise awareness of need to conserve the available antibiotics and the need to accelerate the entry of new agents into the market, there is still a dearth of effective antibiotics. Additional initiatives and investments are the need of the day to drive antibiotic R & D and innovation.

5. Conflict of Interest

The authors declare no conflict of interest

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References

1. Rang H, Ritter J, Flower RJ, Henderson G. Basic principles of antimicrobial chemotherapy. In: Rang and Dale's Pharmacology. China: Elsevier Churchill Livingstone; 2016. p. 615–25.
2. Frère JM, Sauvage E, Kerff F. From "An Enzyme Able to Destroy Penicillin" to Carbapenemases: 70 Years of Beta-lactamase Misbehaviour. *Current Drug Targets*. 2016;17(9):974–82.
3. Rammelkamp CH, Maxon T. Resistance of Staphylococcus aureus to the Action of Penicillin. *Proc Soc Exp Biol Med*. 1942;51(3):386–9. doi:10.3181/00379727-51-13986.
4. Zhen X, Lundborg CS, Sun X. Economic burden of antibiotic resistance in China: a national level estimate for inpatients. *Antimicrob Resist Infect Control* . 2021;10(5). doi:10.1186/s13756-020-00872-w.
5. O'Neill J. Antimicrobial Resistance: Tackling a crisis for the health and wealth of nations The Review on Antimicrobial Resistance Chaired; 2014. Available from: https://amr-review.org/sites/default/files/AMR%20Review%20Paper%20-%20Tackling%20a%20crisis%20for%20the%20health%20and%20wealth%20of%20nations_1.pdf.
6. Vaithinathan A, Vanitha A. WHO global priority pathogens list on antibiotic resistance: an urgent need for action to integrate One Health data. *Perspectives in Public Health*. 2018;138(2):87–8. doi:10.1177/1757913917743881.
7. Brives C, Pourraz J. Phage therapy as a potential solution in the fight against AMR: obstacles and possible futures. *Palgrave Commun*. 2020;6:100. doi:10.1057/s41599-020-0478-4.
8. Hauser AR, Mecsas J, Moir DT. Beyond Antibiotics: New Therapeutic Approaches for Bacterial Infections. *Clin Infect Dis*. 2016;63(1):89–95. doi:10.1093/cid/ciw200.
9. Czaplewski L, Bax R, Clokie M, Dawson M, Fairhead H, Fischetti VA, et al. Alternatives to antibiotics-a pipeline portfolio review. *Lancet Infect Dis*. 2016;16(2):239–51. doi:10.1016/S1473-3099(15)00466-1.
10. Summers WC. The strange history of phage therapy. *Bacteriophage*. 2012;2:130–133.
11. Golkar Z, Bagasra O, Pace DG. Bacteriophage therapy: a potential solution for the antibiotic resistance crisis. *J Infect Dev Ctries*. 2014;8(2):129–36. doi:10.3855/jidc.3573.
12. Jiang Q, Chen J, Yang C, Yin Y, Yao K. Quorum Sensing: A Prospective Therapeutic Target for Bacterial Diseases. *Biomed Res Int*. 2019;p. 2015978. doi:10.1155/2019/2015978.
13. Eidem TM, Roux CM, Dunman PM. RNA decay: a novel therapeutic target in bacteria. *Wiley Interdiscip Rev RNA*. 2012;3(3):443–54.
14. Smith LK, Wissel EF. Microbes and the Mind: How Bacteria Shape Affect, Neurological Processes, Cognition, Social Relationships, Development, and Pathology. *Perspect Psychol Sci*. 2019;14(3):397–418. doi:10.1177/1745691618809379.
15. Garber K. First microbiome-based drug clears phase III, in clinical trial turnaround. *Nat Revi Drug Dis*. 2020;19:655–6. doi:10.1038/d41573-020-00163-4.
16. Singha P, Locklin J, Handa H. A review of the recent advances in antimicrobial coatings for urinary catheters. *Acta Biomaterialia*. 2017;50:20–40. doi:10.1016/j.actbio.2016.11.070.
17. Chauhan A, Bernardin A, Mussard W, Kriegel I, Estève M, Ghigo JM, et al. Preventing biofilm formation and associated occlusion by biomimetic glycocalyxlike polymer in central venous catheters. *J Infect Dis*. 2014;210(9):1347–56. doi:10.1093/infdis/jiu249.
18. Long SW, Olsen RJ, Mehta SC, Palzkill T, Cernoch PL, Perez KK, et al. PBP2a mutations causing high-level Ceftaroline resistance in clinical methicillin-resistant Staphylococcus aureus isolates. *Antimicrob Agents Chemother*. 2014;58(11):6668–74. doi:10.1128/aac.03622-14.
19. Ferguson CL, Cowart MC, Jordan-Villegas A, Laham F. High-level ceftaroline resistance in a paediatric patient with invasive methicillin-resistant Staphylococcus aureus infection without previous ceftaroline exposure. *J Clin Pharm Ther*. 2021;46(2):524–7. doi:10.1111/jcpt.13316.
20. Maviglia R, Nestorini R, Pennisi AM. Role of Old Antibiotics in Multidrug Resistant Bacterial Infections. *Current Drug Targets*. 2009;10(9):895–905. doi:10.2174/138945009789108846.
21. Bergen PJ, Landersdorfer CB, Lee HJ, Li J, Nation RL. Nation. "Old" antibiotics for emerging multidrug-resistant bacteria. *Curr Opin Infect Dis*. 2012;25(6):626–33. doi:10.1097/QCO.0b013e328358afe5.

22. Chandy SJ, Michael JS, Veeraraghavan B, Abraham OC, Bachhav SS, Kshirsagar NA, et al. ICMR programme on antibiotic stewardship, prevention of infection & control (ASPIC). *Indian J Med Res*. 2014;139(2):226–30.
23. World Health Organization. WHO model list of essential medicines - 22nd list, 2021. Technical Document (2021) 2021. Available from: https://www.who.int/publications/i/item/WHO-MHP-HPS-EML-2021.02.
24. Walia K, Madhumathi J, Veeraraghavan B, Chakrabarti A, Kapil A, Ray P, et al. Establishing Antimicrobial Resistance Surveillance & Research Network in India: Journey so far. *Indian J Med Res*. 2019;149(2):164–9. doi:10.4103/ijmr.IJMR_226_18.

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