International Journal of Research and Review
Vol. 10; Issue: 7; July 2023
Website: www.ijrrjournal.com
Review Article *E-ISSN: 2349-9788; P-ISSN: 2454-2237*

A Review on Rational Use of Antibiotics: Strategies and Interventions

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DOI: https://doi.org/10.52403/ijrr.20230741

ABSTRACT

The rational use of antibiotics is essential to combat the growing threat of anti-microbial resistance, improve patient outcomes, and optimize healthcare resources. Effective antibiotic stewardship programs play a crucial role in guiding healthcare professionals and patients towards appropriate antibiotic use. These programs encompass a range of interventions, including education and training, clinical guidelines, antimicrobial stewardship teams, and surveillance systems. By implementing these strategies, healthcare facilities can enhance antibiotic prescribing practices, reduce unnecessary antibiotic use, and prevent the emergence and spread of antibiotic-resistant bacteria. Additionally, public awareness campaigns are vital in empowering individuals to understand the appropriate use of antibiotics, emphasizing the importance of completing prescribed courses, and discouraging self-medication. Promoting awareness among the general population helps mitigate misconceptions and misuse, ensuring antibiotics are used judiciously and only when necessary.

Key words: AMR (Anti-microbial resistance), Anti-microbial Stewardship, rational use, health care professionals.

INTRODUCTION

The rational use of antibiotics not only concerns the actions of providers, in ensuring patients receive appropriate treatment for their condition, at the right dose and duration, but also those of patients, in adhering to the treatment regimens prescribed, completing the full course and not sharing or storing medicines for future use. In 2001, the WHO Global Strategy for containment of antimicrobial resistance [1] highlighted the need for the 'development and use of guidelines and treatment algorithms to foster appropriate use of antimicrobials', as well as the importance of 'supervision and support of clinical practices, especially diagnostic and treatment strategies'. Furthermore, it highlighted that health care providers have an important role to play in educating patients on the importance of treatment adherence [2].

In many resource-poor contexts, with limited surveillance and weaker regulatory systems [3] containment of resistance may be more challenging than in higher-income settings. However, in these settings, there remains a high burden of childhood infectious diseases, such as pneumonia, that often require antibiotic treatment.

Around 78% of the world's population was thought to have been living in developing nations in 1990. 9.2 million Of the 39.5 million deaths in the developing countries were thought to have been brought on by parasitic and infectious diseases. 98% of child deaths take place in underdeveloped countries and are primarily caused by illnesses [4]. The authors evaluate the development and effects of bacterial resistance to antimicrobial treatments in the poor world using data acquired via searches of the Medline and Bath Information and Data Services computerised databases, conversations with colleagues, and personal experiences. Antibiotics are crucial for poor nations, yet they are frequently expensive,

in short supply, and only available to the relatively well-off. Since many underdeveloped nations lack regulations on the use of antibiotics.

Both in hospitals and the general population, antibiotic resistance is developing. Even though it takes time for resistance genes to accumulate and spread, overusing and misusing antibiotics dramatically speeds up the evolution of bacterial resistance. The transmission of resistance genes between and among bacterial species has also been linked to the rise in multidrug-resistant (MDR) bacteria. Abuse of antibiotics has been linked to the establishment of bacterial resistance on numerous occasions, which poses a severe threat to clinical therapy and warrants more study [17]. The likelihood of resistant bacteria developing increases with the frequency of antibiotic use. The advent of the coronavirus disease 2019 (COVID-19), which is thought to worsen drug resistance, hasn't helped. Statistics from five countries show that bacterial infections account for 6.9% of COVID-19 diagnoses, with a higher frequency among patients needing extremely critical care.17 Additionally, 72% of COVID-19 patients in a multicentre trial conducted in the United States received antibiotics even when they were not clinically necessary, which can further increase antibiotic resistance. Due to overuse of antibiotics in humans, continued abuse in agriculture, and a shortage of antimicrobials in the pipeline, antibiotic resistance may have gotten worse under COVID-19[18].

According to WHO, "rational use of medicine" refers to the use of appropriate pharmaceuticals that are pertinent to patients' clinical needs, administered in precise quantities in line with individual requirements, for an adequate period of time, and at the patients' least expensive cost. Numerous studies conducted in many nations have proposed that a number of variables, including age[5,6], gender, educational attainment, level of household income, health insurance, and participant understanding of antibiotic usage, were connected to participants' rational antibiotic use.

The majority of industrialised and developing nations use antibiotics most frequently, particularly when treating patients for the three main infections (upper respiratory infection, acute diarrhoea, and antibiotic prophylaxis for simple/new wounds). One of the main causes of AMR is the inappropriate use of medications, particularly antibiotics, which is a problem in many developing nations with underdeveloped healthcare systems. According to the WHO, community settings consumed 80% of the antibiotics prescribed, with 20–50% of those prescriptions being used erratically [7]. Such inappropriate use of antibiotics can lead to the establishment and spread of antibiotic resistance at the community levels by causing the development of antimicrobial resistance in some bacteria[8] .

Antimicrobial resistance (AMR) is a serious public health concern that has recently expanded around the globe and increased dramatically in a number of nations, with negative health and economic effects on people's quality of life [9] .Due to the greater incidence of AMR infections, there are currently more than 700,000 deaths worldwide each year, and it was predicted that there may be up to 10 million deaths by 2050 if quick and interdisciplinary efforts were not taken to address this grave problem. The Asia region is thought to be the region most at risk, with over 4.7 million fatalities from AMR expected in 2050.

Causes of anti-microbial resistance: -

Understanding the numerous sequential stages required for a drug to reach a patient and the eventual use, which include production, distribution, prescription, dispensing, and lastly intake of the drug by the patient or use in animal production, would help us better understand the causes of AMR. Therefore, any reckless behaviour

along this flow may cause resistance to form.

Antimicrobial resistance (AMR) is a complex issue influenced by several factors. Here are some of the main causes of antimicrobial resistance:

- **Misuse and overuse of antimicrobials:** The inappropriate use of antimicrobial drugs in humans, animals, and agriculture is a significant contributor to AMR. This includes using antibiotics for viral infections, prescribing incorrect dosages, and using antibiotics as growth promoters in livestock and poultry.

- **Lack of proper infection control:** Poor hygiene practices and inadequate infection control measures in healthcare settings can lead to the spread of resistant bacteria. This includes improper hand hygiene, inadequate sterilization of medical equipment, and poor sanitation practices.

- **Substandard and counterfeit drugs:** The availability of substandard and counterfeit antimicrobial drugs in some regions can contribute to the development of AMR. These drugs may contain inadequate amounts of the active ingredients or may be of low quality, leading to treatment failures and the selection of resistant strains.

- **Global travel and trade:** International travel and trade facilitate the spread of resistant bacteria across borders. Resistant bacteria can be carried by individuals or on contaminated food, water, or other goods, contributing to the global dissemination of AMR.

- **Lack of new antimicrobial development:**
  There has been a decline in the development of new antimicrobial drugs in recent years. This limited pipeline of new drugs makes it harder to combat resistant bacteria effectively, as existing antibiotics become less effective over time.

- **Agricultural use of antimicrobials:** The use of antimicrobial drugs in agriculture, such as in livestock farming and aquaculture, contributes to the emergence and spread of antimicrobial-resistant bacteria. The use of antibiotics as growth promoters and for preventive purposes in animals can lead to the selection and spread of resistant strains.

- **Environmental contamination:** The discharge of antimicrobial residues from pharmaceutical manufacturing, hospitals, and agricultural practices can contaminate the environment. This contamination can contribute to the development of antimicrobial resistance in environmental bacteria, which can then be transmitted to humans and animals.

- **Drug dispensers and drug quality: -** Access to and abuse of antimicrobials are also influenced by a lack of effective rules governing their sales. Antimicrobials may typically be acquired without a prescription in poor nations [10] and are typically given out by unskilled individuals on the streets. The sole purpose of these drug sellers' sales is to satisfy customer’s financial needs. Even unlicensed pharmacies seem to be more accessible to the general public because they have lower wait times, don't charge for consultations, and, most importantly, are open to negotiating treatment alternatives to suit the patients' financial capabilities. During storage, unfavourable environmental circumstances including high ambient temperatures and humidity may have an impact on the antimicrobials' overall quality [11, 12]. The risk of the medicine degrading is also increased by inadequate storage. Degraded medications have a lower dose than

what is listed on the label, which suggests that patients are taking less of the medication than is recommended. Another issue is outright fraud, in which the medicine may have insufficient or incorrect antibacterial active ingredient content.

- **Healthcare experts: -** The ability of health care professionals to treat and prevent diseases is crucial, but if their procedures are not supported by evidence, this ability may be compromised. For instance, doctors in most nations have different prescription procedures for antibiotics. Antimicrobial prescriptions may occasionally be unnecessary or for the wrong reasons (wrong medicine, incorrect dose, etc.) [13]. Most developing nations have a high patient-to-doctor ratio, which makes it difficult for doctors to devote enough time to teaching patients about drug adherence standards and the implications of following them poorly or not at all.

- **Patients: -** As was already established, compliance plays a significant role in the growth of AMR [14]. Patients may purposefully or unintentionally miss dosages. Some patients may skip doses when invited to a party in favour of consuming alcohol because they are aware of the negative effects of doing so while taking antibiotics (unpublished data). These procedures expose surviving bacteria to drug concentrations below therapeutic levels, which raises the likelihood that they may acquire drug resistance [15].

Antimicrobial resistance control strategies:

- **Hygiene and sanitation**
  In addition to the inappropriate use of antibiotics, particular environmental factors like squalor and overcrowding aid in the circulation and dissemination of resistant microbes. Person-to-person contact, polluted water, food, or vectors can contribute to the spread of resistant infections. Reducing the spread of resistant microbes will require better basic sanitation and hygiene. The nosocomial spread of microorganisms with acquired resistance, including Staphylococcus aureus and other germs, will be decreased in hospitals with improved infection prevention and control.

- **Vaccination**
  Vaccines are the main method of preventing infectious diseases, even though antimicrobials are also employed as a form of treatment. Prior immunisation can protect against pathogen shedding, lessen the severity of the illness, and even increase the threshold load of germs needed to cause infection [16]. The need for antimicrobials or other treatment alternatives may still arise even with the highest effective vaccine in some circumstances. For instance, immunisation may not offer complete disease protection in the case of genetic drift, escape mutants, or serotype or strain replacement illnesses. The advent of conjugate vaccines against bacterial diseases, such as Streptococcus pneumoniae, has decreased the occurrence of respiratory illnesses in children in underdeveloped nations.

Alternative therapies

Several further alternate strategies are now being researched and developed at various stages.

1. A new alternative method of treating bacterial infections is the use of bacteriophages. Bacteriophage therapy has been recommended by numerous authors as a required substitute for traditional antibiotics [19,20]. Bacteriophages are bacterial viruses that can enter bacterial cells and cause lysis (lytic cycle) in the bacterium. The necessity to vigorously investigate the

potential of phage therapy is unique in the current era of multidrug resistance bacteria and pharmaceutical corporations' hesitation to produce new antibiotics.

2. Probiotics, also known as faecal transplant therapy (FTT), have been used as a treatment option for many years [21,22,23], however with varying degrees of success. FTT is the process of repopulating a recipient's micro biota using faeces from healthy, pathogen-free donors. By producing antimicrobial substances like bacteriocins and organic acids, probiotics are thought to be able to destroy pathogenic microorganisms. They are also thought to improve the gastrointestinal microbial environment by adhering to the intestinal mucosa, preventing pathogens from attaching and competing with them for nutrients. Bacillus, Lactobacillus, Lactococcus, Streptococcus, Enterococcus, Pediococcus, Bifidobacterium, Bacteroides, Pseudomonas, yeast, Aspergillus, and Trichoderma are a few of the probiotics that are frequently utilised.

Consequences of antibiotic resistance:

The use of antibiotics by microorganisms has a number of negative effects. The following events could happen1 when pathogenic microorganisms become resistant to different antibiotics:

- Failure to respond to treatment increases the risk of a lengthy illness and death.
- Longer hospital stays and diseases raise the possibility of more residents of the community being impacted.
- The need to switch to second- or third-line antibiotics, which are always more expensive and occasionally more dangerous, arises when a first-line antibiotic is no longer effective.
- Due to the scarcity of numerous second- and third-line medications in low-income nations, first-line antibiotic resistance is more likely to develop.
- The number of medications available in these countries to treat microbial infections is declining, and the essential drug list does not include key antibiotics necessary to treat infections brought on by resistant microbes.
- The advancements of modern medicine are under jeopardy due to antibiotic resistance. Organ transplants, chemotherapy, and procedures become more dangerous without the proper antibiotics.

Strategies and interventions for Anti-Microbial Resistance: -

The rational use of antibiotics is a critical aspect of antimicrobial stewardship, which aims to optimize the use of antibiotics to ensure their effectiveness while minimizing the development of antibiotic resistance. Here are some strategies and interventions that can help promote the rational use of antibiotics:

- **Education and Awareness:** Healthcare professionals, including physicians, nurses, and pharmacists, should receive education and training on appropriate antibiotic use. They should be aware of the principles of antimicrobial stewardship, the importance of antibiotic resistance, and the potential consequences of inappropriate antibiotic prescribing.

- **Guidelines and Protocols:** Developing and implementing evidence-based guidelines and protocols for antibiotic prescribing can help standardize and guide healthcare professionals' decisions. These guidelines should consider local epidemiology, resistance patterns, and optimal infection treatment regimens.

- **Diagnostic Testing:** Appropriate diagnostic testing should be utilized to confirm the presence of bacterial infections before initiating antibiotic therapy. Rapid diagnostic tests, such as

PCR or antigen tests, can help identify the causative pathogens and guide targeted antibiotic treatment.

- **Empirical Therapy:** When immediate treatment is required before test results are available, empirical antibiotic therapy may be initiated based on the most likely pathogens and local resistance patterns. However, empirical therapy should be reassessed and narrowed once the results of diagnostic tests become available.

- **De-escalation:** Antibiotic therapy should be reassessed and de-escalated whenever possible. Once more specific information about the infection is known, such as the pathogen and its susceptibility, clinicians should adjust the antibiotic regimen to target the identified pathogen while avoiding broad-spectrum antibiotics unnecessarily.

- **Duration of Therapy:** Antibiotic treatment duration should be appropriate for the type of infection being treated. Unnecessarily prolonged courses of antibiotics can contribute to antibiotic resistance. Healthcare professionals should regularly reassess the need for continued therapy and consider early discontinuation when appropriate.

- **Antimicrobial Stewardship Programs (ASPs):** Implementing ASPs in healthcare facilities can significantly improve antibiotic prescribing practices. These programs involve a multidisciplinary team that includes infectious disease specialists, pharmacists, microbiologists, and other healthcare professionals. ASPs monitor antibiotic use, provide feedback to prescribers, and implement interventions to promote appropriate antibiotic use.

Here's a general framework to help you get started:

- ✓ Establish a multidisciplinary team: Form a team consisting of healthcare professionals from various disciplines, such as infectious disease specialists, pharmacists, microbiologists, infection control practitioners, and hospital administrators. This team will be responsible for developing and implementing the antimicrobial stewardship program.
- ✓ **Assess local needs and resources:** Conduct a thorough assessment of your healthcare facility's current antibiotic prescribing practices, antimicrobial resistance patterns, and available resources. Identify areas of improvement and potential barriers to implementing the program.
- ✓ Develop program goals and objectives: Define clear and measurable goals for your antimicrobial stewardship program. Examples of goals could include reducing inappropriate antibiotic use, improving patient outcomes, and minimizing the emergence of antibiotic resistance. Set specific objectives that align with these goals.
- ✓ **Establish guidelines and protocols:** Develop evidence-based guidelines and protocols for antibiotic prescribing and management. These guidelines should be tailored to your local epidemiology, resistance patterns, and patient populations. They should cover various aspects, including appropriate antibiotic selection, dosing, duration, and de-escalation strategies.
- ✓ **Educate healthcare professionals:** Provide comprehensive education and training to healthcare professionals involved in antibiotic prescribing and management. This includes physicians, nurses, pharmacists, and other relevant staff members. Offer educational sessions, workshops, and resources to enhance their knowledge of antimicrobial stewardship principles and best practices.

- ✓ **Implement clinical decision support tools:** Integrate clinical decision support tools into your electronic health record system to provide real-time guidance and feedback to prescribers. These tools can include antibiotic prescribing algorithms, dose calculators, and alerts for potential drug interactions or allergies.
- ✓ **Monitor antibiotic use and resistance:** Establish a system for monitoring antibiotic utilization and resistance patterns within your healthcare facility. Collect and analyze data on antibiotic consumption, appropriateness of prescribing, and resistance rates. Regularly review these data to identify trends, areas for improvement, and to track the impact of your stewardship efforts.
- ✓ **Provide feedback and interventions:** Develop mechanisms for providing feedback to prescribers regarding their antibiotic prescribing practices. This can include individualized reports, benchmarking data, and regular meetings to discuss performance. Implement targeted interventions, such as educational initiatives, audit and feedback programs, and clinical pathways, to address identified areas of concern.
- ✓ **Collaborate with pharmacy services:** Involve pharmacists in the antimicrobial stewardship program to support appropriate antibiotic use. Pharmacists can participate in medication reviews, provide drug information, monitor antibiotic orders, and assist with therapeutic drug monitoring.
- ✓ **Evaluate program outcomes:** Continuously evaluate the impact of your antimicrobial stewardship program. Monitor key performance indicators, such as antibiotic utilization rates, appropriateness of prescribing, patient outcomes, and resistance patterns. Use this information to refine your strategies and demonstrate the program's effectiveness to stakeholders.

- **Patient Education:** Educating patients about the appropriate use of antibiotics, including adherence to prescribed regimens and the importance of completing the full course, can help prevent unnecessary antibiotic use and reduce the risk of resistance.

- **Surveillance and Monitoring:** Continuous surveillance of antimicrobial resistance patterns, as well as antibiotic utilization data, is crucial for identifying trends, detecting outbreaks, and informing local treatment guidelines. Monitoring these data can help guide interventions to address emerging resistance and improve antibiotic prescribing practices.
- Antibiotic Stewardship in the Community: Efforts to promote rational antibiotic use should extend beyond healthcare facilities to the community. Public awareness campaigns, educational initiatives, and collaborations with community healthcare providers can help disseminate information about appropriate antibiotic use to the general public.

By implementing these strategies and interventions, healthcare systems can promote the rational use of antibiotics, preserve their effectiveness, and mitigate the development of antibiotic resistance.

CONCLUSION

Antibiotic resistance is still a serious issue that needs immediate attention on a global scale. An effective alternative to the "one compound, one target" strategy that has dominated the development of antibiotic drugs is the concept of antibiotic potentiation by compounds or strategies that obstruct important metabolic processes. Although there are challenges in terms of clinical trials and regulatory requirements when using this combinatorial approach to develop and improve antibiotics. A promising approach seems to be the creation of drugs that can both inhibit germs and

strengthen the immune system. Furthermore, the ultimate haymaker for combating bacterial pathogens may be antibiotic-induced reduction of bacteria's downstream repair mechanisms.

Declaration by Authors

Ethical Approval: Not Applicable
Acknowledgement: None
Source of Funding: None
Conflict of Interest: The authors declare no conflict of interest.

REFERENCES

1. Okeke IN, Lamikanra A, Edelman R. Socioeconomic and behavioral factors leading to acquired bacterial resistance to antibiotics in developing countries. Emerg Infect Dis. 1999; 5:18–27.
2. Laxminarayan R, Duse A, Wattal C, Zaidi AKM, Wertheim HFL, Sumpradit N, et al. Antibiotic resistance-the need for global solutions. Lancet Infect Dis. 2013; 13:1057–98.
3. Okeke IN, Klugman KP, Bhutta ZA, Duse AG, Jenkins P, O'Brien TF, et al. antimicrobial resistance in developing countries. Part II: strategies for containment. Lancet Infect. Dis. 2005; 5:568–80.
4. Hart CA, Kariuki S. Antimicrobial resistance in developing countries. Br Med J. 1998;317(7159):647–50
5. El Sherbiny NA, Ibrahim EH, Masoud M. Assessment of knowledge, attitude and behavior towards antibiotic use in primary health care patients in Fayoum Governorate, Egypt. *Alexandria J Med*. 2018;54(4):535–540
6. Demoré B, Mangin L, Tebano G, et al. public knowledge and behaviors concerning antibiotic use and resistance in France: a cross-sectional survey. *Infection*. 2017;45(4):513–520
7. Gebeyehu E, Bantie L, Azage M. Inappropriate Use of Antibiotics and Its Associated Factors among Urban and Rural Communities of Bahir Dar City Administration, Northwest Ethiopia. *PLoS One*. 2015;10(9): e0138179
8. Goossens H, Ferech M, Vander Stichele R, et al. Outpatient antibiotic use in Europe and association with resistance: a cross-national database study. *Lancet*. 2005;365(9459):579–587.
9. Prestinaci F, Pezzotti P, Pantosti A. Antimicrobial resistance: a global multifaceted phenomenon. *Pathog Glob Health*. 2015;109(7):309–318.
10. Lansang MA, Lucas-Aquino R, Tupasi TE, Mina VS, Salazar LS, Juban N, Limjoco TT, Nisperos LE, Kunin CM. Purchase of antibiotics without prescription in Manalia, the Philippines. Inappropriate choices and doses. J Clin Epidemiol. 1990; 43:61–7.
11. Okeke IN, Lamikanra A. Quality and bioavailability of ampicillin capsules dispensed in a Nigerian semi-urban community. Afr J Med Med Sci. 2001; 30:47–51.
12. Risha PG, Shewiyo D, Msami A, Masuki G, Vergote G, Vervaet C, et al. In vitro evaluation of the quality of essential drugs on the Tanzanian market. Trop Med Int Health TM IH. 2002; 7:701–7.
13. Usluer G, Ozgunes I, Leblebicioglu H, Turkish antibiotic utilization study group. A multicenter point-prevalence study: antimicrobial prescription frequencies in hospitalized patients in Turkey. Ann Clin Microbiol Antimicrob. 2005; 4:16
14. Malfertheiner P. Compliance, adverse events and antibiotic resistance in helicobacter pylori treatment. Scand J Gastroenterol. 1993; 28:34
15. Calva J, Bojalil R. Antibiotic use in a periurban community in Mexico: a household and drugstore survey. Soc Sci Med. 1996; 42:1121–8.
16. Hinman AR, Orenstein WA. Adult immunization: what can we learn from the childhood immunization program? Clin Infect Dis Off Publ Infect Dis Soc Am. 2007; 44:1532–5.
17. Strathdee SA, Davies SC, Marcelin JR. Confronting antimicrobial resistance beyond the COVID-19 pandemic and the 2020 US election. Lancet. 2020; 396(10257): 1050-1053
18. Faheem SM, Gohar UF, Riaz S. Recent developments in methicillin-resistant Staphylococcus aureus (MRSA) management and potential antimicrobial alternatives to combat the antibiotic resistance challenge: a review. Pure Appl Biol. 2022; 11(2): 353- 382.
19. Alisky J, Iczkowski K, Rapoport A, Troitsky N. Bacteriophages show promise

as antimicrobial agents. J Inf Secur. 1998; 36:5–15.
20. 20. Mathur MD, Vidhani S, Mehndiratta PL. Bacteriophage therapy: an alternative to conventional antibiotics. J Assoc Physicians India. 2003; 51:593–6.
21. Brandt LJ. Fecal transplantation for the treatment of Clostridium Difficile infection. Gastroenterol Hepatol. 2012; 8:191–4
22. Preidis GA, Versalovic J. Targeting the human microbiome with antibiotics, probiotics, and prebiotics: gastroenterology enters the metagenomics era. Gastroenterology. 2009; 136:2015–31.
23. Vrieze A, de Groot PF, Kootte RS, Knaapen M, van Nood E, Nieuwdorp M. Fecal transplant: a safe and sustainable clinical therapy for restoring intestinal microbial balance in human disease? Best Pract Res Clin Gastroenterol. 2013; 27:127–37.
24. Barlam TF, et al. Implementing an antibiotic stewardship program: guidelines by the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America. Clin Infect Dis. 2016;62(10): e51-e77.
25. Banerjee R, et al. Use of PCR for diagnosis of Clostridium difficile infection: Systematic review and meta-analysis. Eur J Clin Microbiol Infect Dis. 2016;35(9):291-310.
26. Davey P, et al. Interventions to improve antibiotic prescribing practices for hospital inpatients. Cochrane Database Syst Rev. 2017;2

How to cite this article: Viola Mendonca. A review on rational use of antibiotics: strategies and interventions. *International Journal of Research and Review*. 2023; 10(7): 298-306. DOI: *https://doi.org/10.52403/ijrr.20230741*

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