

The Global and Regional Challenge of Pan-Antibiotic Resistance: A Review of Emerging Threats and Mechanisms

Sharique Ahmad^{1,*}, Dilshad Ali Rizvi², Md Shumayel Athar Khan³, Subuhi Anwar⁴, Ruvy Verma⁵, Mayuri Agarwal⁵

Abstract

Antimicrobial resistance (AMR) is one of the major and most intricate threats to the health of the 21st century as it directly undermines expertise of the common clinical practice and public health security worldwide. The problem is characterized by the extensive development of bacterial pathogens into extremely drug-resistant (XDR) and pan-drug-resistant (PDR) so-called superbugs faster than it can be done with therapeutics. It is a synthesis of molecular processes that drive this resistance and the evaluating these issue are critically looked at on the global level and a focus on increased burden in India. We explore the effectiveness and shortcomings of the existing interventions – such as antimicrobial stewardship and alternative therapies – to contextualize a needed direction into the future of continuing the use of the existing antibiotics and encouraging new one development.

Keywords: Antimicrobial resistance, multidrug-resistant, pathogens, Extensively Drug-Resistant (XDR) Pathogens, Drug-Resistant Bacteria

INTRODUCTION

The identification of penicillin by Fleming in 1928, followed by the mass production of the drug by Florey and Chain, marked the beginning of the so-called Golden Age of Antibiotics and had a leading role in decreasing morbidity and mortality rates related to infections. These medications turned out to be the foundation of the modern medicine enabling complex surgical procedures, chemotherapy, and intensive care [1]. Nonetheless, therapeutic environment is quickly fading away because of the adaptive ability of the bacteria. Antimicrobial resistance (AMR) can be defined as the mechanism in which microorganisms – such as bacteria, viruses, fungi, and parasites – develop defense measures that make the previously effective treatments of these organisms useless. The giant AMR has been identified by the World Health Organization (WHO) and the United Nations as a global crisis because of its devastating capabilities to place health system back to the pre-antibiotic period whereby common infections are incurable [2].

The magnitude of the crisis was fully captured by Murray et al. [3], who conducted a seminal analysis in the literature in the form of a study in the Lancet and estimated that the deviant consequences of bacterial AMR were directly linked to the death of 1.27 million individuals worldwide in 2019, and

***Author for Correspondence**
Sharique Ahmad
E-mail: Diagnopath@gmail.com

¹Professor, Department of Pathology, Era's Lucknow Medical College and Hospital, Era University, Safarazganj, Lucknow, Uttar Pradesh, India

²Professor, Department of Pharmacology, Era's Lucknow Medical College and Hospital, Era University, Safarazganj, Lucknow, Uttar Pradesh, India

³Intern, MBBS, Department of Medicine, Laxmi Chandravanshi Medical College & Hospital, Bishrampur, Kosiar, Jharkhand, India

⁴Research (Assistant), Department of Pathology, Era's Lucknow Medical College and Hospital, Era University, Safarazganj, Lucknow, Uttar Pradesh, India

⁵Junior Resident, Department of Pathology, Era's Lucknow Medical College and Hospital, Era University, Safarazganj, Lucknow, Uttar Pradesh, India

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were a contributing factor causing close to 5 million deaths. This puts AMR higher than HIV/AIDS and malaria as one of the causes of death on earth. Estimates indicate that the number might increase to 10 million deaths a year by the year 2050 in case there is no urgent and concerted effort to combat the crisis [4]. This review is organized with the consistent identification of the scientific nature of the essential reasons of resistance and the summarized complexity of the problems that restrict the global and national reaction.

Scientific Reason Behind Resistance

Bacteria are known to have an unmatched capacity to plastically change their genetic makeup in that they can easily adapt to the high selection pressure of antibiotics. Development of resistance can broadly be grouped into two major processes namely vertical evolution, based on spontaneous mutation and subsequent selection, and horizontal gene transfer (HGT), based on acquisition of genes with the latter taking the lead in the process of development of rapid, multidrug resistance [5].

THE BACTERIAL RESISTANCE MECHANISMS

There are four main antibiotic resistance mechanisms of bacteria by which four major, non-mutually exclusive biochemical and structural mechanisms can be considered [6]:

- *Enzymatic Inactivation and Degradation*: This is probably the most clinically important mechanism. The bacterium secretes enzymes which will chemically normalize or alter the molecule of the antibiotic and so will make the antibiotic inactive before it can attack its target. The best-known case is the synthesis of the beta-lactamases which break down the amide bond of the beta-lactams ring present in the penicillins, cephalosprins and carbapenems [7].
- The evolution of beta-lactamases closely parallels the clinical deployment of antibiotics. Penicillin was first met with resistance by the narrow-spectrum penicillinases. Third-generation cephalosporins gave way to the development of Extended-Spectrum Beta-Lactamases (ESBLs) that occurred mainly in the organisms of the Enterobacteriaceae family: *Escherichia coli* and *Klebsiella pneumoniae*. Less recently, the discovery of carbapenemases, including the *Klebsiella pneumoniae* carbapenemase (KPC) and the New Delhi Metallo-Beta-Lactamase (NDM -1) has created a significant drug consumption gap. The NDM-1 enzyme was initially described in 2009 by Yong et al. [8] and showed the capacity to hydrolyze nearly all the beta-lactam antibiotics including the last-resort carbapenem. The gene that codes the NDM-1 is frequently contained in highly mobile plasmids, and this has made the gene spread fast across various species and genera of Gram-negative bacteria [9].
- *Drug Target Modification*: Adaptation of the molecular target by bacteria can cause changes in the structure of the molecular target of the antibiotic and decrease its affinity to bind but has no effect on the intracellular concentration of the drug [10]. The most famous example is the mechanism of resistance to methicillin in the bacteria of the genus *Staphylococcus aureus* (MRSA) that occurs through the acquisition of the *gene mecA*. This gene as shown in the seminal study by De Lencastre and Tomasz [11], encodes a new penicillin-binding protein (PBP2a) with a very low affinity with all the antibiotic: the antibiotic may proceed with cell-wall synthesis in the presence of the antibiotic. In a parallel way, acquisition of the *vanA* gene cluster mediates vancomycin resistance in *Enterococcus* species [12].
- *Active Drug Efflux*: Efflux pumps are trans-membrane proteins, which serve as the major defence mechanism and therefore secrete the antibiotic out of the bacterial cell [13]. These pumps are very efficient as they could be multidrug efflux pumps then able to transfer structurally disparate antimicrobial agents through the cell membrane and providing a novel resistance to multiple classes of antimicrobials at once [14]. As an illustration the RND (Resistance-Nodulation-Cell Division) group of effluent pumps, especially MexAB -OprM system in *Pseudomonas aeruginosa* is a major contributor to intrinsic and acquired multi-drug resistance a severe nosocomial pathogen as described by Piddock [15].
- *Reduced Permeability*: This is specific to Gram negatives bacteria which are covered by an outer membrane, and it can be resistant by reducing the uptake of the antibiotic. This is usually achieved

by disturbing or altering the outer membrane porins which are the conduits by which hydrophilic molecule including most antibiotics are transported across the outer membrane [16]. Key mechanisms in loss of carbapenem resistance activity include the loss of certain porins including OprD in *P. aeruginosa*, together with efflux pumps overexpression or beta-lactamase activity [17].

THE DISSEMINATION MOTOR: THE HORIZONTAL GENE TRANSFER (HGT)

Horizontal Gene Transfer is the most important process which supports the rapid spread of antimicrobial resistance (AMR) determinants where bacterial taxa can obtain resistance genes in phylogenetically distant species. This process is induced using Mobile Genetic Elements (MGE) that comprise plasmids, transposons and integrons as the chief agents of mediation [18].

- *Conjugation*: The most common and clinically relevant form of HGT is called conjugation. It involves the one-way transfer of plasmid or other MGE of a donor bacterium to a recipient in direct cell-to-cell contact because of pilus involvement [19]. The resistance gene *NDM-1* and *KPC* are commonly carried on large conjugative plasmids enabling a single resistance event to quickly spread over an entire microbial population as is supported in the study of Toleman et al. [20].
- *Transformation*: Transformation is a process of uptake of extracellular fragments of DNA released by the lysed bacteria into the actual surrounding milieu. Some bacterial species are competent per se and are actively requesting and integrating such fragments, which can contain resistance genes [21].
- *Transduction*: Transduction refers to the resistance determinant transfer that are bacteria-mediated. Segments of bacterial chromosomal or plasmid DNA have the possibilities of being accidentally scene inside the viral head and later injected into a new host organism during the viral replication cycle [22].

DIFFICULTIES IN OVERCOMING THE CRISIS

The greatest challenge facing the authorities dealing with the issue of public health is that AMR is multifaceted and interconnected and cuts across human, animal and environmental spheres the three main pillars of the One Health paradigm [23].

Global Challenges

These are systemic and economic challenges:

- *The Stalled Pipeline*: The shortage of new therapeutics is the oldest problem. The model of economy that is behind the development of the antibiotics is flawed [4]. Drugs dealing with chronic illnesses provide significant more revenues than antibiotics that are taken within a shorter time span and consumption of which is limited by stewardship programs. As a result, the Review on Antimicrobial Resistance conducted by O'Neill found an insufficient innovative power, saying that there is a lack of new antibiotic classes in the new decades, thus leaving the world susceptible to new extensively drug-resistant (XDR) strains progressing rapidly [4].
- *Surveillance and Data Gaps*: Statement Global surveillance is still in bits even despite the importance of the threat. The World Health Organization global antimicrobial resistance and use surveillance system (GLASS) provides the necessary data but there is inconsistent reporting, especially in the low and middle-income countries where the problem is the most significant [24]. Lack of precise, real-time trends of resistance makes clinicians use inaccurate empirical, broad-spectrum regimens which only increases resistance further [25].
- *Failures in Policy and Governance*: In many areas, there is no strictness in the regulatory regulations on the sale of antibiotics and the lack of effective regulation by the governments has led to the proliferation of such abuse. To a certain degree, the international movement and intercontinental trade provide the faster and global spread of resistant clones and MGEs, which turn local resistance issues into global endemic diseases [26].

The Indian Context: Distinct Challenges

The AMR is inordinately burdened in India due to certain peculiarities connected to the population density the level of sanitation and access to healthcare [27]. According to the estimates of the Institute

of Health Metrics and Evaluation (IHME) as of 2021 about 267,000 and almost 1 million deaths in India were directly connected to AMR and had an additional associated death, respectively [28].

- *Uncontrolled Use:* India is also among the largest consumers of the antibiotics globally with self-medication, patient demand and the ubiquitous availability of antibiotics over-the-counter in non-prescription rates being the key factors contributing to the uncontrolled use [29]. Kotwani et al. showed that sales of non-prescription antibiotics were high and noted one of the major factors leading to community resistance [30].
- *Rapidly Increasing Resistance Rates:* According to revelations documented by the ICMR, in the Annual Report of the Antimicrobial Resistance Research and Surveillance Network (AMRSN), resistance rates in relation to the Critically Important Antimicrobials (CIAs) have rapidly decreased. As an example, the 2023 report showed that the susceptibility to meropenem had decreased significantly among *Klebsiella pneumoniae* in the past few years and *Salmonella Typhi* had a resistance of over 95 to fluoroquinolone [31]. Indian clinicians often warn that potent, routine antibiotics are not effective against common infections and many intensive care units in hospitals are doing with the highly toxic and final-line agents [32].
- *Environmental Dimension:* During manufacturing effluents and untreated release of human sewage into rivers and water bodies, the active pharmaceutical ingredients (API) are discharged creating large reservoirs of antibiotics with high concentration [33]. This contamination to the environment can act strongly as a selective pressure in favor of the maintenance and horizontal transfer of resistance genes in the environmental resistome which in turn finds its way back into human and animal populations [34].

PROS AND CONS OF CURRENT INTERVENTION STRATEGIES

The mitigation strategy of AMR globally is arranged with a three-pillar approach namely Stewardship, Surveillance and Innovation. A comparison of the benefits (Pros) and limitations (Cons) of the major interventions shows that the key gaps exist in the implementation especially in the contexts of limited resources [35].

Pros: Advantages of Current Strategies

- *Antimicrobial Stewardship Programs (ASPs):* ASPs, physician-led and overseen by pharmacists are very useful in optimizing the use of antibiotics enhancing clinical outcomes and minimising the healthcare costs in high-income settings [36]. They endorse the so-called 5Ds correct Drug selection, correct Dose, correct Duration, correct De-escalation and correct Diagnosis and via prospective audit and feedback have been demonstrated to significantly decrease unwarranted prescriptions of antibiotics [37].
- *New Drug Combinations:* An attempt to develop beta-Lactam (beta-lactam/beta-lactamase inhibitor) combinations is an effective approach. According to Drawz and Bonomo, novel inhibitors including avibactam (e.g., ceftazidime-avibactam are effective against a wide range of problematic β -lactamases including KPC and some extended spectrum β -lactamases (ESBLs), preserving the effectiveness existing beta-lactams [38].
- *Vaccination and Infection Control:* Prevention of infections is the most effective way of decreasing the need of antibiotics. The evidence-based reduction in the use of first line antibiotics and therefore reduction in resistance rates against that pathogen has been observed due to successful immunisation programmes against pneumococcal disease (*Streptococcus pneumoniae*) resulting in the incidence of invasive disease reduced [39].

Regional and Setting-Specific Resistance Trends in the Indian Subcontinent

The Indian subcontinent forms an adjacent epidemiological area, which means that any resistance mechanism can easily cross the national borderline and pose a single health-related hazard [40]. This heterogeneity is shed light by surveillance activities organized by the National Centre of Disease Control (NCDC) and AMRSN of the ICMR, which states that antimicrobial resistance (AMR) is not a national issue but rather a cluster of regional epidemics connected through mobile genetic factors.

The NDM-1 Phenomenon and Transnational Spread: The rise of the New Delhi Metallo-2-lactamase (NDM-1) clearly shows the subcontinent as a source and a mediator of global AMR. The landmark publication by Kumarasamy et al. [9] revealed NDM1 in not only India but also in Pakistan and the United Kingdom (in patients with recent travel connections with the subcontinent), thus, establishing that resistance mechanisms that begin in areas with high-level numbers like a metropolitan city in India and Pakistan are swiftly transferred through border by conjugative plasmids [35]. Later surveillance has confirmed the prevalence of NDM-1 and other carbapenemases, including OXA-48 to be high across Bengal and Pakistani lands and hence making subcontinent the epicenter of such genes [36].

North and West India: Carbapenemase Hotspots: In India, research that has been conducted on tertiary care centres in the North, i.e., AIIMS Rishikesh, has found that the prevalence of multidrug-resistant organisms (MDROs), specifically *Klebsiella pneumoniae* and *Acinetobacter baumannii*, are the leading causes of infections in general medicine and surgery departments [37]. Western states like Gujarat and Maharashtra are also noted to have high levels of resistance including high levels of cephalosporin resistance caused by the extended-spectrum 2-lactamase (ESBL)-producing pathogens [38]. These northern areas were also confirmed by molecular studies conducted by Walsh et al. [35], as high-volume sources of transmission of the DNV-1 bearing plasmids of NDM-1, which enables its dissemination into other countries.

South and East India: Dual Resistance and Environmental Load: In the southern states, longitudinal data collected in institutions like the Christian Medical College (CMC) in Vellore (which is an ICMR nodal centre) show various resistance phenotypes. A systematic review by Singh et al. [39] of trends in the three states of southern India (Tamil Nadu, Karnataka and Andhra Pradesh) indicated alarming prevalence of multidrug-resistant Enterobacteriaceae (usually over 70 %), dual methoxyphenidine resistance in addition to third-generation cephalosporin resistance, thus greatly complicating the empirical treatment of common community-acquired urinary tract infections (UTI). Evidence of an important environmental element in the crisis is found in data of the eastern areas, such as Sikkim, where the investigation by Singh et al. [41] found that the multidrug-resistant Enterobacteriaceae, such as *Escherichia coli* and *Klebsiella oxytoca*, was present in potable spring-water sources, thus showing a high level of fecal contamination and recycling of antibiotic-resistance genes (qnrB, tetO).

Specific Pathogen Concentrations (MDR-TB and Fungi): In addition to typical nosocomial infectious organisms, the local surveillance demonstrates the presence of severe resistance against endemic diseases, in particular, multidrug-resistant tuberculosis (MDR-TB). India continues to be the nation with the most global case of MDR-TB, and resistance to first-line medicines (isoniazid and rifampicin) has been observed to cluster in the high-density, urban areas [42]. This MDR-TB burden is reflected in Pakistan and Bangladesh where the lack of compliance with long-term treatment courses creates the corresponding selective-pressure conditions favorable to the development of drug-resistant strains [43]. IMCR surveillance in the fungal world suggests that there is a new danger of *Candida auris*, an antifungal-defiant yeast. Whereas the overall prevalence of *C. auris* is comparatively low, the pan-Indian resistance rate, isolated centres in the south and west India have reported cases of fluconazole-resistant strains, thus necessitating a high infection prevention and control (IPC) measure to exclude the possibility of national spread [44, 45].

Gram-Positive Resistance Variations: Though the epidemiology of Gram-negative resistance is superior, distribution of Gram-positive trends also has regional differences. As an illustration, the prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA) differs, with some metropolitan regions reporting higher rates of MRSA than the nationwide average of 40 percent and especially in the south and northeast [46]. However, gram positive infections have still some critical last-line agents including vancomycin and linezolid which have remained highly effective (95 % susceptibility) in most regional centres surveyed by ICMR though great vigilance is still paramount against occasional development of vancomycin-resistance Enterococcus (VRE) [44].

Setting-Specific Severity (ICUs): The intensity of resistance increases significantly in the tertiary care environment especially in the intensive care units (ICUs). The clustering of vulnerable patients, a high dose of antibiotics, and complicated procedures create potent selective pressures [44]. According to reports by ICMR, there is always a tendency to find that isolates in ICUs have a low susceptibility to antibiotics than general ward. Meropenem resistance in acute Gram-negative pathogens like *Acinetobacter baumannii* has been reported to be over 90 % in most national ICUs, and thus has a severe impact on the empirical treatment of these infections, forcing the use of second-line agents, which are toxic, such as colistin or tigecycline [44, 47]. Such local severity highlights the urgency of regional antimicrobial stewardship programme (ASP) to focus on aggressive IPC in the units of the critical care. (95 % susceptibility) in most regional centres surveyed by ICMR though great vigilance is still paramount against occasional development of vancomycin-resistance *Enterococcus* (VRE) [44].

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Regional and Setting-Specific Resistance Trends in the Indian Subcontinent

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Cons: Limitations and Implementation Hurdles

- *Limitations of Resources in ASPs:* In LMICs, like India, infrastructure and lack of expertise have a very serious negative effect on the efficacy of ASPs [41]. Problems that are encountered are the shortage of committed infectious disease specialists the shortage of clinical microbiologists as well as the lack of timely inexpensive diagnostic equipment [42]. In their systematic review Nkuba et al. established that in most ASP countries interprofessional collaboration of the ASPs is usually lacking and nurses and pharmacists are not involved [43].
- *Poor Profitability of New Agents:* The significant flaw of the innovation pipeline is that the trend is unsustainable. The usage of a new antibiotic should be strictly limited even when it is successfully created to ensure the instant resistance is not developed. This low-volume usage is counterproductive to incentive to invest on the private sector undermining a market failure which has not been resolved by suggested mechanisms of transferable exclusivity vouchers or subscription [4].
- *The Diagnostic Lag:* Clinicians across the globe with resource constraints especially need to engage the empirical therapy prior to the culture result [45]. The present sluggish culture and susceptibility testing entails that patients commonly get numerous days of broad-spectrum antibiotics that exposes them to intense choice pressure in grounds of opposition to the ensuing serious antimicrobial treatment though it might not be suitable. The unavailability of affordable and easy-to-access Point-of-Care (POC) diagnostics is still a vulnerable bottleneck [46].

FUTURE ASPECTS AND NOVEL THERAPEUTIC STRATEGIES

The future combat against AMR should be centered on the replenishment of the drug pipeline and adopting the new non-traditional, innovative therapeutic modalities [47].

Non-Antibiotic Interventions

- *Bacteriophage Therapy:* Phages are viruses that particularly infect cells of bacteria and lyse them. The Phage therapy has long been employed in Eastern Europe but now enjoys worldwide resurgence because of its ability to cure the infection posed by PDR bacteria to which no chemical antibiotics are effective anymore [48]. As illustrated in a study by Dabrowska et al., phages have

been proven to be effective against deep-seated and chronic infections especially using small amounts of the phages without many side effects like those caused by common antibiotics [49]. The Antimicrobial Peptides (AMP) is a complex of receptors extending into outer membranes.

- Antimicrobial peptides (AMPs) are host-defense molecules that directly attack and disrupt bacterial cell membranes. They pose less traditional resistance efforts as their mechanisms are promising [50]. Morones-Ramirez et al. reviews mention that there is a big potential in the engineering and production of novel peptides that can have a wide range of bactericidal activity [51].
- *Anti-Virulence Strategies*: This process aims at neutralizing the virulence factors that is toxins, adhesion molecules or biofilm formation of the bacteria instead of killing them [52]. It is based on a type of communication between bacteria called Quorum Sensing (QS) inhibitors that disrupt the formation of large colonies by bacteria that are shielded and secured by their shell [53]. This can hypothetically enable the host immune system to eliminate the infection with a decrease in selective pressure to resist it, since it means that the pathogen has fewer chances to become dangerous.

Policy and Technological Change

- *CRISPR-Cas Technology*: Two main things have been investigated to apply genomic engineering technologies, specifically the CRISPR-Cas system; one is its application as a highly accurate diagnostics tool and the other is the explicit targeting and degradation of antibiotic resistance genes (ARGs) in the bacterial genome [54]. Research indicates that CRISPR-Cas can be introduced by phages effectively to target the removal of resistance plasmids which revert the resistance phenotype (Yang et al.) [55].
- *Policy Innovation*: It is essential that the concept of pull incentives is developed. The governments and other health organizations should not depend the revenues of drug developers on the sales volume possibly by giving rewards in the form of large amounts of money to drug developers to enter the market with successfully developed antibiotics as suggested by the WHO and many other policy groups [4]. This is in relation to eliminating the underlying economic obstacle that led to the discovery gap.

DISCUSSION

Pan-antibiotic resistance is also a crisis due to the collision of increased microbial evolution with failure in global governance. The scientific component of the resistance: HGT via mobile elements that transport genes encoding lactamases, efflux pumps and target alteration is comprehended well nowadays [56]. But the matter falls short in putting this knowledge into practical just acting within the One Health spectrum.

The ICMR statistics firmly indicate that India is increasingly becoming a desert of therapeutic choice especially dealing with Gram-negative ESKAPE pathogens especially those ones that are resistant to carbapenem drugs like carbapenem-resistant *Acinetobacter baumannii* and *Klebsiella pneumoniae* [57]. Though the direct and catastrophic effect is experienced in ICUs, the drivers of the community; unregulated access, inadequate hygiene and environmental pollution [33], make sure that there is a permanent pool of resistance genes that contribute to clinical failure [40]. The diffusion of MGEs, including the NDM-1 plasmid [8, 9], implies that a solution to the problem created in one part of the world can quickly spread to the world, which is why this problem is interrelated.

ASPs achieve success in high-income environments [36] and a blueprint exists but their application in LMICs must be specific. As described by Nkuba et al. [43], imitation of the western models cannot explain the absence of resources, diagnostic constraints and behavioral forces behind antibiotic misuse [58]. An effective reaction would involve both infrastructure investment in terms of the rapid diagnostics of the situation and the strict control of the sale of antibiotics through governmental regulations, which would take the efforts of not only scientists but of political actions as well. The aspects of the promising future include phage therapy and anti-virulence drugs which are promising in terms of being provided as alternatives to treatment [48]. Nevertheless, these new agents should be backed by viable economic

systems and safeguarded by strict stewardships to eliminate the probability of rejection. Finally, to resolve the AMR crisis the perception paradigm should be changed so that antibiotics are perceived as limited world resource but not as something that can be replenished without end [44].

CONCLUSION

The current situation of antimicrobial resistance is a competition of microbial evolution against which humanity is losing as the number of people dying grows and the effectiveness of the last-resort drugs against XDR pathogen develops in all countries worldwide and in the most important healthcare systems of individual nations (such as India). Scientific causes of resistance are well clarified through the acquisition of resistance genes successfully through horizontal gene transfer which resulted into enzymatic inactivation, target modification in addition to active efflux. The deep roots of the crisis lie in the fact that to find new molecules is not enough, but rather to radically fix the broken economic, regulatory and environmental regimes that are the sources of the crisis. The only alternative that can be used to address the existential threat of severe consequences is coordinated global policy response guided by One Health framework and bold local stewardship and next generation therapeutics investment.

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