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Review article

Impacts of pathogen-host-drug interaction in the evolution and spread of antimicrobial-resistant pathogens

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ABSTRACT

Background: The single antibiotic drug monotherapies have been used by clinicians in medical treatments of various infectious diseases including tuberculosis (TB); however, World Health Organization accredited the rise of antimicrobial resistant bacterial pathogens, is a major global health crisis. As a result, a widely promising strategy known as antibiotic drug combination therapies have been designed to combat the evolution of drug-resistant pathogens, to enhance the current treatment efficacy by combining more than two antibiotic drugs, and for the efficient treatment of numerous infectious diseases including TB, HIV/AIDS, malaria. However, the disease-causing pathogens became resistant to multiple antibiotic drugs and can no longer be destroyed. One of the influencing factors of antibiotic drug combination treatment success failure is pathogen-host-antibiotic interaction which affect the combined drug outcomes and may influence evolution of multidrug-resistant strains. In such context, the main objective of this review paper was to assess the impacts of pathogen-host-antibiotic interaction in the evolution and spread of multi-drug resistant pathogens against drug-combination therapy. Understanding the potential mechanisms of drug-drug, host-antibiotic and host-pathogen interactions help to inform decisions as to set-up in clinical settings in order to limit the evolution and spread of multi- drug resistant bacterial strains. Most significantly, in the near future sustainable bacterial infection therapies for potential adaptive pathogens include synergy-based drug combination and host-directed therapies in drug combination could be exercised to tackle the multi-drug resistance crisis by enhancing the combined drug treatment efficacy and prevent bacteria adapting to combination treatments.

Background

Antibiotic drugs are unquestionably the most effective form of chemotherapy and have a significant impact on the survival of bacteria. However, microbes have an amazing ability to adapt to these antibiotic drugs. The rapid emergency and evolution of antimicrobial resistant strains of

pathogenic bacteria have a serious health risks since the earliest days of antibiotic research because bacteria have an evolved mechanism to overcome the effect of antibiotics and thereby become resistant, which is depending on species type and geographical location [1]. Even though, a

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widespread use of antibiotic drugs for almost a century, numerous bacterial pathogens including *M. tuberculosis* showed an increase in their antimicrobial resistance (AMR) leading to the evolution and spread of multi-drug resistant (MDR) strains via chromosomal mutations [2]. It has been suggested that the progressive accumulation of mutations can simultaneously change either an organism's sensitivity or resistance to many different antimicrobial agents. As a result, the existed antibacterial drugs are becoming less effective and are currently losing, and then antibiotic resistance pathogens being a significant growing global public health threat and it has forced the investigators to develop newer approaches as modern medicine relies heavily on effective drugs for combatting bacterial infections [3]. Consequently, globally the AMR related deaths have reached alarming rates and more than 700,000 people die annually; this could rise to 10 million by 2050, far greater than cancer as the major cause of death worldwide [4].

The ranking list of antimicrobial resistance pathogens reported by World Health Organization [4] was important to help researchers and funders in focusing on resources and attentions, to encourage interdisciplinary research initiatives on the occurrence, epidemiology, dissemination and molecular characterization of the most risky MDR pathogens with the aim to develop effective prevention strategies against the emergency and spread of these harmful resistant pathogens; *Mycobacterium tuberculosis* had the highest priority of MDR strain followed by *Acinetobacter baumannii* and *Pseudomonas aeruginosa* in the past three decades.

Thus, to tackle the antimicrobial resistance crisis in which a single drug monotherapy is no longer satisfactory to treat infectious disease including TB, researchers have been developing a novel effective promising treatment strategies known as drug combination therapies in order to combat the evolution of MDR phenotype, especially in low-resource settings of Sub-Saharan Africa where co-morbidity is endemic [5]. For example, a combination of four drugs (i.e., isoniazid (INH), rifampicin (RIF), ethambutol (ETB), and pyrazinamide (PZA)) are being used for the treatment of *M. tuberculosis* infections [6].

Currently, although antibiotic drug combination therapies have been employed for increasing the efficacy of the treatment, but in fact,

it may actually promote the evolution and spread of AMR pathogens including many multi-drug, extended drug and now fully drug resistance strains, which implies that the use of antibiotic drug combination therapy is going to be uncertain [2]. When antibiotic drugs are combined, the mechanism of action of drugs in high-order antibiotic drug combination therapy can significantly differs on bacterial cells, may either be raised or weakened by impacting on the epistatic host-pathogen-drug interactions during antibiotic therapy, even if in the absence of human interventions [3]. In this context, the main objective of this review paper is to assess the impacts of pathogen-host-drug interaction in the evolution and spread of MDR pathogens against drug combination therapy.

Antibiotic combination therapy

Previously, clinicians have used our current arsenal of drugs by prescribing high doses of a single antibiotic drug monotherapy strategy in order to minimize the probability of bacterial infectious diseases including TB [3]. However, high doses applying of monotherapies are often associated with stronger side-effects in patients and have been reported to increase the risks and rapid evolution of resistant bacterial strains, that involved by long-term regimes. As a result the single-drug monotherapies often fail and become more challenging for clinicians worldwide [7]. In order to overcome the drug resistance ability of the bacteria, one such potential promising and life-threatening strategy in many areas of medicine is the use of high-order antibiotic drug combination therapy of two or more antimicrobial agents during a treatment regimen from different classes targeting different bacterial mechanisms as a standard of care for active infections in multi-drug environment, which is important to effectively combat the spread of MDR phenotype of bacterial infections [5], and efficient treatments for many infectious diseases such as TB, cancer, HIV/AIDS and Malaria since the 1970s [8]. Therefore, assuming that there is no overlap in the resistance mutations, the simultaneous use of multiple antibiotic drugs (i.e., administration in mixture of antibiotic drugs) during the treatment will reduce the development of drug resistance strains. However, designing multi-drug combination therapies are difficult when the overall effect of a drug combinations are changing their behavior either strengthening or weakening through different ways and increasing the antibiotic treatment failure,

that is not easily predicted based on the individual effects of the drug [3].

Generally, there are multiple key features for antibiotic drug combination therapies compared to single-drug monotherapy strategy: (i) a broadened activity range by combining the different modes of action of different antibiotics; simultaneous resistance to two drugs often requires two independent genetic events, each of which on its own occurs with low probability; (ii) stronger enhancement of antibiotic treatment effect that show high efficacy by synergistic effect against resistant strains, that restore the efficacy of a particular drug; and (iii) slow-down the risks and rate of resistance evolution during treatment regime [8,9], (iv) improvement of antibiotic drugs penetration to cells [3], and (v) inhibition of virulence factors, such as lowered toxicity effects or enzyme production in pathogens [10].

Currently, the bacteria evolution in multi-drug environment is one of the major causes of drug resistance, whereby drug resistance mediated mutations become resistant to multiple drugs and can no longer be destroyed using the current antibiotic drug combination treatment approaches as it is [11]. Moreover, even though a patient who have been treated with drug combination therapy, the antimicrobial resistance pathogens including *M. tuberculosis* increase time to time and evolved into many multidrug and extensively drug-resistant strains, and achieving the STOP/End-TB strategy at the global level by 2035/2050 remains questionable and challenging, it is important to understand what are and how the influencing factors in multi-drug environment change treatment efficacy [12], that needs for designing novel effective drug [13] suggested that the proper selection of antibiotic drug combination therapy at the right dose and for the right length of time for crucial treatment efficacy, and necessitates by understanding the potential mechanisms of the influencing factors such as epistatic pathogen-host-antibiotic interactions and the frequency of mutations with pleiotropic fitness effects is the current critical and serious tasks in order to treat the patients efficiently and to slow-down the emergency and evolution of multidrug-resistance bacterial strains, when the combined inhibitory effect of two drugs are stronger for their ability to clear infections under multi-drug environment [2]. Likewise, high-throughput studies on these influencing factors for understanding the evolution of bacterial pathogens under high-order

drug combination therapies that balance short-term drug efficacy with long-term evolutionary trade-off considerations is a burning issue nowadays [14].

Factors modulating evolution of resistance in multi-drug environments

Epistatic drug-drug Interactions (DDIs)

Like genetic epistatic interaction, drugs should be also interacted with each other. Importantly, the first focusing of epistatic interactions between and within genes is now starting a useful analogy to drug-drug epistatic interactions, that providing to introduce some of the principal concepts of the relationship between drug interactions targeted by different drugs and uncovering the action of drugs for biological function. Establishing the basic concepts of drug-drug interactions then allows us to explore the impact of these interactions on the evolution of drug resistance pathogens [15].

Combinations of antibiotic drugs have been classified depending on the prior assumptions about epistatic drug-drug interactions by assuming Loewe additivity model, that the combined effect may be significantly different, what is expected based on a predictive additive effect of their individual outcomes or effects, that may change bacterial growth rate at a given concentration in evolving bacterial lineages, which are (i) antagonistic (is a situation where the effect of drug combination is less than the combined effect of the individual drugs, that results in a significantly worse bactericidal effect or less growth reduction than expected additive effect when used of either drug in monotherapy, and because of their reduced efficacy and leads to longer time for infectious bacteria clearance); (ii) synergistic (a situation where the drug-combination effect is greater than the combined effect of the individual drugs, that the presence of one drug intensify the effect of the other drug, that leads to a significantly better growth reduction than expected additive effect when used of either drug in monotherapy, and mutually improve their therapeutic effects that enhance antibacterial treatment efficiency without increasing drug toxicity); and (iii) additive or non-epistatic drug interaction is the situation where the effect of a drug combination is equal to the combined effect of the individual drugs [7,15-17].

Previous studies have suggested that the high-order antibiotic drug combinations may be chosen due to their non-overlapping resistance mechanisms and their favorable drug-drug interactions. Such drug

interaction networks could be used to classify drugs by the cellular function they inhibit, namely by their underlying mechanism of action. So that, a deeper understanding of the underlying mechanisms of antibiotic drug-drug interaction in drug combination is urgently needed and helps to inform decisions as to which drug combinations to set up in clinical settings in order to limit the evolution and spread of drug resistant strains, minimize adverse drug effects and reduce treatment duration, improve treatment outcomes of patients, and design the potential synergy based antibiotic combinations of existing drugs [2,12,18,19].

Indeed, scientific studies have shown that co-treatment with different pairs of clinically relevant antibiotic drugs exhibit drug-drug interaction patterns depending on; (i) physicochemical effects between drugs, that one drug modifies bacterial physiology in a way that alters the impact of the other drug [5], for instance when one drug simply enhances the permeability of the cell envelope for another, alternatively they may have more complex causes, specifically if one drug triggers a regulatory response, which affects the action of another, (ii) genetic variation or certain drug resistance mutations in the bacterium that affect drug interactions, but it is unclear to what extent genetic perturbations can alter drug interactions. To determine their underlying causes, identifying genes that reshape drug-drug interactions must be established, which enables the quantitative prediction of mutant growth rate under antibiotic drug combinations [14], and (iii) physiology of specific bacterial strains and/or lineages within a species or geographical locations, which are currently not considered for drug combination therapy in clinical settings [20,21].

Studies have been recommending that the different classes of antimicrobial drugs in drug combination for treating bacterial infections might result in synergistic antibiotic interactions that enhance the inhibitory effect or generate increased antimicrobial efficacy at lower doses, and this synergy has been used by clinicians; for instance, a study has done by **Omollo et al.** [12]. using Streptomycin (SPT)- Folic acid (FA) drug combination for treating two resistant strains FA^R and SPT^R mutant, the FA exerted a greater 90% inhibitory effect or restoring susceptibility against a genotypically confirmed SPT^R mutant carries a g1379t mutation in *rrs*; however, the same combination did not return any synergy against the FA^R mutant carrying a c1384t in

fusA1. This result suggested the capacity for synergistic combinations to restore drug activity against mutant strains genetically resistant to either of the partner compounds.

However, antagonistic and especially suppression or ‘hyper-antagonism’ drug-drug interactions in drug combinations have been shown to either reduce the drug efficacy or completely neglected in the context of antimicrobials inhibition effect at fixed drug dosage, which leads to longer time for infectious clearance, thereby increasing the evolution of resistance [15]. A study has done by **Bhusal et al.** [22] testified that the interaction between RIF-mono-resistant *rpoB* S531L and INH-mono-resistant *inhA* mutants against *M. tuberculosis* to have no interaction or to be mildly antagonistic, however further study on a triple SPT-RIF-INH drug combination interactions in *rpoB* and *inhA* mutants has been reported that 24 out of 70 random drug combinations tested were synergistically active in the *in-vitro M. smegmatis* and suggests that a triple SPT-RIF-INH combination may be an effective therapeutic option for the treatment of both the drug susceptible and resistant *M. tuberculosis* infections through restoring susceptibility against *M. tuberculosis* strains carrying genetic resistance to any one of the partner drugs [12].

Host-antibiotic interactions

One key parameter to be consider for any types of antibiotic drug combination therapies is the precise prescribed dose of antibiotic(s) into the host patients, which is crucial for clearance of all bacteria, and yet most of the commonly-used dosages of antibiotic drugs were only considering their pharmacokinetics (PK) and pharmacodynamics (PD) parameters, as such “one size fits all” approach, indifferently of the host patients genetic characteristics [23]. Significantly, to treat patients efficiently while avoiding drug resistance strains, it is crucial to use the right dose antibiotic for the right length of time. Ensuring an appropriate dose of antibiotics during treatment strategies, it should be considering how the host genetics can alter antibiotic drug circulating concentrations in patients by impacting on antibiotic metabolism, but yet the current prescriptions rarely take it into account [7].

So that, considering and/or understanding the prescribing antibiotic drug and host genetics interaction is vital for the development of optimized medical treatments. Host patient’s genetic variations

at the antibiotic metabolism genes involving single nucleotide polymorphisms (SNPs) can affect the antibiotic metabolism processes. This affects the duration and the intensity of the pharmacological activity (alter bioavailability) of the antibiotic drug by impacted on their appropriate dosage [24]. Moreover, the epistatic interactions between antibiotics and host patient's genetic variants or SNPs at the antibiotic metabolism genes coding for antibiotic metabolizer enzymes have a potential impact on the (i) antibiotic metabolism gene expression regulation by altering transcription, alternative exonic splicing or silencing mechanisms that can alter the protein sequence (leading to non or dysfunctional enzymes), the gene transcription or the gene stability (leading to differences in the enzymatic concentrations), and/or (ii) enzyme activity could promote differences in drug metabolism (either higher or lower leads to poor metabolizer in patients) capable of significantly altering the degradation of various antibiotic drugs, affect the circulating drug concentrations, influence the critical antibiotic drug dose required to eliminate wholly bacteria, and affecting its bioavailability and treatment efficacy; for instance, a study has been conducted amongst the world population ethnic groups, eight SNPs on the cytochrome CYP3A4 gene (rs28988603, rs28988604, rs28969391, rs28371763, rs28988606, rs12721620, rs2242480 and rs2687116) have been recognized on CYP3A4 gene expression or enzyme activity for adapting treatment dosages and influence on drug efficacy to the average patients against Methicillin-Resistant *Staphylococcus aureus* (MRSA) infections using the combination of vancomycin and rifampicin [7]. This could lead to increased combination treatment failure, may promote the emergence of antibiotic drug resistance and excessive side effects in patients, for example, SNPs or deletions on GSTT1 genes are expressed as non-functional alleles in patients that encode antibiotic metabolism Glutathione S-Transferase T1 resulted an increasing chance of toxicity in TB-patients treated with isoniazid, pyrazinamide and rifampicin drugs [25]. Furthermore, during epistatic drug-drug-host interactions, one particular drug can stimulate or inhibit the expression of one particular enzymatic gene which is influencing the degradation of another drug, leading to reducing or increasing its bioavailability and low treatment efficiency and the emergence of drug resistant strains [7,24]. However, too much limited studies have done, and in the near

future the scientific community should be investigate the antibiotic metabolism of every clinically relevant antibiotic drugs, as well as the host patients' genetic polymorphisms affecting the enzymes responsible for the metabolism of these drugs.

Host-pathogen interactions

Previously, bacterial pathogens have often studied as alone, and grow independently from other bacteria or host organisms and evolve antibiotic drug resistance as an adaptation to antibiotic therapy. However, pathogens are part of a complex ecosystem within the host organisms including human, which can greatly influence the outcome of antibiotic drug treatments [14].

As bacteria are forced to interact with other microbes upon colonization or infection of the host organisms. Significantly, host-bacteria and bacteria-bacteria interactions may interfere the ecological and evolutionary pressures that exhibit clinical importance [26]. These eco-evolutionary mechanisms affect the existence of pathogens [14]. It is critical to understand pathogenic bacteria with respect to the surrounding microbial communities; however, for instance, active pulmonary TB infection requires long-term combined antibiotic treatment, which can alter the lung microbial community profile and subsequently affect the outcome of the combined drug treatment [27]. This increase the possibility of foreign bacteria colonization in the lung microenvironment that become more susceptible.

The colonizing bacteria can be influenced by a variety of host mechanisms, and importantly play a role in susceptibility to infection. The effect of antibiotic drug therapy on microbiome diversity has only recently been explored and depends on the antibiotic spectrum, dosage, length of treatment, route of administration, and pharmacological properties of the agent [26]. It is important for clinicians and researchers to further explore the relationship between host organism and pathogens including *M. tuberculosis*, as these may constitute a risk factor for drug resistance development and failure of drug combination treatments.

Pathogens have an evolved strategy to adapt the changed multi-drug environment and promote alternative ways to survive and grow inside the host organism. The host-pathogen interactions should be one mechanism that take places between a host and a pathogen through the proteins and genes with

the aim to evade the antibacterial host defense mechanisms by performing hijacking of the host cells they infect, forming biofilms, disrupting normal functioning of pathway such as inhibiting macrophage activity/ mechanisms, and preventing host receptor cells [27], for instance, urease (an enzyme) is present in many mycobacterium species, that plays an important role in MTB-host interaction, and the growth of *M. tuberculosis* within the host cells [28]. Moreover, *M. tuberculosis* actively transcribes a number of genes involved in protection and evasion of a host defense system by performing hijacking of the host cells they infect, for instance, genome of the strain of H37Rv *M. tuberculosis* made up of 4000 genes, of them 194 genes are required for the growth of *M. tuberculosis* [29].

The host-pathogen interaction in the development of infectious disease are complex and multidimensional, and vary depending on factors such as the overall host genetic background, evolution of new pathogen variants in the host, and other host and nonhost factors. These microbial and host factors are significantly increase more than 20% risk of TB treatment failure in TB patients completing the standard combination therapy (i.e., 6-month HRZE) [30].

Biofilm formation plays a major role in host-pathogen interactions. This is a mechanism of pathogens by which they form a biofilm that provides a barrier for antibiotic to reach the cellular level for their survival in the host. Bacteria present in the biofilm also gets protection against the impact of host immune response and antimicrobial combined treatments in harsh multi-drug environmental conditions, and results in antibiotic treatment failure [31].

Furthermore, macrophage inhibition is another factor by which the pathogen attempts to survive in the host by preventing the macrophages to act on them, or evades the host immune mechanism, which is one of the crucial host defenses. Efficient functions in macrophages require activations using multiple components which include signal transduction molecules, transcription factors that can activate the gene transcription by binding to cis-regulatory elements (transcription binding sites) and genes encoding receptors such as stimulatory pathogen/pattern recognition receptors (PRR), a group of receptors which sense the presence of bacteria or that recognize specific pathogen-associated molecular patterns (PAMPs) on the

surface or inside of microorganisms including transmembrane proteins such as Toll-Like Receptors (TLRs), C-type lectin receptors (CLRs), as well as cytoplasmic proteins such as the Retinoic acid-inducible gene (RIG)-I-like receptors (RLRs) and Nucleotide-binding Oligomerization Domain (NOD)-like receptors (NLRs); however for instance the *M. tuberculosis* bacilli evade and modulate PRR signaling to promote further recruitment of macrophages and manipulate the host adaptive immune response [32], for example, during early primary *M. tuberculosis* infection, direct mycobacterial phagocytosis is mostly mediated by C-type lectin receptors (CLRs), which is the first-line innate immune defenses that play a central role in TB pathogenesis for drug resistant or persistent *M. tuberculosis*-killing and reducing bacilli growth. Currently existed antibiotic drugs have been developed by targeting only pathogens. As a result, the evolutionary adaptation and spread of MDR strains consequently increase in drug combination therapy by impacting on the host-pathogen interactions in terms of protein and/or gene, for instance, the pathogen/ pattern recognition receptors (PRR) gene mutation interaction leads to improved bacterial growth in the host cell by evading the host immune system, and forming biofilms that greatly influence the outcome of infections by increasing the antibiotic treatment failure [33]. So that, primarily the predictions of pathogen-host-antibiotic interactions play a vital role in designing new and effective treatment strategies to overcome the health challenge in this 21st century, and that favor enhancing a host protective response. The first crucial step of designing new treatment strategy is the identification of drug targets within the bacterial pathogen and host drug targets that prevent potential adverse reactions in the host by understanding the host system and antibiotics [27]. However, studies on the characterization of pathogenic bacteria strains and host drug targets are too much limited, and further studies will be needed for identifying the potential drug target candidates for MDR strains by considering proteins or genes which do not interact with human proteins or genes and antibiotics, respectively [33].

Host-directed therapeutics (HDTs)

Understanding the host-pathogen-antibiotic interaction complex interplay between protein and/or gene functional interactions between the human host, pathogen and antibiotics play a vital role in designing rational-therapeutic strategies.

Hence, predicting the putative protein-protein interaction (PPIs) between a pathogen and its host genetic variants is of paramount importance as novel target for effective infectious disease therapies including TB. Recently, scientists have developed the host-directed therapies (HDTs), which have a promising results against infections by increasing the effectiveness of currently available antibacterial drugs that directly kill the pathogens or slow down bacterial replication, and to enhance host-immune responses that might be beneficial in eliminating bacteria [34]. A recent research work has conducted by **Cyrielle** [7] suggests that directly targeting host factors through host-directed therapeutics (HDTs) by focusing on pathogen-host-antibiotic interactions may be beneficial for infection treatments, for instance, the use of lipoxygenase inhibitors, tyrosine-kinase inhibitor shown promises as targets of HDTs candidates for reducing pathogen replication and treating MDR-TB and HIV/TB co-infections [35].

Novel HDTs can help decrease the emergence and spread of MDR strains by enhancing the effect of currently available antibiotic drugs or increase the success of treatment by immunomodulation (modifying the immune response), targeting new mechanisms, and improve long term outcome by shortening treatment length or durations and require minimal doses which would facilitate patient compliance for avoiding resistance, however, HDTs alone might not be enough to clear bacilli in an active TB patient, but used in combination with currently available anti-TB drugs to enhance their overall effect [33]. Moreover, HDTs may require minimal doses, short treatment durations and may be more effective than the currently approved treatment strategies. Targets of HDTs include host factors such as cytokines, receptors, immune cell functions, and essential enzyme activities [35], that potentially inhibit pathogen development via various host target pathways, such as signal transduction mediating cytokines production, modulation of pathogen recognition receptors and immune cell regulation [36], modulation of antibiotic metabolism gene regulation and as such can be used to verify the antimycobacterial activity of an approved drug [7].

Conclusion and future perspectives

The discovery and development of novel antibiotic classes have halted due to extremely long, time consuming and challenging process. Moreover, the up-to-date treatment called one drug-one target has several limitations, include the long period of

treatment, a significant problem of resistance acquisition and/or evolution of drug resistant strains, and toxicity of the drug. Ideally, drug combination treatments are a widely used strategy for controlling resistance evolution; however, currently the emergency and spread of multidrug resistance strains are an intensifying public health challenge around worldwide [37], due to several risk associated factors include epistatic pathogen-host-antibiotic interactions, that the combined effect results becoming uncertain [7].

Now a days, molecular characterization of drug resistance mutations in pathogenic strains including *M. tuberculosis* are largely limited and not clear, because of our current knowledge of mutation pattern complexities, and other influencing factors that the resistance conferring mutations can evolve dynamically over time under antibiotic pressure in patients [38]. Furthermore, the mechanisms of factors that facilitate resistance development within a patient are still poorly understood and require further explanation. There is an urgent need to understand the mechanisms by which the antibiotic combination therapy in the role of resistance evolution. According to previous studies, the two best strategies involved in drug combination therapy against drug-resistant strains have been explained, which are (i) synergy based drug-drug interactions in drug combination can slow down the evolution of resistance [15,17], however, studies on the selection of antibiotic pairs with different drug-drug epistatic interactions in drug combination for proper treatment strategies is too much limited. The choice between synergy and antagonism may involve the efficacy treatment inhibition of microbial growth and the evolution of resistance, that remains an interesting avenue for future work in order to limit the emergency and spread of MDR strains [16]; and (ii) host-directed therapy (HDTs) based on host and pathogen factors is another promising treatment strategy used to treat bacterial infections through overcoming the limitations of current drug combination treatments [35]. The combination of HDTs with currently available antibiotic drugs may improve clinical outcomes by adding to the effectiveness of anti-bacterial drugs [33]. In such setting, this review assessed the impacts of pathogen-host-antibiotic interaction on the development and transmission of antimicrobial resistant pathogens against combination therapy in multi-drug environments. However, understanding of the dynamic complexity of pathogen-host-

antibiotic interactions in patients is still difficult, and further investigations will be needed for identifying the potential drug target candidates by considering pathogen proteins and/or genes which do not interact with human proteins/genes and antibiotics.

Abbreviations and Acronyms

AMR	Antimicrobial resistance
GSTT1	Glutathione S-Transferase T1
HDTs	Host-directed therapies
MDR	Multi-drug resistance
MRSA	Methicillin-Resistant <i>Staphylococcus aureus</i>
MTB	<i>Mycobacterium tuberculosis</i>
SNPs	Single nucleotide polymorphisms
TB	Tuberculosis
WHO	World Health Organization

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Authors' contributions

AS involved in proposing of the review title, searching and collection different literatures, and writing the manuscript. NB, TA and ST involved in guiding of the review, and commenting the manuscript. All authors read and approved the final manuscript.

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References

- 1-**Marten E, Demain AL.** The antibiotic resistance crisis, with a focus on the United States. *J Antibiot* 2017;70:520–526.
- 2-**Khan MSA.** Combination of Drugs: An Effective Approach for Enhancing the Efficacy of Antibiotics to Combat Drug Resistance. *Springer Nat* 2019;
- 3-**Khameneh B, Diab R, Ghazvini K.** Breakthroughs in bacterial resistance mechanisms and the potential ways to combat them. *Microb Pathog* 2016;95:32–42.
- 4-**WHO.** World Health Organization. Global priority list of antibiotic-resistant bacteria to guide research, discovery, and development of new antibiotics. 2017.
- 5-**Baym M, Stone LK, Kishony R.** Multidrug evolutionary strategies to reverse antibiotic resistance. *Science* (80-) 2016;351(6268):1–21.
- 6-**WHO.** World Health Organization. Treatment guidelines for drug-resistant tuberculosis, Geneva, Switzerland. 2016.
- 7-**Cyrielle FT.** Host-pathogen-drug interactions in the context of antibiotic resistance: How host xenobiotic metabolism can affect antibiotic efficacy in a Methicillin-Resistant *Staphylococcus aureus* infection. PhD Dissertation. University of Exeter. 2018.
- 8-**Worthington RJ, Melander C.** Combination Approaches to Combat Multi-Drug Resistant Bacteria. *Trends Biotechnol* 2013;31(3):177–84.
- 9-**Vestergaard M, Paulander W, Marvig RL, Clasen J, Jochumsen N, MS.** Antibiotic combination therapy can select for broad-spectrum multidrug resistance in *Pseudomonas aeruginosa*. *Int J Antimicrob Agents* 2016;47(1):48–55.
- 10-**Hagihara M, Crandon JL, Nicolau DP.** The efficacy and safety of antibiotic combination therapy for infections caused by gram-positive and gram negative organisms. *Expert Opin Drug Saf* 2012;11:221–233.
- 11-**Barbosa C, Roemhild R, Ronaldh P, Schulenburg H.** Evolutionary stability of collateral sensitivity to antibiotics in the model

- pathogen *Pseudomonas aeruginosa*. *Elife* 2019;8:1–22.
- 12-**Omollo C, Singh V, Kigundu E, Wasuna A, Agarwal P, Moosa A, et al.** Developing synergistic drug combinations to restore antibiotic sensitivity in drug-resistant *Mycobacterium tuberculosis*. *bioRxiv* 2019;
- 13-**Chevereau G, Bollenbach T.** Systematic discovery of drug interaction mechanisms. *Mol Syst Biol* 2015;11(807):1–9.
- 14-**Merker M, Tueffers L, Vallier M, Groth EE, Lindsay S, Daniel U, et al.** Evolutionary Approaches to Combat Antibiotic Resistance : Opportunities and Challenges for Precision Medicine. *Front Immunol* 2020;11(1938):1–7.
- 15-**Yeh PJ, Hegreness MJ, Aiden AP, Kishony R.** Drug interactions and the evolution of antibiotic resistance. *Nat Rev Microbiol* 2009;7(6):460–6.
- 16-**Yilancioglu K, Cokol M.** Design of high-order antibiotic combinations against *M. tuberculosis* by ranking and exclusion. *Sci Rep* 2019;9:1–11.
- 17-**Michel JB, Yeh P, Chait R, Moellering RC, Kishony R.** Drug interactions modulate the potential for evolution of resistance. *Proc Natl Acad Sci* 2008;105:14918–14923.
- 18-**Cokol M, Kuru N, Bicak E, Larkins-Ford J, Aldridge BB.** Efficient measurement and factorization of high-order drug interactions in *Mycobacterium tuberculosis*. *Sci Adv* 2017;3.
- 19-**Tekin E, Beppler C, White C, Mao Z, Savage VM, Yeh PJ.** Enhanced identification of synergistic and antagonistic emergent interactions among three or more drugs *Journal of The Royal Society Interface* 2016;18–20.
- 20-**Brochado AR, Telzerow A, Bobonis J, Banzhaf M, Mateus A, Selkrig J.** Species-specific activity of antibacterial drug combinations. *Nature* 2018;559:259–263.
- 21-**Freschi L, Vincent AT, Jeukens J, Emond-Rheault J-G, Kukavica-Ibrulj I, Dupont M-J.** The *Pseudomonas aeruginosa* Pan-Genome Provides New Insights on Its Population Structure, Horizontal Gene Transfer, and Pathogenicity. *Genome Biol Evol* 2019;11:109–120.
- 22-**Bhusal Y, Shiohira CM, Yamane N.** Determination of in vitro synergy when three antimicrobial agents are combined against *Mycobacterium tuberculosis*. *Int J Antimicrob Agents* 2005;26:292–7.
- 23-**Lam SW.** Medication Administration/Critical Care Research -Pharmacokinetics, Pharmacodynamics, and Pharmacogenomic. Critical Care Self-Assessment Program (CCSAP). *Am Coll Clin Pharm* 2016;7–25.
- 24-**Zanger UM, Schwab M.** Cytochrome P450 enzymes in drug metabolism: regulation of gene expression, enzyme activities, and impact of genetic variation. *Pharmacol Ther* 2013;113:103–41.
- 25-**Piacentini S.** GSTT1 and GSTM1 gene polymorphisms in European and African populations. *Mol Biol Rep* 2011;38:1225–30.
- 26-**Hong BY, Adami AJ, Granados H, Balcells ME, Cervantes J.** Microbiome Changes during Tuberculosis and Antituberculous Therapy. *Clin Microbiol Rev* 2016;29(4):914–25.
- 27-**Mulder NJ., Mazandu GK, Rapano HA.** Using Host-Pathogen Functional Interactions for Filtering Potential Drug Targets in *Mycobacterium tuberculosis* *Mycobacterial Diseases. J Mycobac Dis* 2013;3(1):1–8.
- 28-**de Keijzer J, Mulder A, de Beer J, de Ru AHV, Veelen PA, van Soolingen D.** Mechanisms of phenotypic rifampicin tolerance in *Mycobacterium tuberculosis* Beijing genotype strain B0/W148 revealed by

- proteomics. *J Proteome Res* 2016;15:1194–1204.
- 29-**Sasseti CM, Rubin EJ.** Genetic requirements for mycobacterial survival during infection. *Proc Natl Acad Sci* 2003;100(22):12989–12994.
- 30-**Tweya H, Feldacker C, Phiri S, Ben-Smith A, Fenner L, Jahn A.** Comparison of Treatment Outcomes of New Smear-Positive Pulmonary Tuberculosis Patients by HIV and Antiretroviral Status in a TB/HIV Clinic, Malawi. *PLoS One* 2013;8(2).
- 31-**Fazlurrahman K, Dung-thuy NP, Youngmog K.** Alternative strategies for the application of aminoglycoside antibiotics against the biofilm-forming human pathogenic bacteria. *Appl Microbiol Biotechnol* 2020;104:1955–76.
- 32-**Rajaram MV, Arnett E, Azad AK, Guirado E, Ni B, Gerberick AM.** tuberculosis-initiated human mannose receptor signaling regulates macrophage recognition and vesicle trafficking by FcR-gamma-Chain, Grb2, and SHP-1. *Cell Rep* 2017;21(126).
- 33-**Abreu R, Giri P, Quinn F.** Host-Pathogen Interaction as a Novel Target for Host-Directed Therapies in Tuberculosis. *Front Immunol* 2020;11:1–14.
- 34-**Zumla A, Maeurer M.** Host-Directed Therapies Network Consortium. Host-directed therapies for tackling multi-drug resistant tuberculosis: learning from the Pasteur-Bechamp debates. *Clin Infect Dis* 2015;61:1432–1438.
- 35-**Kim YM, Yang C.** Host-Directed Therapeutics as a Novel Approach for Tuberculosis Treatment. *J Microbiol Biotechnol* 2017;27(9):1549–58.
- 36-**Zumla A, Rao M, Dodoo E, Maeurer M.** Potential of immunomodulatory agents as adjunct host-directed therapies for multidrug-resistant tuberculosis. *BMC Med* 2016;14(89).
- 37-**Gygli SM, Borrell S, Trauner A, Gagneux S.** Antimicrobial resistance in *Mycobacterium tuberculosis*: Mechanistic and evolutionary perspectives. *FEMS Microbiol* 2017;41(3):354–373.
- 38-**Navisha D, Santhuri R, Padayatchi N, Mahomed S, Naidoo K.** Evolution of drug resistance in *Mycobacterium tuberculosis*: A review on the molecular determinants of resistance and implications for personalized care. *J Antimicrob Chemother* 2018;73(5):1138–1151.

Seid A, Berhane N, Abayneh T, Tesfaye S. Impacts of pathogen-host-drug interaction in the evolution and spread of antimicrobial-resistant pathogens. *Microbes Infect Dis* 2022; 3(2): 286-295.