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Review Article
Antibacterial Resistant Pathogens Potential Reservoirs

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Abstract

Resistant pathogen's potential reservoirs include patients and the general community, health care centres as well as food-producing animals. Moist, warm environments (intestine, sewage and sludge) with abundant nutrients that contain a large gene pool (high numbers of microbial cells) are ideal locations for efficient development and transmission of resistance genes, potentially mobilized to the clinically relevant strains. Stressor nutrient concentration determines the resultant antimicrobial pathogens. Antimicrobial-resistant pathogens include Extended-spectrum β-lactamase, Methicillin-resistant *Staphylococcus aureus*, Vancomycin-resistant Enterococcus, Vancomycin-resistant *Staphylococcus aureus*, Glycopeptide-resistant *Enterococci*, Fluoroquinolone-resistant and carbapenem-resistant *Enterobacteriaceae* and *Pseudomonas aeruginosa* and Penicillin- and cephalosporin-resistant *Streptococcus pneumoniae*. These pathogens may exist in the environment as small colony variants or as persister cells. The interchange of the microbiome from one environment to another different from the original habitat is essential to pathogen breeding and mutations that lead to drug resistance. The intensity of antimicrobial use is proportional to the emergence and prevalence of antimicrobial-resistant organisms.

Key words: Antimicrobials, pathogenic bacteria infections, clinical interventions, drug resistance, resistant microorganisms, resistance genes transmission, microbial populations

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INTRODUCTION

The rapid and steady spread of Extended-Spectrum Beta-Lactamase (ESBL)-producing *Enterobacteriaceae* (*Escherichia coli* and *Klebsiella pneumoniae*), *carbapenemase*-producing *Enterobacteriaceae*, multidrug-resistant *Pseudomonas aeruginosa,* Methicillin-Resistant (oxacillin and methicillin-resistant) *Staphylococcus aureus* (MRSA) are reported worldwide[1,2]. MRSA are resistant to all beta-lactam agents, including cephalosporins and carbapenems. Some strains remain susceptible to fluoroquinolones, trimethoprim/sulfamethoxazole, gentamicin, or rifampin. Some *enterococci* species are resistant to vancomycin drugs. The situation concerning gram positives such as *Streptococcus pneumoniae*, *Staphylococcus aureus* and *Enterococcus faecalis/faecium*, is worrisome, although the trend is currently less critical than for gram negatives. Resistant pathogens exhibit complex, habitat-specific, adaptive ecosystems that are attuned to relentlessly changing environmental conditions. These microbiomes are the trophic organization of species-rich communities with extreme heterogeneities. There may be time-dependent compositional variation. Thus, extirpations of pathogenic species can occur in an environment when exposed to stress. Stress can eliminate susceptible strains leaving behind resistant microbes that multiply and become the dominating population and as such, can transfer (both horizontally and vertically) the genes responsible for their resistance to other microbes. Thus, despite the extensive resilience inherent in a complex ecosystem, there may be a loss of recovery from continued perturbations[3], with important implications for human and animal health[4].

Antimicrobial resistance genes (ARG) abound in chronic, non-healing wounds (e.g., diabetic foot ulcers). Wastewater from treatment plants, hospitals and agricultural practices are excellent sources of pathogenic and antimicrobial-resistant pathogens[5], hence excellent hotspots of Horizontal Gene Transfer (HGT) between bacterial species since they are in close contact. Polymicrobial species (*Candida* species, *Pseudomonas*, *Acinetobacter*, *Enterococcus*, *Staphylococcus* and *Enterobacteriaceae*) are prevalent opportunistic pathogens infecting patients with compromised immunity, including transplant recipients, cancer patients and those suffering from AIDS[6]. Enteric pathogens, bacteria (*shigellosis*, *Campylobacter* infection, or *Salmonella* infection), viral (hepatitis A, B and C viruses) and parasitic (giardiasis or amebiasis) frequently result from consuming contaminated food or water, antibiotic therapy or transmitted via sexual practices, especially those that can involve faecal-oral contamination. However, the diversity of resistance determinants is most pronounced in natural environments than that contaminated with antibiotics from anthropogenic activities. Environments with a wide range of nutrient or stressor concentrations maintain higher diversity of genes compared to strong microbial control environments (intensive care unit and industrially used clean rooms). Long-term persistence of stress might lead to increased stabilization of microbial populations that might persist for years[7-9]. Increased confinement and stress are associated with a loss of microbial diversity. Biological processes are shaped by the environment across the life course.

Resistant pathogens thrive in their respective habitats by symbiotic association and the evolution of a variety of distinct regulatory mechanisms. Symbiotic associations between microorganisms are widespread and diverse, catalyzing metabolic processes, e.g. by producing hormones. These partnerships may be for nutrition, protection, detoxification or behavioural manipulation. Physiological changes (such as ion fluxes or changes in enzyme activity) also affect microbial adaptation. The oxygen content of an environment influences detoxification mechanisms, catalases, hydroperoxidases and mutational processes. Hence nutrient or stressor concentration gradients may induce ecological specialisations. Therefore, the interchange of the pathogen from one environment to another, different from the original habitat have significant health consequences. It is essential to pathogen breeding and mutations that lead to drug resistance. Antimicrobial resistance leads to a reduction in health care options (infectious diseases treatment, chemotherapy, surgery, transplantations, etc.) and as well affect the economies of states. Thus, the present study seeks to understand the various habitats of resistant pathogens to guide the formulation and coordination of measures across human, veterinary, agriculture and environmental sectors as regards antibiotic-resistant pathogens.

Bacterial diversity and functionality: Microbial populations, composed of multiple diverse organisms, are found in a wide variety of environments, including freshwater, soil, rhizosphere (a zone enriched with nutrients from plant root exudation), phyllosphere, sludge, fish, midgut of insects, raw dairy products, raw chicken, faeces of millipede, industrial plants and clinical samples. The collective metabolic activities of the diverse microbial groups maintain a functional microbiome with specialized microbial communities evolving in the particular compartment of the microbiome[10]. Microbial diversity is, therefore, a common feature of microbial communities but connected by synergistic, antagonistic or neutral relationships[11].

Phytopathogens: These pathogenic microbes are accountable for extensive devastation to the plants and crops. *Ralstonia solanacearum* induce wilting disease in tomato, *Pseudomonas aeruginosa* invasibility in the wheat rhizosphere. Aerobic endospore-forming bacteria induce food and products quality deterioration and shelf life reduction. These bacteria survive in the form of endospores in soil and on their host as biofilms. They affect spoilage through the production of several extracellular enzymes (biocatalysts) like proteases, phospholipases, lipases and β-galactosidases. Mesophilic spore-formers (bacteria that live and thrive at moderate temperatures in the range of 20°C and 45°C, with optimal growth temperature at 37°C). Mesophilic and thermophilic spore-forming bacteria species are shown in Table 1.

Airborne bacteria and fungi have a wide range of sources, such as soil, vegetation, animals and water bodies. They are affected by environmental factors such as temperature, relative humidity, precipitation and wind speed. Though there are variations in the concentration of specific microbial communities (composition and structure) under different meteorological and geographical factors[12], these do not correlate with their abundance and pollution levels. Cold weather condition is an ideal season for the growth and reproduction of microorganisms in contrast to summer.

Waste dumpsites contain diverse antimicrobial resistance genes that include airborne pathogens within the vicinity of waste dumpsites. Gram-negative bacteria, produce airborne immune-toxicant endotoxin that causes inflammatory responses in the lungs of exposed humans and animals[13]. This immune-toxicant endotoxin evokes toxic pneumonitis, chronic bronchitis, mucous membrane irritation, or aggravate the adverse pulmonary reactions caused by exogenous allergens[14]. Wastes are the source of environmental vectors necessary for the horizontal transfer of antimicrobial resistance genes. Microbial lineage includes *Escherichia coli*, *Staphylococcus aureus*, *Enterobacter* spp., *Pseudomonas* spp., *Proteus* spp., *Shigella* spp., *Klebsiella* spp., *Salmonella* spp., *Bacillus* spp., *Citrobacter* spp. and *Serratia* spp. Others include *Bacillus subtilis*, *Bacillus cereus*, *Streptococcus* spp. and *Micrococcus* spp. Fungal isolates include *Aspergillus fumigatus*, *Aspergillus niger*, *Penicillium notatum* and *Fusarium* spp.

Lipase-producing bacteria: Lipases are carboxyl ester hydrolases (bio-enzymes) that catalyse a wide variety of hydrolytic and synthetic reactions at lipid-water interfaces. They also synthesis long-chain acylglycerols under micro-aqueous/ non-aqueous conditions. The latter reaction (reverse hydrolysis) leading to esterification, alcoholysis and acidolysis occurs in low water and organic solvent rich media. Lipases display a high degree of specificity and enantioselectivity in esterification and transesterification reactions. This characteristic makes them very important in biotechnological fields such as the production of cosmetics and biodiesels and the leather, pharmaceutical, food, especially dairy and detergent industries[15]. Lipases producing bacteria (Table 2) exist in a pH optimum of 7.5-8.0 and an optimum temperature of 37 C. The enzyme cleaves fatty acid ester bonds at the 1,3-site.

Lipases from bacteria share a group of well-kept amino acids, including a serine in a highly conserved Gly-XSer-X-Gly pentapeptide and an aspartate or glutamate residue that is hydrogen-bonded to histidine to form a catalytic triad. The variations in the amino acid sequences distinguish the lipases biological properties. Therefore, the ability to manipulate these lipases and give them new properties depends on knowledge about the role of their domains and amino acids.

Table 1: Mesophilic and thermophilic phytopathogenic bacteria species

Mesophilic spore-formers	Thermophilic spore-formers
Brevibacillus parabrevis	*Bacillus coagulans*
Bacillus circulans	*Bacillus cereus*
Bacillus subtilis group	*Geobacillus thermoleovorans*
Bacillus cereus group	*Geobacillus thermoleovorans*
Bacillus pumilus group	*Aeribacillus pallidus*
Bacillus shackletonii	*Laceyella sacchari*
Bacillus aerophilus	*Thermoactinomyces vulgaris*
Bacillus clausii	*Anoxybacillus flavithermus*
Brevibacillus brevis	*Geobacillus stearothermophilus*
Lysinibacillus sphaericus	*Bacillus thermoamylovorans*
Paenibacillus cookii	
Paenibacillus macerans	
Sporosarcina contaminans	
Virgibacillus proomii	

Table 2: Lipases producing bacteria species

Bacillus licheniformis
Bacillus subtilis
Beta *proteobacterium*
Burkholderia cepacia
Burkholderia multivorans produces organic solvent tolerant lipase[17]
Chromobacterium spp.
Flavobacterium
Geobacillus bacteria
Paenibacillus illinoisensis produces cyclodextrin glucanotransferase resistant to organic solvents[18]
Pseudomonas aeruginosa
Pseudomonas cepacia
Pseudomonas fluorescens
Pseudomonas glumae
Pseudomonas mendocina
Pseudomonas pseudoalcaligenes
Pseudomonas putida
Serratia marcescens
Staphylococcus saprophyticus produces organic solvent-stable lipase[19]

Table 3: Bio-Colours producing bacteria

Hymenobacter species	*Pedobacter* spp.
Hymenobacter soli	*Flavobacterium columnare*
Hymenobacter aerophilus	*Flavobacterium saccharophilum*
Hymenobacter gelipurpurascens	*Flavobacterium johnsoniae*
Hymenobacter chitinivorans	*Chryseobacterium* spp.
Hymenobacter psychrotolerans	
Hymenobacter actinosclerus	
Hymenobacter rigui	
Flexibacteracea bacterium	

Table 4: Nitrogen-fixing bacteria (bio-fertilizers)

Agrobacterium spp.	*Devosia riboflavina*
Azospirillum spp.	*Herbaspirillum lusitanum*
Blastobacter denitrificans	*Herbaspirillum seropedicae*
Bradyrhizobium japonicum	*Mesorhizobium loti*
Burkholderia cepacian	*Methylobacterium nodulans*
Burkholderia phymatum	*Ochrobactrum lupini*
Burkholderia tuberum	*Ralstonia taiwanensis*
Cupriavidus taiwanensis	*Rhizobium etli*
Devosia natans	*Rhizobium leguminosarum*
Devosia neptunia	*Sinorhizobium meliloti*

Aside from organic synthesis, *Pseudomonas* lipases have great potential for degradation of hydrocarbons, oils and organic polymers and hence, are also good candidates for bioremediation applications[16].

Bio-colours producing bacteria: Pigment synthesis (carotenoids, melanin's, lavins, monascins, violacein and indigo) as secondary metabolites by microorganisms is subjected to light, pH, temperature and media components[20]. The purpose of pigment production by microorganisms (Table 3) is to protect and stabilise their cells from light, heat and pH of their seasonal or geographical environment. These pigments are used in many biotechnological industries as additives, antioxidants, colouring agents for the food industry and also as dyestuff in cosmetics and pharmaceutical manufacturing processes.

A growth temperature of $\leq$15-20°C favour the psychrophilic (cold-loving) while the psychrotolerant (cold-tolerant) bacteria grow at low temperatures such as 0°C but the growth rate becomes progressively slower with the temperature downshift. The *Hymenobacter* species are yellow pigment-producing microorganisms. *Pedobacter* spp. (Gram-negative, short rods) are red pigment-producing organisms.

The carotenoid content in the genus *Pedobacter* includes pyrrhoxanthin, violaxanthin, fucoxanthin and nostoxanthine-sulfate. The mixed extract possessed strong antioxidant capacity and protected the bacterium against oxidative damage caused by high levels of UVB radiation. Violaxanthin has antiproliferative and anti-inflammatory activities, fucoxanthin has antilymphangiogenic, antitumoral, neuroprotective, antidiabetic, anti-obesity and anti-inflammatory effects. Fucoxanthin also prevents carcinogenesis and depressive behaviour, such as the attenuation of bleomycin-induced lung fibrosis and ulcerative colitis. Other pigments from psychrophilic (cold-loving) or Psychrotolerant (cold-tolerant) bacteria include lycopene, torulene, xanthophylls (lutein), prodigiosin, melanin, pheomelanin, eumelanin, violacein, indigoidine, scytonemin.

Nitrogen-fixing bacteria (bio-fertilizers): Nitrogen-fixing endophytes (Table 4) are known to associate with maize, rice, sorghum, wheat and sugarcane and can be isolated from the inside of leaves, stems and roots of this gramineous plants[21]. Thus, legume plants such as bean (*Phaseolus vulgaris*), soybean (*Glycine* max) and pea (*Pisum sativum*) can overcome dependence on soil nitrogen sources by forming a nitrogen-fixing symbiosis with rhizobial bacteria. The rhizobia reside in special root organs, the nodules, where reduction of atmospheric dinitrogen and nutrient exchange between bacterial and host cells takes place. These microbes convert atmospheric nitrogen gas into soluble nitrogenous compounds. Such type of soil beneficial microbes colonizes the plant roots, improve the fertility prominence of the soil and ultimately help in plant growth and development.

Biological N_2 fixation is a process of conversion of elemental-unavailable N_2 into ammonia (NH_4-N) available to bacteria and plants. In the elemental form, N_2 can be used only by specialised microorganisms possessing an enzymatic nitrogenase system.

These bacteria, collectively referred to as the rhizobia, are taxonomically and physiologically diverse members of the α and β subclasses of the Proteobacteria and mostly comprise members of the genera *Rhizobium*, *Bradyrhizobium*, *Mesorhizobium*, *Sinorhizobium* and *Azorhizobium*. Some species of bacteria can produce and secrete phytohormones, stimulating plant growth and protecting the host against pathogenic microorganisms[22].

Phytostimulating bacteria: These bacteria (Table 5) produce vitamins and plant growth hormones that help in maintaining plant health and promoting crop productivity. Actinobacteria can produce ample secondary metabolites involved in soil microbiostasis[23], indicating that negative interspecies interactions play an important role in determining the fate of invading species.

Biopesticides: Plant diseases such as wilt, blight, stem rust, potato blight, rice blast, false mildew, etc., affect plant

Table 5: Phytostimulating bacteria

Bacteria	Functions
Bacillus spp.	Alleviate cold stress and modulate phytohormones
	Enhance K^+ uptake in crop species
Bacillus licheniformis	Increase saline-alkaline tolerance
	Phosphate solubilizing and capable of enhancing seed germination
	Tolerance to salt stress
	Antifungal agent
Bacillus subtilis	Elicit active defence responses in harvested fruits
	Biological control agent of fungi diseases in plant roots and seed
	Enhanced tolerance to drought and salt stresses
Bacillus altitudinis	Alleviates iron stress seedling by both bioleaching of iron and up-regulation of genes encoding ferritins
Bacillus toyonensis	Enhances plant growth and aluminium tolerance
Bacillus velezensis	Exerts antifungal effect on plant pathogenic fungi
Bacillus flexus	Growth-promoting effect in plants under salt stress
Bacillus pumilus	Alleviates drought stress and increases metabolite accumulation in plants
Bacillus amyloliquefaciens	Antibacterial activity against plant pathogens
	Induce plant systemic resistance
	Induced drought tolerance in plants
Bacillus aryabhattai	Tolerates oxidative and nitrosamine stress and promotes the growth of soybean by modulating the production of phytohormones
Bacillus thuringiensis	Increases available phosphorus and growth of peanut in acidic soil
Paenibacillus peoriae	Antimicrobial broad-spectrum effects on phytopathogenic microbes
Paenibacillus polymyxa	Enhances plant iron absorption
	Induced systemic resistance and growth promotion
Paenibacillus illinoisensis	Promotion of iron nutrition and growth

Table 6: Biopesticides

Bacteria	Functions
Pseudomonas fluorescens	Suppression of bacterial wilt (*Ralstonia solanacearum*)
	Bioherbicide
	An anti-fungal
Pseudomonas syringae	Biocontrol of *Bacillus subtilis* infections
Bacillus subtilis	Suppresses *Ralstonia solanacearum*
	Stimulates induced systemic resistance
Bacillus thuringiensis	Armyworms, diamondback moth, chewing and sucking insects and mites, nematodes, mosquitoes and blackflies
Bacillus firmus	Nematodes
Burkholderia spp.	Chewing and sucking insects and mites, nematodes
Chromobacterium subtsugae	Chewing and sucking insects and mites

developmental growth and quality. Biopesticides (the use of living organisms' nematodes, bacteria, etc) to kill pests. Bacteria (Table 6) secrete various inhibitory substances, such as secondary metabolites, including antimicrobial metabolites, antibiotics and extracellular enzymes which prevent or limit the spread of infection in plants. They also help in stimulating the natural defense mechanisms of the plant and facilitate its resistance to various phytopathogens. The application of bacteria-based pesticides to crops in high concentrations raises the possibility of unintentional contributions to the movement and generation of antimicrobial resistance genes in the environment.

BACTERIA FROM CARBON-RICH ENVIRONMENTS

Petroleum reservoirs, as well as composting sites, are identified with high temperature, high pressure, high salinity and anoxic conditions, representing an extreme environment to life. The bacterial lineages include *Proteobacteria*, *Firmicutes*, *Deferribacteres*, *Bacteroidetes*, *Actinobacteria* and *Thermotogae*. Others are *Spirochaetes*, *Synergistetes*, *Thermodesulfobacteria*, *Chloroflexi*, *Nitrospira*, *Atribacteria*, *Acidobacteria*, *Fusobacteria* and *Planctomycetes*. Plant communities can influence associated soil bacterial communities through the types and amounts of carbon and nutrient inputs (e.g., plant litter, exudates, epiphyte litter, animal and atmospheric depositional inputs) and by altering the temperature and water content of the soil[24].

Under conditions of carbon excess but limited nitrogen and/or phosphorus, bacteria (Table 7) can synthesize natural polyester polymers (polyhydroxyalkanoate) as carbon and energy storage compounds. Under conditions of carbon-limitation in the presence of sufficient concentrations of other nutrients (nitrogen, phosphorus, etc.), synthesised natural polymers are hydrolysed into monomer subunits that are metabolized to generate ATP and growth via the β-oxidation pathway[25].

Table 7: Bacteria species found in compost

Bacteria	Function
Geobacillus toebii	A hydrocarbon-degrading, heavy metal resistant bacterium
Geobacillus galactosidasius	Thermophilic galactosidase producing degradation of complex substrates, such as the cellulose polymer
Geobacillus thermoleovorans	Geothermal volcanic environment
Nitrosarchaeum koreense	Anaerobic and mesophilic, ammonia-oxidizing
Saccharopolyspora rectivirgula	Agents for extrinsic allergic alveolitis (hypersensitivity pneumonitis)
Geobacillus thermodenitrificans	
Aeribacillus pallidus	
Ureibacillus terrenus	

Human bacteria: The dominant nutrient in the human intestine influences the microbial community formed. Proteins encourage oligosaccharide-fermenting bacteria (*Bifidobacterium*)[26]. Polysaccharides (carbohydrates) generally indigestible by human enzymes, results in the growth of the bacterial population of the *Bacteroides*, *Clostridium*, *Ruminococcus* families, with a simultaneous decline in the population of *Bifidobacterium* and *Enterobacteriaceae*[27]. Breastfed newborns have advanced levels of *Bifidobacteria* spp., whereas formula-fed infants have higher levels of *Bacteroides* spp., as well as amplified *Clostridium coccoides* and *Lactobacillus* spp.[28].

The human microbiota colonizes organs such as the mouth, skin, birth canal and other surface organs exposed to the environment, with the gastrointestinal tract reaching the highest densities of bacterial cells in mammals. Faeces, ileal and colonic digesta are majorly colonised by Firmicutes, followed by *Bacteroidetes*, phyla *Verrucomicrobia* and *Proteobacteria*. These microbial compositions help shape the host's physiology, e.g., modification of endobiotic metabolites.

Helicobacter pylori live in the acidic environment of the human stomach. This Gram-negative bacterium, widely distributed, is beneficial in early human life but can develop the disease that manifests as stomach ulcers or gastric carcinoma. Predominant intrafamilial transmission of *H. pylori* and the long-term association with humans has resulted in a phylogeographic distribution pattern of *H. pylori* that is shared with its host. Thus, the bacterium can be used for tracing complex demographic events in human prehistory.

Healthcare centres: Pathogenic bacteria (*Pseudomonas*, *Acinetobacter*, *Enterococcus*, *Staphylococcus* and *Enterobacteriaceae*), including multidrug-resistant bacteria, can survive for prolonged periods on dry surfaces (handrails, doorknobs, lockers and table surfaces of inpatients)[29-31]. These microorganisms have exceptionally malleable and plastic genomes that provide their vast adaptability potential. The adaptation characters may be through changes in membrane lipid composition, thermo stabilities of the membrane proteins, turnover rates of the energy transducing enzymes and/or the (exclusive) use of ions rather than protons as coupling ions in energy transduction[32]. They reversibly adhere to surfaces via van der Waals' forces through the production of exopolysaccharide matrix during cell growth[33]. These resistant bacterial pathogens include:

Extended-spectrum β-lactamase (ESBL): Patients suffering from Urinary Tract Infections (UTIs) caused by *Escherichia coli*, pneumonia and bloodstream infections are likely to develop extended-spectrum beta-lactamase resistance. Other common uropathogens include *Staphylococcus saprophyticus* in uncomplicated UTIs and Gram-negative rods (enterobacteria other than *E. coli* or *Pseudomonas aeruginosa*) and Gram-positive cocci in complicated UTIs[34]. Clinical risk factors include the presence of a chronic indwelling urinary catheter, sex of the patient, prolonged hospitalisation, home infusion therapy, chronic hemodialysis or underlying immunosuppression[35].

Potential transference of ESBL genes from animals to humans, most likely through the food chain[36], increases the prevalence of clinical *Escherichia coli* pathogens harbouring extended-spectrum beta-lactamases (ESBLs). ESBL-producing *E. coli* are associated especially with individuals with specific risk factors such as the sanitary staff, poultry farmer, veterinarian, medical doctor and healthy human population[37]. The intestinal tract of healthy humans seems to be a reservoir of ESBL-producing *E. coli* pathogens.

Extended-spectrum beta-lactamases are molecular class A beta-lactamases, capable of inactivating third-generation cephalosporins(ceftazidime, cefotaxime and cefpodoxime) as well as monobactams (aztreonam). ESBLs are derivatives of common beta-lactamases (e.g., TEM and SHV beta-lactamases) that have undergone one or more amino acid substitutions near the active site of the enzyme, thus increasing their affinity for and hydrolytic activity against third-generation cephalosporins and monobactams. Extensive use of newer generation cephalosporins drives the evolution of an

increasing range of new ESBLs. ESBLs are encoded by transferable conjugative plasmids that are responsible for the dissemination of resistance to other members of Gram-negative bacteria.

CTX-M enzymes, a family of ESBL from the *Kluyvera* species, from which they are mobilised by plasmids, transposable sequences or other mobile elements. *Kluyvera* is a genus widely distributed in nature, occasionally isolated from human and animal clinical samples. After mobilisation from *Kluyvera*, CTX-M enzymes evolve by mutation and recombination to generate the numerous CTX-M clusters presently found among humans. Plasmid lineages contribute to the dissemination of CTX-M-1 genes in the food chain, the environment and humans.

β-lactamase production accounts for ampicillin resistance in a notable proportion of *Haemophilus influenzae* and is widespread in *Moraxella catarrhalis*. The β-lactamases act by cleaving the amide bond of the β-lactam ring to produce an inactive penicilloic acid derivative. They confer resistance to penicillin and the aminopenicillins (e.g., ampicillin and amoxicillin) and some cephalosporins. The most common β-lactamases in *H. influenzae* are TEM-1 and ROB-1, both of which are inhibited by the b-lactamase inhibitor, clavulanate.

Methicillin-resistant *Staphylococcus aureus* (MRSA): Methicillin-resistant *Staphylococcus aureus* is the most problematic gram-positive bacterium in public health. It is implicated in a very wide infection spectrum ranging from nosocomial to community-acquired infections. Methicillin-resistant *Staphylococcus aureus* (MRSA) transmission between farm animals and humans causing MRSA colonization in farmers[38,39] and care veterinarians[40]. Patients colonized with MRSA originating from the livestock reservoir might introduce antibiotic-resistant pathogens into the hospitals. Multilocus Sequence Typing (MLST), an MRSA clone is common among patients epidemiologically linked to regions with a high density of pig farming[41]. Younger patient groups are usually less frequent carriers of MRSA[42] and less frequently associated with classical MRSA risk factors. An increasing number of infections caused by community-associated methicillin-resistant *Staphylococcus aureus* (CA-MRSA) carrying the panton-valentine leukocidin (PVL) genes spread easily among children[43]. It is resistant to almost known antibiotics and highly prevalent[44].

Vancomycin-resistant *Enterococcus* (VRE): *Enterococci* species are natural flora in the human and animal gastrointestinal tract as well as in the soil, water and food. *Enterococci* can be spread by carriage on the hands of personnel, or by equipment. *Enterococcus faecium* is one of the most frequently detected *Enterococci* species in the human intestinal tract[45]. Their ability to acquire high- or low-level resistance during infections in the bloodstream, urinary tract and cardiovascular are an increasing threat in modern medicine[46]. There are limited treatment options with a range of routine antibiotics commonly used in humans and veterinary medicine. Vancomycin-resistance occur in patients by the acquisition of different van gene clusters (vanA, vanB, vanC, vanD, vanE and vanG)[47]. The enterococcal surface protein genes are responsible for the pathogen colonisation, adherence and biofilm formation as well as the high-level resistance in *Enterococcus faecium*. The cytolysin genes significantly worsen the severity of endocarditis, endophthalmitis and peritonitis in animals[48].

The competence of Vancomycin-Resistant *Enterococci* (VRE) to spread in different environments and to transfer antibiotic resistance genes among different species is aided by their ability to aggregate into biofilms[49]. Microbial biofilms are found in food processing environments, oil drilling and health-related fields[50]. VRE patients are usually associated with severe underlying disease or immune suppression, intra-abdominal or cardiothoracic surgical procedures, an indwelling urinary catheter or central venous catheter, multi-antimicrobial therapy and extended length of hospital stay. VRE infections harm mortality and the cost of hospitalization.

Risk factors for the acquisition of vancomycin-resistant enterococci include the length of stay. Enteral feeding may alter the gastrointestinal environment in a manner favourable to the growth of vancomycin-resistant *Enterococci*[51]. Sucralfate administration could aid in the introduction of vancomycin-resistant *enterococci* to patient's gastrointestinal tract[52]. Metronidazole was significantly connected with an outbreak of vancomycin-resistant enterococcal bacteremia in adult oncology[53].

Vancomycin-resistant *Staphylococcus aureus* (VRSA): Patients with VRSA infection may also be infected with a vancomycin-resistant *enterococcus* (VRE)[54]. Use of vancomycin is noted as a risk factor for the emergence of vancomycin-resistant *Enterococci*[55] Vancomycin-resistant *enterococci* are cause for alarm not only because effective antibiotics are lacking, but also because vancomycin resistance may spread to other bacteria, particularly *Staphylococcus aureus*.

Glycopeptide-resistant *enterococci* (GRE): Glycopeptide-resistant *enterococci* (*Enterococcus faecalis*, *Enterococcus*

faecium, *Enterococcus gallinarum*, *Enterococcus casseliflavus*, *Enterococcus flavescens*, *S. aureus* and *Staphylococcus epidermidis*) pathogens are often resistant to multiple antibiotics, have a broad geographical distribution and are a major cause of nosocomial infections[56]. *Enterococci* species host a wide variety of mobile genetic elements and are considered a reservoir for the acquisition and distribution of antibiotic resistance genes among Gram-positive bacteria.

Glycopeptide resistant enterococci genes distinguished on ligase structural sequence include vanA, vanB, vanC, vanD, vanE and vanG.VanA-type resistance is characterized by high-level resistance to both vancomycin and teicoplanin[57]. Three glycopeptide-resistant *Staphylococcus aureus* strains with a vanA genotype have been recently isolated in the United States[58]. VanB-type strains are resistant to variable levels of vancomycin but susceptible to teicoplanin[59]. VanD-type strains are characterized by resistance to moderate levels of vancomycin and teicoplanin[60]. VanC, VanE and VanG isolate exhibit low-level resistance to vancomycin only[61,62]. Glycopeptide antibiotics are used in the treatment of infections caused by Gram-positive bacteria in case of resistance or allergy to other antibiotics.

Fluoroquinolone-resistant and carbapenem-resistant *Enterobacteriaceae* and *Pseudomonas aeruginosa*: *Enterobacteriaceae* are a group of opportunistic microorganisms that exhibit antibiotic resistance in septicaemia, respiratory tract infections and diarrhoea as well. These pathogens place hospitalized patients at serious risk largely because of the high intrinsic antibiotic resistances of these organisms.

Penicillin- and cephalosporin-resistant *Streptococcus pneumoniae* (PRSP): *Enterobacter* species are common pathogens that cause cephalosporin-resistant infections in patients due to non-susceptible *S. pneumoniae*. The emergence of antimicrobial resistance in *Enterobacter* species result in increased mortality, length of hospital stay and hospital charges.

Due to different clinical features, pneumonia is classified into community-acquired pneumonia (CAP), Healthcare-Associated Pneumonia (HCAP) and hospital-acquired pneumonia (HAP)[63]. Patients with HCAP have a higher prevalence of drug-resistant pathogens such as *Pseudomonas aeruginosa* and Methicillin-Resistant *Staphylococcus aureus* (MRSA)[64]. Administration of a broad-spectrum multidrug antibiotic regimen is not necessary for all patients with HCAP because of the wide regional variation of the frequency of multidrug-resistant pathogens in this type of pneumonia[65]. The spectrum of pathogens identified in patients with HCAP may vary because of the wide range of clinical situations in which HCAP develops. The pathogens in HCAP included those frequently found in both CAP and HAP (*S. pneumoniae*, *K. pneumoniae*, methicillin-susceptible S. *aureus*, MRSA and *P. aeruginosa*)[66].

Soil physicochemical properties and bacterial diversity: Microbes in soil are found as single cells or as biofilms embedded in a matrix of polysaccharides. These microbial communities moderate the heterogeneity of the soil, altering not only the chemical environment but also the physical structure of the soil using hydrophobic films and aggregate formation Soil can therefore be regarded as being highly heterogeneous to the distribution of soil matter and organisms[67].

Bacterial diversity depends on physicochemical characteristics like substrate concentrations, redox potential, pH, available water, temperatures (cold, ambient, hot), inorganic salts. These characteristics depend upon the size of the soil aggregate. Even small soil aggregates a few mm in size can offer many different microenvironments, resulting in different types of microbial settlement. The heterogeneity of soil particles and their structural arrangement aids the variation in the diversity and richness of soil microbial communities. This heterogeneity also leads to spatial heterogeneity of nutrient availability and other physicochemical properties[68]. The abundance of Actinobacteria and Firmicutes suggests that the microbial diversity signature may have been influenced by stressful climatic conditions (warming and dehydration). Carbon-rich environments encourage the emergence of the Proteobacteria and Bacteroidetes[68,69]. Diverse microbial communities show preference to different soil minerals (nutrients) and their particle size fractions due to the physical or chemical properties of the minerals[70].

Soil pH: Bacteria have an optimum pH range that varies between species and many physiological processes are pH-dependent. It is therefore critical that intracellular pH is maintained by the homeostatic system[71]. The maintenance of the intracellular environment depends on the external pH, cytoplasmic buffers, the intracellular generation of acids and bases and the active transport of H^+ (or OH^-). However, the diversity of bacterial communities is strongly affected by soil temperature and soil moisture.

Microbial growth and metabolism depend on maintaining a neutral cytoplasmic pH, regulating intracellular osmotic potential and obtaining sufficient quantities of nutrients.

However, pH could directly impose a physiological constraint on individual taxa to inhibit their growth when pH falls outside a certain range, resulting in altered viable consequences. Some can grow over a wide range of pH values while others are inhibited by acidic pH. Acidification of the internal microbial cell hinders the activity of most enzymes and overall cell metabolism. It is therefore only microorganisms that had developed adaptive responses to survive in acidic environments that thrive[72]. Low pH inhibits soil nutrient availability and ion toxicity. High pH bacteria diversity include *Proteobacteria*, *Firmicutes*, *Actinobacteria*, *Bacteroidetes* and *Cyanobacteria*.

Salinity: Salinity is a major driver of bacterial community composition and diversity across a wide variety of natural environments, including those posing multiple stressors. It ensures uneven temporal and spatial water distribution and localized high concentrations of salts. Salinity reduces soil respiration, thus, influencing microbial community abundance, composition, diversity and metabolic functions[73]. In natural environments, pH, texture, organic carbon content influences microbial diversity[73].

Halophilic and halotolerant microbes possess enzymes with unique structural features to sustain high salt conditions. Such enzymes are useful for restoration of conditions in salt-affected soils, remediation of pollutants, industrial biocatalysis, food processing, washing, biosynthetic processes, synthesis of exopolysaccharides, compatible solutes, carotenoids[73]. Halophilic and halotolerant Bacteria and Archaea communities are essential for the biogeochemical processes in soils[73].

Carbon: Dissolved organic carbon enhances soil biological activities. Labile organic carbon is the main source of carbon that enhances the microbial biomass and soil respiration rates. Due to selective transportation, labile organic carbon fractions (dissolved organic carbon) are more possibly moved compared to soil organic carbon[74]. Soil organic carbon and nitrogen exerts no significant individual influence on microbial community structure variation. Heterogeneity in soil microbial diversity is directly related to the soil organic matter source, particularly to the availability of labile soil organic matter. Soil microbial diversity, as indicated by their phospholipid fatty acid profiles changed with the seasonal fluctuations in soil nitrogen availability.

Nitrogen: Nitrogen availability maintains soil microbial diversity but is dependent on the quantity available. However, increasing the concentration of nitrogen decreases the microbial diversity. Increasing nitrogen induces a reduction in soil pH, leading to the leaching of magnesium and calcium and the mobilization of aluminium. This may induce the microbes to become magnesium- or calcium-limited or suffer aluminium toxicity, resulting in reduced microbial biomass[74].

Moisture: Soil properties and bacteria behaviour are significantly influenced by the moisture content. Moisture content enhances vegetation growth, soil respiration, soil organic carbon content and oxygen availability. High moisture content maintains the spatial distribution of microorganisms in soils, increasing the microbial biomass, as well as the nonselective migration of soil microbial species. High moisture percolation disturbs carbon-rich topsoil and preferentially removes the finer particles and associated soil organic carbon. It increases the overall diversity of microbial diversity and composition. The moisture content is influenced by the soil texture. Bacterial movement and communities are largely limited to moisture filled areas. High temperature and moisture support a higher rate of microbial mediated processes (organic matter decomposition and nitrogen mineralization) and thus faster microbial reproduction rates.

Particle size: Soil particle size fractions provide diverse surface properties and micro-environments that influence the adsorption of chemicals and diverse microbial communities. There are differences in the composition of minerals and organic matter in the coarse sand, fine sand, silt and clay components of soil. Particle size fractions harbour structurally distinct microbial communities with different functional potentials for mineralising organic pollutants.

Coarse sand fractions are characterised by high concentrations of labile C and N originating predominately from plant residues. organic C (fresh or labile) derived from crop residues is first incorporated into the coarse sand fraction during the initial decomposition period and subsequently accumulates and becomes stable in silt or clay soils[75]. Consequently, the high fresh SOC contents could be the first accumulate in the coarse sand fractions, particularly in soils receiving large amounts of crop residues. Another reason for the higher SOC content observed in the coarse sand than in the clay fraction may be the high contribution of finer minerals (i.e., particulate organic matter) and clay to the coarse sand fraction during the formation of macroaggregates, as micro aggregates are formed within macroaggregates[75]. Coarse sand fractions thus have high SOC composition as well as a high acid bacteria population.

Clay acts as a bridge between particles because it binds soil particles effectively together. But clay is easier to leach

than the larger soil particles. However, clay soil protects organic matter from microbial decomposition and leaching loss. The higher the clay content, the higher the soil's capacity to bear greater stresses at higher initial water contents without severe compaction. However, soil basal respiration is lowest in the clay fraction. Clay back humus formation through reactions like deamination, polymerization and condensation of organic molecules. The presence of metal oxides and hydroxides and electronegative charges in clay makes it a catalyst for abiotic chemical reactions.

Silt has high carbon fractions and aggregates. silt fractions are usually characterised by high concentrations of relatively stable organic C and N[75]. Acidobacterium division and Proteobacter are present in small particles (silt and clay). Proteobacteria and Acidobacteria, are facultative organisms that can survive in water-saturated anaerobic habitats, whereas fungi are intolerant of anoxia. Large particles (sand) favour a few members of the Acidobacterium division and could be dominated by bacteria belonging to the Proteobacteria.

Non-antimicrobial factors and resistance selection: Pesticides (herbicides, fungicides and insecticides), though very specific and restricted to a narrow range of target organisms, can, however, be modified in the environment and have developmental toxicity to non-target organisms. The effect of pesticides on soil microbes depends on their bioavailability, which is, in turn, is influenced by the crop being grown, as well as soil properties affecting the sorption and leaching of pesticides. Bacteria can develop resistance to pesticides through their ability to decompose or transform them into less toxic compounds. Bacteria communities that establish after soil fumigation can determine the fate of the invading species, while the reduction in microbial diversity due to increasingly enhanced disinfection depths can result in higher pathogen persistence in soil[76].

Petroleum is a rich source of hydrocarbons. Hydrocarbons are biodegraded by microorganisms. The rate of degradation is usually low since there are low concentrations of phosphorus and nitrogen in hydrocarbons. This characteristic does not allow the extensive growth of indigenous hydrocarbon-degrading bacteria in hydrocarbon-contaminated soils. Bioremediation success in such environments depends on the presence of biodegrading microbes that are adapted to the prevailing environmental conditions as well as the addition of phosphorus and nitrogen fertilizers.

The presence of SO_4 and NO_3 released from Nitrogen Oxide (NOx) and Sulphur Dioxide (SO_2) into the atmosphere cause acid precipitation. The effect of acid deposition on the soil ecosystem depends on the concentrations of SO_4 and NO_3, the amount of precipitation and the buffering capacity of the soil (the cation exchange capacity via bases). Although the nitrogen and sulphur from the precipitation process may stimulate the growth of some soil microorganisms, acid precipitation enhances soil acidification, which may have adverse effects on soil bacteria. Low pH reduces the solubility of organic matter and thereby reduce substrate availability for microbes. It can also reduce the concentrations of divalent cations (Ca^{2+}, Mg^{2+}), leading to the mobilization and increased bioavailability of heavy metals and other toxic compounds. The effect of toxic substances on soil microbes depends on soil factors such as organic matter and clay content, divalent cation concentrations (cation exchange capacity) and pH. These factors influence the complex formation and immobilization of heavy metals. Heavy metals are available to microbes as ions either in solution or adsorbed on soil colloids. Soil microorganisms vary widely in their tolerance to heavy metal contamination. Heavy metal toxicity reduces bacterial enzyme activities (dehydrogenases, acid phosphatases and ureases). Microbial survival in polluted soils depends on core biochemical and structural properties, physiological and/ or genetic adaptation including morphological, changes of cells, as well as environmental modifications of metal speciation[77]. Mechanisms for metal resistance include stable complex binding (chelation) with organic ligands (extracellular or intracellular sequestration), transportation out of the cells and biotransformation of the ions to less bioavailable or less toxic metal species.

Impoverished environments distress soil microbial diversity and species distribution, preferring the growth of selective dominant species. Environmental stress inversely affects the input of organic matter content in the soils, which would otherwise serve as a source of nutrients. Because there are low levels of organic matter, these microorganisms obtain energy by oxidizing the toxic substances[78]. Some bacteria develop and adopt diverse detoxifying mechanisms such as biotransformation, bioaccumulation and biosorption which can be utilized in either ex-situ or in-situ bioremediation of heavy metal polluted sites[78]. Bacteria and lichens produce acidifying and chelating metabolites such as protons, organic acids or siderophores, which increase mineral dissolution. Such an adaptive strategy ease access to limiting nutritive elements, involving induction or repression of enzymes[78]. Such microorganisms are a potential reservoir of biotechnologically important genes.

What potentiates the loss of resistance genes? The collapse of a balanced microbiome could be the reduction in microbial diversity and /or over-growth of some microbial species.

Developing evidence-based standards for prudent antimicrobial use: Currently, there are limited data upon which to base prescribing decisions regarding the optimal length of antimicrobial treatment. To reduce the overall selective pressure being exerted by antimicrobial therapy, there is a need to establish a dose and treatment period to limit opportunities for resistance to develop. Short therapeutic courses reduce the development of resistance[79,80].

Prudent use of antimicrobials is being hampered by the lack of data regarding the effectiveness of specific measures, coupled with the general perception by physicians that antibiotics represent a therapeutically neutral treatment choice for infectious diseases.

Metabolic adaptation: Metabolic adaptation among others, promote the occurrence of both non-pathogenic and pathogenic organisms in a wide range of environments. This adaptation is achieved through inter-and intracellular communication involving the building blocks of life, DNA, RNA and proteins (enzymes, aminoglycoside modification enzymes, including N-acetyl transferases, O-phosphotransferases and O-adenylyltransferase). These molecules are activated upon exposure to harsh conditions. Microbes rapidly alter their physiology and cellular activities through metabolic modifications to enhance their fitness under varying conditions, allowing their persistence and circulation between environments and also the nature of their pathogenesis[81]. However, despite the extensive resilience inherent in a complex ecosystem, there may be a loss of recovery from continued perturbations[82].

Cessation of use of antimicrobial compounds for therapy: The epidemiology of antimicrobial resistance in the commensal flora of human hosts indicate that as long as antimicrobial-resistant pathogens exist and a fraction of hosts receive antimicrobial therapy, resistant pathogens will persist, even when resistance engenders a cost in fitness. Thus, when the frequencies of resistance are quite low, if resistant microbes are present in a population, the use of selecting drug to any extent, encourages resistant microbes to soar to high frequencies quickly (within days or months). The frequency of resistant cells in the population is directly related to the rate at which hosts are treated and the rate at which the microbes are the transmitted from their human host to the common environment. Numerous experimental *in vitro* and *in vivo* studies have shown that after complete removal of antibiotic selective pressures, the frequency of resistance will decline as a function of the magnitude of these biological costs to the level where mutations or horizontal gene transfer eventually maintain it. There is a plethora of evidence that antibiotic treatment will increase the frequency of resistance both in the species being treated and in non-targeted, commensal bacterial species[83]. However, resistance can persist for many months after the cessation of use of an antimicrobial[84] and many years[85,27] if the resistance determinant is linked to genes or transposons conferring resistance to other agents in continued use.

The withdrawal of some regularly used antimicrobial first-line treatment drug options may lead to the restoration of bacterial susceptibility through the re-expansion of the wild-type (WT) allele of the resistance transporter gene at the expense of less fit mutant alleles carrying the antimicrobial resistance marker. In low-transmission settings, drug resistance mutations can attain 100% occurrence, thereby preventing the return of wild type genes after the complete removal of drug pressure. complete eradication of antimicrobial resistance in bacterial populations following relaxed drug-selective pressures is not straightforward. Resistance determinants may persist at low, but detectable, levels for many years in the absence of the corresponding drugs.

Plasmid-borne antimicrobial resistance genes decrease with time because the host cells and/or their plasmids adapt to each other. Under any conditions, the infectious transfer of these elements will retard the rate at which they would be lost due to selection against their carriage. Multiple genes are carried on many resistance transposons and plasmids, even when specific resistance genes are no longer under positive selection, these genes could be maintained for extended periods by associated linkage selection favouring other loci. Therefore, the complete cessation of use of a particular antimicrobial compound for which there are resistant microbes, as long as there is a cost associated with resistance, the frequency of these microbes' resistance to that drug will decline to low levels.

Interactions between vulnerable and resistant organisms: Interactions between vulnerable and resistant organisms within a mixed community can determine how populations change over time. The high number of resistant cells within the community can shield the sensitive organisms from the effect of the drug, which effectively removes the drugs

from the environment. When the number of antibiotic-sensitive cells is too high in a community, antimicrobial therapy can cause the entire population to collapse. Sensitive only populations exhibit a monotonic decrease.

High- and low-density populations of resistant cells exhibit divergent behaviour towards the influx of an antimicrobial, with high-density populations surviving and low-density populations collapsing. However, the spread of drug-resistant determinants exhibits rich and counterintuitive dynamics, even in a simplified single-species population. Species evenness decrease indicates an increase in the dominance of particular species in the community.

Genetic contamination: Microbial contaminations are made possible through strains able to grow at low pH and provided with an oxidising respiratory metabolism, and strains capable of consumption of head-space oxygen with CO_2 production. The most frequent microbial contaminants include yeasts and moulds[86]. Their presence is indicated by the presence of superficial coloured spots.

Contaminant microbes, as a consequence of their resistance capabilities, may, if anoxic conditions are created, germinate and produce toxins that will eliminate other microbes. An aerobic environment can enhance the development of toxin-producing microflora. Aerobic conditions may serve to enhance the risk of toxin formation, probably due to the depletion of O_2 by the respiration of the microflora[87,88]. The growth of these microorganisms may inhibit the growth and toxin production of some of the community microbes. Toxin production at these limits, however, requires that all other growth conditions are optimal. A high background microflora[89] hampers the growth of pathogens. Lactic acid bacteria, either by acid or by bacteriocin production, may inhibit the growth and toxin formation of *C. botulinum*[84].

Environmental influences: Climatic factors (ambient temperature and rainfall patterns) have a great influence on pathogen populations. Climate change and global warming have an even greater influence on the selection of resistant gene types. The level of fitness obtained in an environmental transition through a regulated response may not be as high as that potentially available in a mutant present in the population. The new environment can either reduce or increase the growth rate, in either case, the response in the new environment will change patterns of gene expression as well as the selection environment for fitter mutants.

CONCLUSION

Antimicrobial resistance genes abound in chronic, non-healing wounds (e.g., diabetic foot ulcers), wastewater from treatment plants, hospitals and agriculture. Contaminated food or water, antibiotic therapy or sexual practices and agriculture practices aid their transmissions, impacting soil microbial community structure, functioning and development of antibiotic resistance genes. While resistance gene diversity is most pronounced in natural environments, environments with a wide range of nutrient or stressor concentrations maintain higher diversity of these genes. In resistant pathogens reservoirs, there may be time-dependent compositional variation despite the extensive resilience inherent in a complex ecosystem. Thus, extirpations of pathogenic species can occur in an environment when exposed to stress. Therefore, the interchange of the pathogen from one environment to another, different from the original habitat have significant health consequences. Judicious use of antibiotics is essential to slow the development of resistance, prevent outbreaks of untreatable infections and extend the useful lifetime of our most urgently needed antibiotics.

SIGNIFICANCE STATEMENT

This study discovers that despite the extensive resilience inherent in a complex ecosystem, environmental stress and climate change enable microbes to travel freely, imposing compositional variation of microorganisms. Thus, any interchange of pathogens from one environment to another may encourage the emergence of transboundary antibiotic resistance. Thus, the movement of microorganisms, mobile genetic elements and drugs among human, animal and environmental compartments makes it difficult to effectively control in a single environment microbial resistance. This could be the reason why microbial resistance to antibiotics persists.

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