Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
Future impacts and trends in treatment of hospital wastewater

Bhagyashree Tiwari\textsuperscript{1}, Balasubramanian Sellamuthu\textsuperscript{2}, Patrick Drogui\textsuperscript{1}, R.D. Tyagi\textsuperscript{1}

\textsuperscript{1}INRS-EAU, TERRE, ENVIRONNEMENT–INSTITUT NATIONAL DE LA RECHERCHE SCIENTIFIQUE, QUEBEC CITY, QC, CANADA \textsuperscript{2}CENTRE DE RECHERCHE DU CHUM, AXE IMAGERIE ET INGÉNIERIE, MONTRÉAL, QC, CANADA

17.1 Introduction

The research advancement and discoveries in the field of medical science and a concomitant increase in population lead to high demand for production of pharmaceutical compounds due to microbial infection and health illness. Pharmaceutical (biologically active) compounds are not fully metabolized by the human body and excreted out in the environment through wastewater. Conventional treatment technologies are not efficient enough for the removal of these persistent compounds. Since the 1970s, a significant amount of research studies have been conducted for the detection of pharmaceuticals in aquatic environments. The principal sources of pharmaceutical pollutants in the environment are pharmaceutical industries, hospitals, domestic waste, animal waste, and research activities utilizing therapeutic compounds. The presence of pharmaceuticals in wastewater hinders the growth of natural sludge-dwelling microbes and contributes to the development of multidrug-resistant bacteria. The presence of multidrug-resistant bacteria and pharmacological products changes the structure and function of the microbial community in the sewage treatment plant and receiving environments. The published investigation reported that among various sources, hospitals are the major contributors of pharmaceuticals released in the environment \cite{1}.

This book aimed to provide a holistic summary of (1) pharmaceuticals release, (2) their impact on environment, (3) factors governing microbial evolution in the environment due to the presence of pharmaceuticals, and (4) the different treatment processes specifically employed for hospital wastewater treatment in detail. This chapter aims to conclude with a meticulous discussion on ongoing research, and future perspectives on advanced treatment methods, microbial evolution, pathogens, antibiotic-resistance development, and future directions to maintain and protect the environment through microbiological, molecular biology, and by policymaking approaches.
17.2 Emerging infectious diseases

Infectious diseases are the second leading cause of death annually across the globe. The causative agent of most emerging infectious diseases is viruses; every year approximately more than two novel viral pathogens are identified, which can cause illness in a human. Since the 1970s, an average of 40 infectious diseases has been emerged and known to cause pandemics such as Ebola, swine flu, chikungunya, and Zika (Table 17–1) [4]. The emergence of infectious diseases has severe health and socioeconomic impacts; thus the following section discusses the various infectious disease that emerged within the last two decades and presenting few pandemic viral diseases as a suitable example [5,7]. Factors for emergence include natural process (evolution of pathogen), infectious agents transfer from vertebrate to mammals, antimicrobial resistance (AMR), and climate change. The factors responsible for the emergence of infectious diseases such as (1) the evolution of new strain, (2) the introduction of a host to enzootic, (3) translocation of infected wildlife, (4) farming practices, and (5) others were provided.

17.2.1 Emerging virus diseases

The viral evolution rate occurs through mutation and adaption, which are much faster than any other microscopic organisms that is why a large fraction of emerging and reemerging pathogens are viruses (37%). Among these 37% of emerging viruses, RNA viruses are prominent one because of their higher nucleotide substitution rate which enables them to invade and amplify in broad host range [22]. The environment changes, social condition, and their interaction are the important factors which lead to the viral evolution and ultimately to disease emergence. The decrease in biological diversity due to deforestation, prevalence of micropollutant in natural environment, and climate change triggers the evolution of opportunistic pathogen [23]. For instance, the outbreak of Nipah virus diseases was occurred due

| Emerging infectious disease | Pathogen | References |
|----------------------------|----------|------------|
| Severe fever with thrombocytopenia syndrome | Viruses belongs to Bunyaviridae family | [2] |
| Nipah virus disease | Nipah virus | [3] |
| Severe acute respiratory syndrome | Coronavirus | [4] |
| Canine parvovirus disease | Canine parvovirus | [3] |
| Chikungunya | Chikungunya virus | [4] |
| Hepatitis C | Hepacivirus C | [4] |
| Lyme disease | Borrelia burgdorferi | [5,6] |
| West Nile fever | West nile virus | [7] |
| Babesiosis | Babesia | [7] |
| Anaplasmosis | Anaplasma phagocytophilum | [7] |
| Buruli ulcers | Mycobacterium ulcerans | [8] |
to the extensive deforestation of a forest of Southeast Asia [24]. The deforestation leads to migration of fruit bats for food quest to the agriculture land. These fruit bats are natural reservoir (host) of Nipah virus and their migration to cultivable land lead to transmission of Nipah virus disease in farm animals and subsequently in humans [24]. The increase in temperature due to climate change affects the ecology, survival, and behavior of arthropod vectors, which subsequently changes population dynamic with increased disease transmission rate. For example, the rise in temperature from 10°C to 15°C decreases the proliferation time of *Plasmodium falciparum* in Anopheline mosquitoes vector from 20 to 13 days. Usually, *P. falciparum* requires 20 days to proliferate in the vector at 20°C. However, the high temperature reduces its proliferation time by increasing egg production, by increasing metabolic rate, and by reducing the larval and pupal period duration [25]. Moreover, the proximity of natural host such as Rodents and human is the ease and travel aids for the spread of emerging viruses.

The viral infection begins from binding of virus to the receptor of host cell, and during the emergence of new disease, viruses develop either the ability to bind the new receptor or use homologue receptor in new host species. The spread of coronavirus (CoV) which causes severe acute respiratory syndrome (SARS) in human occurs due to cross-species transmission from raccoon dogs and Chinese ferret badgers [1]. The examination of wild species of CoV did not have the sign of SARS—CoV infection but the CoV viruses isolated from horseshoe bats have SARS—CoV infection. The CoV binds to angiotensin-converting enzyme 2 (ACE2) receptor to infect humans. However, in bats, ACE2 viral receptor is not use for infection by CoV. Later it was studied that the mutation in ACE2 receptor aids the adaptation of CoV in human cells. The spread of Ebola, Marburg, and measles viruses is some of the example of virus evolution and which contributes to the emergence of disease. The virus evolution and adaptation is difficult to predict and thus raises a question how the effect of emerging viral infection can be reduced. This requires a holistic approach to identify the drivers of emergence with effective surveillance.

### 17.2.2 Emergence of Bunyvirus in China

In 2009 an increased cases of severe fever with thrombocytopenia syndrome (SFTS) were frequently reported in rural areas of China. The associated pathogens of thrombocytopenia and other similar diseases were not detected in majority of the pathogen samples which implies that the pathogen associated with SFTS was newly evolved. The emergence of this unknown infection having average fatality rate of 10% due to organ failure leads to the implementation of enhanced surveillance to identify causative agent of SFTS infection [2]. The surveillance data revealed 20 strain of viruses as causative of SFTS infection and regarded as SFTS viruses (SFTSVs). SFTSVs are RNA virus with three single-stranded RNA genomes. The complete sequencing of SFTSV, RNA genome reveals that they belong to genus *Phlebovirus*, family Bunyaviridae.

The SFTSV is transmitted in human through infected ticks and transmission of blood and other body fluid of infected person lead to human-to-human transmission of infection. The
Phlebovirus infection in human results in mild febrile illness. However, the major symptoms of SFTS include thrombocytopenia, high fever, leukocytopenia, and lymphadenopathy. Currently, it is believed that the vertical transmission of Phlebovirus in arthropod vector (ticks such as Haemaphysalis longicornis) helps in maintenance cycle of virus and amplification of virus occur in vertebrate host (human). The laboratory diagnosis of body fluid samples of SFTS patient showed elevated level of serum and important enzymes and cofactor such as creatine kinase, alanine aminotransferase, lactate dehydrogenase, and aspartate aminotransferase. The SFTSV replicates in the spleen of infected patient which increases the number of macrophages and platelets. The in vitro assay revealed that SFTSV facilitates the phagocytosis of platelets by adhering on the surface of platelets and ultimately causing thrombocytopenia. The spread of SFTSV in China and the detection of SFTSV like viruses in other parts of world such as in the United States and Europe emphasized on the urgent need of understanding of pathogenesis and transmission cycle of virus which help in the development of efficient vaccine.

17.2.3 Pathogen–host–environment interplay

The changes in the host–environment lead to the evolution of opportunistic and novel pathogens due to which infectious diseases emerge. The forces which shape the emergence of disease in human are similar to the drivers found in wildlife and domestic animals. These drivers alter the interplay of hosts, environment, and pathogen thereby modulating disease ecology and developing or acclimatizing pathogen in hosts. The drivers alter interaction pattern of pathogen–host and environment which to either of three events (1) altering the genetic trait of pathogen which causes severe disease in same host; (2) emergence of pathogen in new hosts; and (3) redistribution of pathogens that result in its establishment in new geographical area.

Frequent use of antimicrobial compounds and mass rearing of animals result in AMR and eventually increase virulence pathogenicity of a pathogen. Mass rearing of food animals to meet the demand of growing population results in intensification of genetically similar animals of same sex and age at confined place. This leads to transmission of pathogen with increases population turnover which supports emergence of novel trait. The transmission of Highly Pathogenic Asian Avian Influenza A (H5N1 HPAI) is the well-known example of mass rearing [26].

The drivers which are responsible for the disease emergence in new host include interspecies contact, wildlife migration, and increase contact between different hosts. The worldwide change in ecological landscape results in close contact between human and animals which eventually lead to transmission of microbial reservoir of animals (birds, rodents, and bats) to human. For instance, the emergence of Nipah virus in human was due to transmission of virus from foraging fruit bat to pigs [7]. The transport of food, live animals, plants with accompany insects for international trade, migration of birds, and wild animals results in geographical jump of pathogens. The bacterium Ralstonia solanacearum hitchhikes to the United States via geranium plant which is imported from Kenya [7].
17.2.4 Persisters and multidrug tolerance

Persisters are slow growing or nongrowing organisms which remain in stagnant during the presence of antimicrobial compound but have the capacity to resuscitate and grow under specific conditions. The persisters formation is mediated by variety of stress such as due to nutrient depletion, oxidative stress heat, acidic pH, and the presence of toxic compound (antibiotics). Antibiotics such as tetracycline, rifampin, and ciprofloxacin were shown to enrich persisters formation by inhibiting protein synthesis, RNA synthesis, or by antioxidative defense [5].

Persisters are the cause of biofilm infection, recurrent infection, and chronic infection and contribute toward prolongation of therapy time (e.g., tuberculosis, Lyme disease). The repeated treatment of persistent infection may result in the development of drug-resistance microbes, often seen in the case of tuberculosis. Persistent could be pre- or postantibiotic depending on its development in the host. The capacity of formation of persisters varies greatly among the bacterial species. For instance, persisters of Mycobacterium tuberculosis are not removed from the host even after chemotherapy, while the single antibiotic treatment is sufficient for curing infection caused by Streptococcus pneumoniae. The physical and psychological stress, host immune and hormonal factor, and coinfection also affect the persisters formation in the host.

The mechanism behind the persisters formation is not well understood. However, it is believed that epigenetic changes, changes in DNA modification, and posttranslational modification induce expression of persisters gene. The genes which involve in persisters formation are relA, sucB, hipA, ubiF, and phoU. The mutagenesis approach is used to study genes involved in persisters formation; however, the short antibiotic exposure, screening of partial mutant library, and aeration during antibiotic exposure are factors which result in failure of mutagenesis process for identifying persisters genes.

17.2.5 Vector borne zoonotic diseases

Zoonotic diseases are vector (mosquito, ticks, and bugs) aided or nonaided disease caused by bacteria, virus, parasites, prions and fungi, and transmitted from animals to human. Various modes of transmission are direct contact between infected animal and human, via arthropod vector, consumption of contaminated animal food (meat and pork), and ingestion of aerosolized pathogens present in the environment. In last two decades, many vector borne pathogens spread in new geographical regions. The emergence and reemergence rate of zoonotic infection has increased inescapably due to urbanization, deforestation, climate change, international trade (frequent travel), population movement, and encroachment into animal habitats. The most emerging zoonotic vector borne diseases in the United States and Canada include tick borne Lyme disease, Babesiosis, human granulocytic anaplasmosis and mosquito borne West nile virus (WNV), California serogroup viruses, and cache valley virus [7].

The change in land use alters the abundance and interaction of vectors and hosts (wildlife and domestic animals) which results in emergence of vectors. For instance, deforestation in
amazon and eastern Africa enhances the breeding of anopheles’ mosquito due to sunlight and standing water. Similarly in North America, increased hunting changes the predator community and results in increased abundance of small animals such as mice, chipmunks, and shrew which are main host of spirochete Borrelia burgdorferi, causative agent of Lyme disease [6]. Socioeconomic changes and human activities are the another factor which governs spread and emergence of pathogen. The Lyme disease was reported to occur more in high-income people in Europe due to the more recreational activity and living in new homes in broad-leaf woodlands with cooccurrence of wildlife result in frequent exposure to vector. Vector born zoonotic disease could be controlled by prompt identification of cause with subsequent action which requires integration of public health officials, researchers, and public [23].

17.2.6 Emergence of arboviruses

Arbovirus is an acronym for arthropod-borne viruses. Dengue virus, WNV, and chikungunya virus are recent examples of arboviruses which are transmitted from the arthropods (ticks, bugs, and mosquito) to vertebrate. Arboviruses use arthropods as a vector (carrier) for transmission and do not causes any sickness in them. Bunyaviridae, Reoviridae, Flaviviridae, and Togaviridae are the most prevailing arboviruses families that cause diseases in human and animals [27].

The emergence of arboviruses is governed by three factors, that is, high mutation frequency, varying anthropological behavior, and climate change. They easily adapt new host by altering receptor specificity, antigenicity, environmental conditions, and by efficient transmission. For instance, emergence of chikungunya virus in Asia due to mutation in surface protein which increases its reproduction, transmission, and infection efficiency in Aedes albopictus. They are able to maintain themselves for years in mosquito eggs or via attaining transstadial stages in ticks. Domestic animals, livestock, and human are not important part of arbovirus life cycle because of nonviraemic transmission of arbovirus between ticks without infecting vertebrate host. This feature of arbovirus adds additional limitation for controlling disease emergence [27].

Mosquito eradication, development of live-attenuated vaccines, antiviral drugs, and molecule are few methods used to control and prevent arboviral infection. However, high mutational frequency will result in emergence of new pathogenic arboviruses. Since it has been proven by genome sequencing of mosquitoes that they are the carrier of various known and unknown viruses, control of localized arthropod during endemic could be a possible solution for regulating the emergence of arbovirus [24].

17.2.7 Emergence of Buruli ulcer

Buruli ulcer (BU) is necrotizing skin disease caused by Mycobacterium ulcerans recognized as one of most neglected tropical disease by World Health Organization (WHO). The BU lead to the formation of skin ulcers which results in osteomyelitis. It causes pandemic in humid tropical and subtropical region, often where humans are in proximity with slow moving or stagnant contaminated water. The transmission of M. ulcerans follows multihost transmission
dynamics, that is, multiple hosts of aquatic environment such as scrapers, scavengers, and predators become contaminated with *M. ulcerans* and result in its passive dissemination via organism-to-organism contact. Phylogenetic studies revealed that the *M. ulcerans* was emerged from species *Mycobacterium marinum* which causes cutaneous disease in human and also shown to infect fish. *M. ulcerans* are widely distributed in Africa; however, the BU cases reported in specific geographical villages. Researchers postulates that a specific *M. ulcerans* strain might have pathogenicity or virulence to cause BU [8]. The current knowledge lacks the understanding of spatiotemporal distribution of *M. ulcerans* and required detailed scenario of diversity of *M. ulcerans* strains existing in environment [2].

**17.2.8 Age of superbugs**

Superbug is a term coined for bacterial species which confers resistant toward majority of antibiotics. Emergence of superbugs implies the frequent detection of novel bacterial pathogens which caused unrecognized life-threatening infections. The frequent emergence and spread of superbugs worldwide causes a concern that human life is heading back, toward the preantibiotic era, where the entire population of a society was wipe out due to the simple infection. United Nation (UN) General Assembly of 2016 addresses the AMR [28] as a health emergency and acknowledge that AMR has deleterious effect on human health and sustainable development. WHO identified a group of AMR resistant “priority pathogens” that requires urgent strategic action (Table 17–2). WHO categorize these priority pathogens into three categories, that is, critical, high, and medium priority based on the need for new antibiotics. The criteria for prioritization of pathogens were developed using multicriteria decision analysis technique which includes AMR pathogens which causes mortality, prevalence of resistance, transmissibility, treatability, healthcare and community burden, 10-year trend of resistance, preventability in hospital and community settings, and current pipeline [9].

To fight against increasing prevalence of antibiotic-resistant superbugs and to limit the indiscriminate use of antibiotics, WHO prepared three groups of antibiotics namely ACCESS, WATCH, and RESERVE group to ensure appropriate prescription and use. Access group comprises of antibiotics which are prescribe as in common infection as first and second choice. The first-choice antibiotics are narrow spectrum with low-resistant potential, whereas the second-choice antibiotics are broad spectrum having higher resistant potential. Antibiotics such as β-lactam, chloramphenicol, and clindamycin come under this category. Watch group identifies pharmacological antibiotic classes which prescribes as first or second choice but have a limited number of indication. The watch group has higher resistance potential compared with the access group. Watch group comprises macrolides, quinolones and fluoroquinolones, and glycopeptides class of antibiotics [29].

WHO created reserve group of antibiotics to reserve some antibiotics as the last resort in superbug infection. This group of antibiotics should be recommended as “last resort,” in case of life-threatening infection when other alternatives are failed in treatment. Reserve groups include eight antibiotic or antibiotic class which are aztreonam, fosfomycin,
fourth-generation cephalosporins (cefepime), oxazolidinones (linezolid), fifth-generation cephalosporins (ceftaroline), tigecycline, polymyxins (polymyxin-B, colistin), and daptomycin [6]. Recently, among these eight antibiotic classes, resistant determinant against colistin was detected in people of rural Vietnam. The prevalence of colistin resistant *Escherichia coli* in intestine of resident of Vietnam was extremely high, that is, approximately 70%. Previously, mutation that causes colistin resistant was not transferable; thus it is not considered as pathogenic, as intestinal *E. coli* is nonpathogenic. Finally, a transmissible colistin resistance gene (*mcr*) was detected in China, which has the potential to transfer colistin resistant to pathogenic microbes. The prevalence of *mcr* gene represents a serious concern regarding the emergence of superbugs that are resistant to last resort of antibiotic [30]. Currently, there are only fewer option (such as last resort antibiotics) to tackle antibiotic-resistant superbugs, and the finding of *mcr* gene indicates toward the needs of innovative research which results in better understanding of superbug emergence and also to research and development on quality, safe, efficacious, and affordable antimicrobial medicines, especially new antibiotics and alternative therapies, vaccines, and diagnostics.

| Category | Priority pathogen | Resistant antibiotics | Disease caused | References |
|----------|-------------------|-----------------------|----------------|------------|
| Critical | *Acinetobacter baumannii* | Carbapenem | Urinary tract infections, wound, and surgical site infections | [9,10] |
| Critical | *Pseudomonas aeruginosa* | Carbapenem | Nosocomial infections | [9,11] |
| Critical | Enterobacteriaceae | Carbapenem and ESBL-producing | Urinary tract infections, intraabdominal infections, and meningitis | [9,12] |
| High | *Enterococcus faecium* | Vancomycin | Nosocomial infection | [9,13] |
| High | *Staphylococcus aureus* | Vancomycin and methicillin | Postoperative wound infection, skin, soft tissue, bone, and bloodstream infections | [9,14] |
| High | *Helicobacter pylori* | Clarithromycin | Peptic ulcers, gastric marginal zone lymphoma, and gastric carcinoma | [9,15] |
| High | *Campylobacter spp.* | Fluoroquinolone | Foodborne gastroenteritis | [9,16] |
| High | *Salmonella* | Fluoroquinolone | Enteric fever, foodborne diarrhea, and bloodstream infections | [9,17] |
| High | *Neisseria gonorrhoeae* | Cephalosporin and fluoroquinolone | Gonorrhea | [9,18] |
| Medium | *Streptococcus pneumoniae* | Penicillin | Pneumonia, meningitis, and otitis | [9,19] |
| Medium | *Haemophilus influenzae* | Ampicillin | Meningitis and septicemia | [9,20] |
| Medium | *Shigella spp.* | Fluoroquinolone | Diarrhea and Shigellosis | [9,21] |
17.3 Threats

The various chapters of this book discussed about the occurrence and prevalence of human and veterinary pharmaceuticals (antibiotics, antidepressant, antidiabetic, radioactive agents, etc.) at different environmental sites. These pharmaceutical compounds are biologically active compounds that are known to have a specific mode of action (MOA) in human and animals even at low concentration. Due to genetic relatedness (presence of conserved gene) across species, these compounds interact with protein and cell lineage of nontarget organisms (conserved therapeutic drug targets) and elicit a response in their body (targets metabolic pathway, enzyme or mediators of cell signaling molecule). For instance, ibuprofen which is a cyclooxygenase inhibitor was found to interfere with arachidonic acid signaling pathway in marine clams *Ruditapes philippinarum* [31]. However, the effect of pharmaceuticals may vary from species to species due to difference in gene expression of the same gene across species or due to change in solubility or potency of drugs because of binding of pharmaceuticals with organic molecules present at environmental sites. Therefore to understand the environmental risk posed by these contaminants, conceptual model of MOA of pharmaceuticals was used. The MOA [15] approach involves the assessment of drug targets and its evolution between mammals and the model species. The conceptual model of MOA approach in marine organisms reveals the presence of fluoxetine at environmental concentration was able to control the serotonin signaling pathway, and this alteration in physiological signaling pathway results in defects in reproduction, locomotion, and metabolism of aquatic organisms [31].

Many short-term toxicity studies reported that the drug molecules do not have an acute toxic effect on aquatic organisms because of their presence in low concentration (ng/L to low μg/L), but their constant release and exposure to aquatic biota have long-term chronic effects [32,33]. However, many laboratory studies at high concentration of pharmaceutical compounds report direct lethal effects. Tetracycline concentration around 10–100 μg/L leads to low periphyton (nematode, bacteria, and algae) concentration in mesocosm stream [34]. Structure disruption in kidney and intestine of rainbow trout and brown trout due to diclofenac (5 μg/L) was reported [35]. Prolonged exposure to pharmaceuticals in low concentration leads to the change in species trait and behavior of aquatic organisms. Antidepressant and psychiatric drugs such as fluoxetine and oxazepam cause disruption in ecological interaction even in low concentration [9]. Indeed, even by considering that these drugs are diluted after their release, it is evident that they have a toxic effect on the aquatic ecosystem.

The widespread occurrences of pharmaceuticals at various environmental sites such as in ocean, river, and groundwater raise a concern regarding the risk associated with human health. For instance, the birth control and growth stimulator agent like estrogen have the potential to cause prostate and breast cancer in humans (If the estrogen concentration is used above the threshold limit). The worldwide discharge of estrogen from livestock and human ranges approximately 86,000 and 30,000 kg/year, respectively. The US National Toxicology Program declared estrogen as carcinogen, the no adverse effect concentration of estrogen in human is 0.3 mg/day and frequent detection of estrogen in drinking water
concentration ranging from 0.1 to 2.0 ng/L represent a health risk [33]. Estrogen was reported to cause abnormalities in animals such as permanent infertility (clover disease in sheep due to feeding on clover plant which has high phytoestrogen level) [33]. However, human health risk assessment studies reported no appreciable risk to human due to exposure of pharmaceuticals mixture [32].

17.4 Required research action and proposed remedies

Due to emergence of antibiotic-resistant pathogens and unavoidable use of antibiotics, concomitant environmental perturbation caused by climate change might make the earth is not suitable for humans and other livings. Thus researchers focus on finding alternative methods to avoid use of antibiotics and developing novel treatment technologies to degrade and remove the pharmaceutical compounds.

17.4.1 Prediction of emergence microbes

Prediction of emerging signals by theoretical and bioinformatics tool will highly help to alarm the researchers, hospitals, and public about the nearby occurrence of resistant bug. Such predictions are underway by monitoring microbial community dynamics in different environmental samples; however, these studies facing enormous challenges in the developmental face [28,36–43]. Several research studies have been conducted to observe a change in microbial metabolic pathways for a while. Such study results could predict microbial interactions and route of evolution, and might apply to precisely pinpoint the emerging organism in the mixed microbial community. These studies are still under research stage, such studies are using genomic, metabolomic, and transcriptomic tools to predict the bug emergence. Recently, Geoghegan and Holmes [44] attempted predicting the virus emergence with an interest of biomedicine and preventing unpredicted incidence [44]. They have monitored the evolution of viruses in short-term period to highlight the cross-species transmission and emergence. They have concluded that predicting emergence requires a new mechanistic and integrated approach, which might permit or stop the emerging viral spread into new hosts [44].

17.4.2 World Health Organization’s global action plan—resistant bacteria

With the fact that microbial resistant to pharmaceuticals, the treatment options are reduced; however, alternative methods have been explored to protect human and animal from microbial illness. The microbial drug resistance leads to direct and indirect consequences as described by WHO report 2015 [45]. The severe direct consequences are prolonged illness, impossible to protect the patients undergoing surgery and augmented treatment cost. Whereas the indirect impacts of AMR are depleting the global economy (due to the loss of productivity by sickness) and higher costs of treatment. Thus WHO proposed a global action plan to assure preventing the transmission of infectious disease and providing complete
treatment with the help of safe and effective medicines [45]. To achieve the global action plan successfully, five objectives have been proposed by WHO: (1) to improve awareness and understanding of AMR; (2) to strengthen knowledge through surveillance and research; (3) to reduce the incidence of infection; (4) to optimize the use of antimicrobial agents; and (5) to ensure sustainable investment in countering AMR. These objectives are likely to be met through political leaders, Member States, the Secretariat, and international and national partners across multiple sectors. Notably, individual responsibilities like recycling unused medicines, intake of only prescribed medicines, and keeping the environment clean would highly help to achieve the WHO’s global action plan for the betterment of human and animal health.

17.4.3 Phage therapy to fight against multidrug-resistant pathogens

Increasing resistance to antibiotics and the emergence of “superbugs” that are resistant to drugs of last resort have highlighted the great need for alternative treatments of bacterial disease. This has led to renewed interest in the potential of phage to treat bacterial pathogens. The term “phage therapy” usually refers to the treatment of bacterial infections with intact phage; however, there are other ways in which phage can be used as antibacterials.

17.4.3.1 Therapy delivery systems

Phage can be used as “lethal agent delivery systems” to introduce nonspecific or toxic antimicrobials [46,47], or genes encoding antimicrobials [48] into selected pathogenic bacteria. In another method (targeted gene transfer), filamentous phage can be modified to carry therapeutic genes and to target cell surface antigens or receptors on mammalian cells, transducing them by receptor-mediated endocytosis [49]. Although phages are not an antimicrobial tool in itself, this approach could be used to deliver antimicrobials to intracellular bacterial pathogens.

17.4.3.2 Lytic enzymes

Phage secrets lysins enzymes which lyse the host bacteria. Lysins are host specific and use cell wall components that are essential for viability as receptors; therefore bacterial resistance is rare [50]. Initial tests of lysins against clinically relevant Gram-positive bacteria, such as methicillin-resistance Staphylococcus aureus, look promising [51,52]. The use of multiple phage lysins with different cleavage sites could increase therapeutic effectiveness and further reduce the chance of bacteria developing resistance. Lysins can also be used to make bacterial ghost vaccines.

17.4.3.3 Pathogen removal in treated effluent

To produce better quality of treated sludge, wastewater treatment processes must achieve a minimum 6 log reduction in E. coli loads and a final end product (sludge) with a maximum admissible concentration of E. coli $1 \times 10^3$ CFU/g [dry solids (DS)] and zero Salmonella in 2 g (DS). Similarly, United States Environmental Protection Agency regulations are categorized
into Class A and Class B sludges. Class A pathogen reduction requirements are more stringent than those of Class B sludges which are subject to application restrictions. Class A sludges are required to reduce pathogens to below the detectable limit (<3 most probable number of *Salmonella*, <1 plaque forming unit of enteric viruses, and <1 viable helminth ovum per 4 g DS). Treatment processes designed to achieve pathogen reduction to a required level can incur substantial capital and operating costs [53].

Development of phage treatment of sludge may provide long-term and cost-effective control of potentially pathogenic bacteria (e.g., *E. coli* and *Salmonella*). Successful phage treatment of wastewater bacterial pathogens would be dependent on the prevalence and diversity of pathogen species within wastewater. It would be virtually impossible to produce phage targeted at all pathogenic serotypes. For example, there is a high diversity of *E. coli* serotypes [54] and around 2400 known *Salmonella* serotypes [55]. However, wastewater treatment conditions intrinsically reduce the numbers of some pathogenic bacteria. Therefore there is potential for phage treatment to be used successfully in combination with biological sludge stabilization processes to reduce the abundance of specific pathogenic bacterial strains such as *E. coli* O157. Indeed, research on phage therapy for reduction of this pathogen in animal reservoirs is already underway [53].

### 17.4.4 Phage and antibiotics mixed with polymer composite

Although phage-derived therapies have several advantages compared with antibiotics, the combined use of phage, or phage lysins, and antibiotics is an attractive treatment regime. Indeed, such a product is available commercially in Georgia: PhagoBioDerm is a biodegradable polymer composite impregnated with a lytic phage cocktail and ciprofloxacin [56]. Using phage with antibiotics should increase the efficiency of treatment and reduce the emergence of resistant mutants because the surviving bacteria would need to acquire at least two separate resistance mechanisms.

To kill the multidrug-resistant bacteria researchers from IBN (Institute of Bioengineering and Nanotechnology), Chin et al. [57] developed a novel synthetic molecule and demonstrated selectively destroying five multidrug-resistant bacteria [57]. Recently polymer-based advanced drug designing to combat multidrug resistances is widely explored, which are described in detail [58,59].

### 17.5 Effect of global warming on pathogens survival

Due to climate change, a steady increase in temperature (about 0.75°C) was recorded in the past 100 years, which was clearly observed on lands than the ocean in recent days [60]. However, ice melting in north pole, increase in sea level, and alteration in raining patterns are clear and known effects of examples of global warming. Climate change affects the water cycle in the following aspects: (1) poor water quality, (2) less availability (quantity for consumption and use), (3) evaporation leads increases the microbial load (concentration) and toxic ions concentration, (4) water depletion in animal-farming and agriculture
(leads to food scarcity), and (5) effects on freshwater biodiversity is still undetermined. Ultimately, these changes will hugely affect wastewater microbiome (including beneficial and pathogenic microbes), the concentration of toxic pollutants and biological process performance, which was discussed in detail in Chapter 13, Treatment of wastewater containing pharmaceuticals: biological treatment. Recently, WHO reported that climate change affects the infectious disease transmission pattern (Fig. 17–1).

Various infectious diseases and their agents (viruses, bacteria, protozoa, and multicellular parasites) have adapted (via evolution) humans as a primary host, which raises serious threat mankind to face in near future. Due to the negligent, persistent and accidental activities of humans (industrial) raised the environmental pollution (chemicals including pharmaceuticals), which led to inseparable effect like climate change. Furthermore, development of drug-resistant organisms and increased pathogen survival rate, only raising panic about the human, animal, and environmental health. Thus researchers are continuously searching alternatives to these environmental problems.

17.6 Conclusions and perspectives

Due to pharmaceuticals release in the environment and climate change, the survival of pathogens prolongs. High load of infectious bacterial strains dwelling in wastewater further favors the transfer of antibiotic-resistance gene. This could be a classical example for
multidrug-resistant bacterial strains that are prevalence in tropical countries (like China and India). This draws immediate attention of public, health, and international sectors to fight against, pollution, climate change, and drug resistance.

The advancement in medicinal research helps in control and elimination of various infectious diseases such as smallpox. However, emergence and reemergence of infectious diseases due to various factors, that is, natural evolution, climate change, AMR, and many more, is a matter of concern. The knowledge about the evolution and life cycle of pathogens (bacteria, virus, or parasite) using omics study (proteome, metabolome, epigenome, and transcriptome) and via next-generation sequencing could help in the prevention and control of infectious diseases. The implantation of ecological approaches, network, and system biology approaches could provide a better understanding of the environmental factors of disease-emergence and drug-resistance mechanisms. The information gained from these approaches could help in assessing the immune mechanisms of pathogen and a developing treatment strategy.

Abbreviations

ACE Angiotensin-converting enzyme
AMR Antimicrobial resistance
BU Buruli ulcer
CoV Coronavirus
DS Dry solids
MOA Mode of action
SARS Severe acute respiratory syndrome
SFTS Severe fever with thrombocytopenia syndrome
WNV West nile virus

References

[1] B. Tiwari, B. Sellamuthu, Y. Ouarda, P. Drogui, R.D. Tyagi, G. Buelna, Review on fate and mechanism of removal of pharmaceutical pollutants from wastewater using biological approach, Bioresour. Technol. 224 (2017) 1–12.
[2] D. Li, A highly pathogenic new bunyavirus emerged in China, Emerg. Microb. Infect. 2 (1) (2013).
[3] P. Daszak, A.A. Cunningham, A.D. Hyatt, Emerging infectious diseases of wildlife—threats to biodiversity and human health, Science 287 (5452) (2000) 443–449.
[4] K.B. Chua, D.J. Gubler, Perspectives of public health laboratories in emerging infectious diseases, Emerg. Microb. Infect. 2 (6) (2013) e37.
[5] Y. Zhang, Persisters, persistent infections and the Yin-Yang model, Emerg. Microb. Infect. 3 (1) (2014) e3.
[6] A.M. Kilpatrick, S.E. Randolph, Drivers, dynamics, and control of emerging vector-borne zoonotic diseases, Lancet 380 (9857) (2012) 1946–1955.
[7] M.A. Kulkarni, L. Berrang-Ford, P.A. Buck, M.A. Drebot, L.R. Lindsay, N.H. Ogden, Major emerging vector-borne zoonotic diseases of public health importance in Canada, Emerg. Microb. Infect. 4 (2015) e33.

[8] M. Combe, C.J. Velvin, A. Morris, A. Garchitorena, K. Carolan, D. Sanhueza, et al., Global and local environmental changes as drivers of Buruli ulcer emergence, Emerg. Microb. Infect. 6 (4) (2017) e21.

[9] World Health Organization, Global Priority List of Antibiotic-Resistant Bacteria to Guide Research, Discovery, and Development of New Antibiotics, World Health Organization, Geneva, 2017.

[10] J.M. Pogue, T. Mann, K.E. Barber, K.S. Kaye, Carbapenem-resistant Acinetobacter baumannii: epidemiology, surveillance and management, Expert Rev. Anti Infect. Ther. 11 (4) (2013) 383–393.

[11] X.Q.P.C.K. Stover, A.L. Erwin, S.D. Mizoguchi, P. Warrener, M.J. Hickey, F.S.L. Brinkman, et al., Complete genome sequence of Pseudomonas aeruginosa PAO1, an opportunistic pathogen, Nature 406 (2000) 959–964.

[12] T. Naas, P. Nordmann, L. Poirel, Global spread of carbapenemase producing Enterobacteriaceae, Emerg. Infect. Dis. 17 (10) (2011) 1791–1798.

[13] A.R. Freitas, A.P. Tedim, M.V. Francia, L.B. Jensen, C. Novais, L. Peixe, et al., Multilevel population genetic analysis of vanA and vanB Enterococcus faecium causing nosocomial outbreaks in 27 countries (1986-2012), J. Antimicrob. Chemother. 71 (12) (2016) 3351–3366.

[14] R.I. Gordon, F.D. Lowy, Pathogenesis of methicillin-resistant Staphylococcus aureus infection, Clin. Infect. Dis. 46 (Suppl. 5) (2008) S350–S359.

[15] P. Malfertheiner, F. Megraud, C.A. O’Morain, J.P. Gisbert, E.J. Kuipers, A.T. Axon, et al., Management of Helicobacter pylori infection—the Maastricht V/Florence consensus report, Gut 66 (1) (2017) 6–30.

[16] J. Lackner, M. Weiss, C. Muller-Graf, M. Greiner, The disease burden associated with Campylobacter spp. in Germany, 2014, PLoS One 14 (5) (2019) e0216867.

[17] F. Marks, V. von Kalckreuth, P. Aaby, Y. Adu-Sarkodie, M.A. El Tayeb, M. Ali, et al., Incidence of invasive salmonella disease in sub-Saharan Africa: a multicentre population-based surveillance study, Lancet Glob. Health 5 (3) (2017) e310–e323.

[18] M.A.W. Jessica, M.A. Blair, A.J. Baylay, D.O. Ogbolu, L.J.V. Piddock, Molecular mechanisms of antibiotic resistance, Nat. Rev. Microbiol. 13 (2014) 42–51.

[19] E. Balsells, L. Guillot, H. Nair, M.H. Kyaw, Serotype distribution of Streptococcus pneumoniae causing invasive disease in children in the post-PCV era: a systematic review and meta-analysis, PLoS One 12 (5) (2017) e0177113.

[20] R. Whittaker, A. Economopoulou, J.G. Dias, E. Bancroft, M. Ramli, D. Celentano, Epidemiology of invasive Haemophilus influenzae disease, Europe, 2007-2014, Emerg. Infect. Dis. 23 (3) (2017) 396–404.

[21] E. Mattock, A.J. Blocker, How do the virulence factors of shigella work together to cause disease? Front. Cell. Infect. Microbiol. 7 (2017) 64.

[22] M.E. Woolhouse, S. Gowtage-Sequeria, Host range and emerging and reemerging pathogens, Emerg. Infect. Dis. 11 (12) (2005) 1842.

[23] J.A. Patz, P. Daszak, G.M. Tabor, A.A. Aguirre, M. Pearl, J. Epstein, et al., Unhealthy landscapes: policy recommendations on land use change and infectious disease emergence, Environ. Health Perspect. 112 (10) (2004) 1092–1098.

[24] K.B. Chua, B.H. Chua, C.W. Wang, Anthropogenic deforestation, El Niño and the emergence of Nipah virus in Malaysia, Malaysian J. Pathol. 24 (1) (2002) 15–21.

[25] S. de La Rocque, J.-A. Rioux, J. Slingenbergh, Climate change: effects on animal disease systems and implications for surveillance and control, Rev. Sci. Technol. 27 (2) (2008) 339–354.
A. Engering, L. Hogerwerf, J. Slingenbergh, Pathogen-host-environment interplay and disease emergence, Emerg. Microb. Infect. 2 (2) (2013) e5.

G. Liang, X. Gao, E.A. Gould, Factors responsible for the emergence of arboviruses; strategies, challenges and limitations for their control, Emerg. Microb. Infect. 4 (3) (2015). e18.

W.R. Harcombe, W.J. Riehl, I. Dukovski, B.R. Granger, A. Betts, A.H. Lang, et al., Metabolic resource allocation in individual microbes determines ecosystem interactions and spatial dynamics, Cell Rep. 7 (4) (2014) 1104–1115.

World Health Organization, The Selection and Use of Essential Medicines: Report of the WHO Expert Committee, 2017 (Including the 20th WHO Model List of Essential Medicines and the 6th Model List of Essential Medicines for Children), World Health Organization, 2017.

Y. Yamamoto, R. Kawahara, Y. Fujiya, T. Sasaki, I. Hirai, D.T. Khong, et al., Wide dissemination of colistin-resistant Escherichia coli with the mobile resistance gene mcr in healthy residents in Vietnam, J. Antimicrob. Chemother. 74 (2) (2019) 523–524.

E. Fabbri, S. Franzellitti, Human pharmaceuticals in the marine environment: focus on exposure and biological effects in animal species, Environ. Toxicol. Chem. 35 (4) (2016) 799–812.

B.M. Sharma, J. Becanova, M. Scheringer, A. Sharma, G.K. Bharat, P.G. Whitehead, et al., Health and ecological risk assessment of emerging contaminants (pharmaceuticals, personal care products, and artificial sweeteners) in surface and groundwater (drinking water) in the Ganges River Basin, India, Sci. Total. Environ. 646 (2019) 1459–1467.

M. Adeel, X. Song, Y. Wang, D. Francis, Y. Yang, Environmental impact of estrogens on human, animal and plant life: a critical review, Environ. Int. 99 (2017) 107–119.

E.L. Quinlan, C.T. Nietch, K. Blochsom, J.M. Lazorchak, A.L. Batt, R. Griffiths, et al., Temporal dynamics of periphyton exposed to tetracycline in stream mesocosms, Environ. Sci. Technol. 45 (24) (2011) 10684–10690.

B. Hoeger, B. Kollner, D.R. Dietrich, B. Hitzfeld, Water-borne diclofenac affects kidney and gill integrity and selected immune parameters in brown trout (Salmo trutta f. fario), Aquat. Toxicol. 75 (1) (2005) 53–64.

J. Weitz, S. Wilhelm, Ocean viruses and their effects on microbial communities and biogeochemical cycles, F1000 Biol. Rep. (2012).

J.D. Orth, I. Thiele, B.O. Palsson, What is flux balance analysis? Nat. Biotechnol. 28 (3) (2010) 245–248.

D. Machado, S. Andrejev, M. Tramontano, K.R. Patil, Fast automated reconstruction of genome-scale metabolic models for microbial species and communities, Nucl. Acids Res. 46 (15) (2018) 7542–7553.

W.R. Harcombe, J.M. Chacón, E.M. Adamowicz, L.M. Chubiz, C.J. Marx, Evolution of bidirectional costly mutualism from byproduct consumption, Proc. Natl. Acad. Sci. U.S.A. 115 (47) (2018) 12000–12004.

S.P. Hammarlund, J.M. Chacón, W.R. Harcombe, A shared limiting resource leads to competitive exclusion in a cross-feeding system: role of environment for cross-feeder coexistence, Environ. Microbiol. 21 (2) (2019) 759–771.

J. Friedman, L.M. Higgins, J. Gore, Community structure follows simple assembly rules in microbial microcosms, Nat. Ecol. Evol. 1 (5) (2017) 0109.

L.M. Chubiz, B.R. Granger, D. SegrÃ, W.R. Harcombe, Species interactions differ in their genetic robustness, Front. Microbiol. 6 (2015).

J.M. Chacón, W. Möbius, W.R. Harcombe, The spatial and metabolic basis of colony size variation, ISME J. 12 (3) (2018) 669–680.

J.L. Geoghegan, E.C. Holmes, Predicting virus emergence amid evolutionary noise, Open Biol. 7 (10) (2017) 170189.

World Health Organization, Global Action Plan on Antimicrobial Resistance 2015, 2017.
Chapter 17 • Future impacts and trends in treatment of hospital wastewater

[46] I. Yacoby, M. Shamis, H. Bar, D. Shabat, I. Benhar, Targeting antibacterial agents by using drug-carrying filamentous bacteriophages, Antimicrob. Agents Chemother. 50 (6) (2006) 2087–2097.

[47] C. Westwater, L.M. Kasman, D.A. Schofield, P.A. Werner, J.W. Dolan, M.G. Schmidt, et al., Use of genetically engineered phage to deliver antimicrobial agents to bacteria: an alternative therapy for treatment of bacterial infections, Antimicrob. Agents Chemother. 47 (4) (2003) 1301–1307.

[48] D. Larocca, M.A. Brug, K. Jensen-pergakes, E. Ravey, A. Gonzalez, A. Baird, Evolving phage vectors for cell targeted gene delivery, Curr. Pharm. Biotechnol. 3 (1) (2002) 45–57.

[49] V.A. Fischetti, Bacteriophage lytic enzymes: novel anti-infectives, Trends Microbiol. 13 (10) (2005) 491–496.

[50] I. Jado, Phage lytic enzymes as therapy for antibiotic-resistant Streptococcus pneumoniae infection in a murine sepsis model, J. Antimicrob. Chemother. 52 (6) (2003) 967–973.

[51] S. O’Flaherty, A. Coffey, W. Meaney, G.F. Fitzgerald, R.P. Ross, The recombinant phage lysin LysK has a broad spectrum of lytic activity against clinically relevant Staphylococci, including methicillin-resistant Staphylococcus aureus, J. Bacteriol. 187 (20) (2005) 7161–7164.

[52] K. Markoishvili, G. Tsitlanadze, R. Katsarava, J. Glenn, A. Sulakvelidze, A novel sustained-release matrix based on biodegradable poly(ester amide)s and impregnated with bacteriophages and an antibiotic shows promise in management of infected venous stasis ulcers and other poorly healing wounds, Int. J. Dermatol. 41 (7) (2002) 453–458.

[53] D. Sainsbury, P. Singleton, Dictionary of Microbiology and Molecular Biology, third ed., John Wiley and Sons, Chichester, 2002.

[54] M.Y. Popoff, Antigenic Formulas of the Salmonella Serovars, WHO Collaborating Center for Reference and Research on Salmonella, 1997.

[55] F.R. Spellman, Dewatering Biosolids, CRC Press, 1997.

[56] A. Coffey, R.P. Ross, Bacteriophage-resistance systems in dairy starter strains: molecular analysis to application, in: R.J. Siezen, J. Kok, T. Abee, G. Schasfsma (Eds.), Lactic Acid Bacteria: Genetics, Metabolism and Applications, Springer, The Netherlands, Dordrecht, 2002, pp. 303–321.

[57] W. Chin, G. Zhong, Q. Pu, C. Yang, W. Lou, P.F. De Sessions, et al., A macromolecular approach to eradicate multidrug resistant bacterial infections while mitigating drug resistance onset, Nat. Commun. 9 (1) (2018) 917.

[58] N.D. Stebbins, M.A. Ouimet, K.E. Uhrich, Antibiotic-containing polymers for localized, sustained drug delivery, Adv. Drug Deliv. Rev. 78 (2014) 77–87.

[59] V. Van Giau, S.S.A. An, J. Hulme, Recent advances in the treatment of pathogenic infections using antibiotics and nano-drug delivery vehicles, Drug Des. Dev. Ther. 13 (2019) 327–343.

[60] S. Shrestha, A.K. Anal, P.A. Salam, M. Van der Valk, Managing Water Resources under Climate Uncertainty, Springer, 2016.