

PERSPECTIVE

EARTH SCIENCES

Super pathogens from environmental biotechnologies threaten global health

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Microbial pathogens are viruses, bacteria, fungi and protozoa infecting humans, animals or plants. Super pathogens (also known as superbugs) able to resist multiple antimicrobials and cause fatal infections have been increasingly considered an emerging threat to global health [1]. The COVID-19 pandemic has caused more than 3.8 million deaths as of 15 June 2021, reminding us that we should always be alert to the next pandemic caused by super pathogens. We know little, however, about the origin and transmission of super pathogens in environment. Among the various potential sources of super pathogens, special attention should be paid to environmental biotechnologies (EBTs) for treating wastewater.

Human activities generate wastewater, with a global production of about 330 km³/year [2], that contains heavy metals, carbohydrates, antimicrobials and pathogens polluting the environment and spreading diseases. Various methods have been developed to purify wastewater,

but EBTs are the most common ones because they use microbes to degrade pollutants economically, e.g. <0.1 US\$/m³ municipal wastewater in China.

EBTs are valuable for purifying wastewater, but they also induce the risks of incubating and releasing super pathogens. Millions of microbial species exist in EBTs, many of which are pathogens playing important roles in degrading pollutants [3]. EBTs, e.g. municipal wastewater-treatment plants, have been widely reported as hotspots of pathogens and antimicrobial resistance genes (ARGs) [4]. During the long-term running of EBTs, pathogens can evolve to resist multiple pollutants, which unfortunately enhances their resistance to antimicrobials, because microbes use similar strategies to resist antimicrobials and other toxic pollutants such as heavy metals [5]. Microbial genes can also be transferred between microbes [6], enabling pathogens to acquire new ARGs from others to become super pathogens. Furthermore, traditional disinfection can also increase the spread of ARGs between different microbes.

Fecal coliforms or *Escherichia coli* are widely used microbial indexes for discharge of treated wastewater, e.g. 100-10 000 colony-forming units/L in some countries. The abundance of fecal coliforms in EBTs is low, e.g. <0.22% in most wastewater-treatment plants [3], suggesting that a substantial volume of other microbes, including super pathogens, is released to the natural environment and then spread around the world by human activities [7]. For example, super pathogens that produce New Delhi metallo-beta-lactamase 1 (NDM-1) conferring resistance to multiple antimicrobials are spread to rivers via effluents from wastewater-treatment plants lacking proper sanitation [8]. Super pathogens from EBTs can be transferred to humans mainly via accidental contact with reclaimed water and bioaerosols from EBTs and foods contaminated by EBT effluents. We therefore call for close cooperation between research community, industry and government to reduce the threat to global health caused by super pathogens from EBTs

(Figure 1).

“Know yourself and know your enemy, and you will never be defeated”. First, we must better understand the evolution of super pathogens in EBTs at global scale. Many studies have investigated the dynamics of ARGs in the ecosystem, but little is known about super pathogens. Monitoring the emission of super pathogens from EBTs and tracking their fates in various environments are important for evaluating their risks to human health. Such research can inform the public to avoid environments and products contaminated by EBTs effluents, and most importantly, can support governments to appropriately supervise EBT industry. High-throughput sequencing of nucleic acids provides community-level information, but information about pathogens is lacking. Third-generation sequencing targeting single DNA molecules is a better alternative, which generates long sequence reads linking super pathogens with their ARGs or virulence genes.

Current EBTs mainly aim at removing traditional carbohydrates and nutrients instead of super pathogens, so substitutive or complement technologies are needed to eliminate the release of super pathogens. For example, macrophyte-assisted vermifiltration can efficiently treat wastewater, and the earthworms can consume and kill pathogens. Complementing current EBTs with sustainable disinfection processes, e.g. eBeam and nanobubble technologies, rather than replacing them with new technologies, however, is more cost-effective. eBeam technology, using electron beams for disinfection and pollutants degradation, was launched in a demonstration project in 2017 in Zhejiang, China. Nanobubble technology uses bubbles (<1000 nm) without chemicals to degrade pollutants and inactivate pathogens. Researchers from Harvard University,

for example, created tiny, aerosolized water nanodroplets containing reactive oxygen species or other non-toxic, nature-inspired disinfectants to kill pathogens efficiently [9].

Governments play key roles in solving the problem of super pathogens by guiding the public, supervising industry and supporting research, but most governments have not yet recognized the public health threat of super pathogens from EBTs. To solve the problem of super pathogens, the most efficient way for governments is to set stricter standards of microbial pathogens for EBTs' discharge. Setting standards, however, is extremely challenging, which requires a comprehensive understanding of the diversity, evolution, spread and risk of super pathogens. Complementary facilities can help current EBTs to satisfy stricter standards, which would substantially increase the cost of treating wastewater. Current EBTs for hospitals, livestock farms and pharmaceutical factories can easily incubate super pathogens and should be given the highest priority for complementing disinfection.

Our world is a closely connected community, and microbes can be spread around the world by human activities [7], which requires all countries acting together to defeat super pathogens. Low-income countries lack funds constructing wastewater-treatment plants with new but expensive technologies, and cost-effective EBTs like vermifiltration are valuable options for them. High-income countries have complete wastewater-treatment systems, but they could better complement their current EBTs with sustainable disinfections like eBeam and nanobubble technologies. Intergovernmental cooperation, e.g. by high-income countries providing financial and technological aid to low-income countries, is crucial for preventing worldwide pandemics. High-income countries could also train researchers and engineers from low-income countries to protect the environment.

Untreated wastewater can exacerbate the problems of sanitation, which can create barriers to

achieving the 2030 Sustainable Development Goals (SDGs) of the United Nations, such as good health and well-being (SDG3), clean water and sanitation (SDG6). The world, however, is still rapidly urbanizing, which brings challenges to pollution reduction, supplying freshwater and ensuring health (e.g. by eliminating super pathogens). Though EBTs contribute to these SDGs, we need to recognize the dangers of super pathogens from EBTs. The outbreak of COVID-19 has indicated the potential spread of viruses by wastewater-treatment systems [10], but little has been done to eliminate the health threat of super pathogens from EBTs, which requires systems approaches of One Health (inter-connectivity of human, animal and ecosystem health) for understanding the microbial cycling among environment, animals and humans.

Supplementary Data

Supplementary Data are available at NSR online.

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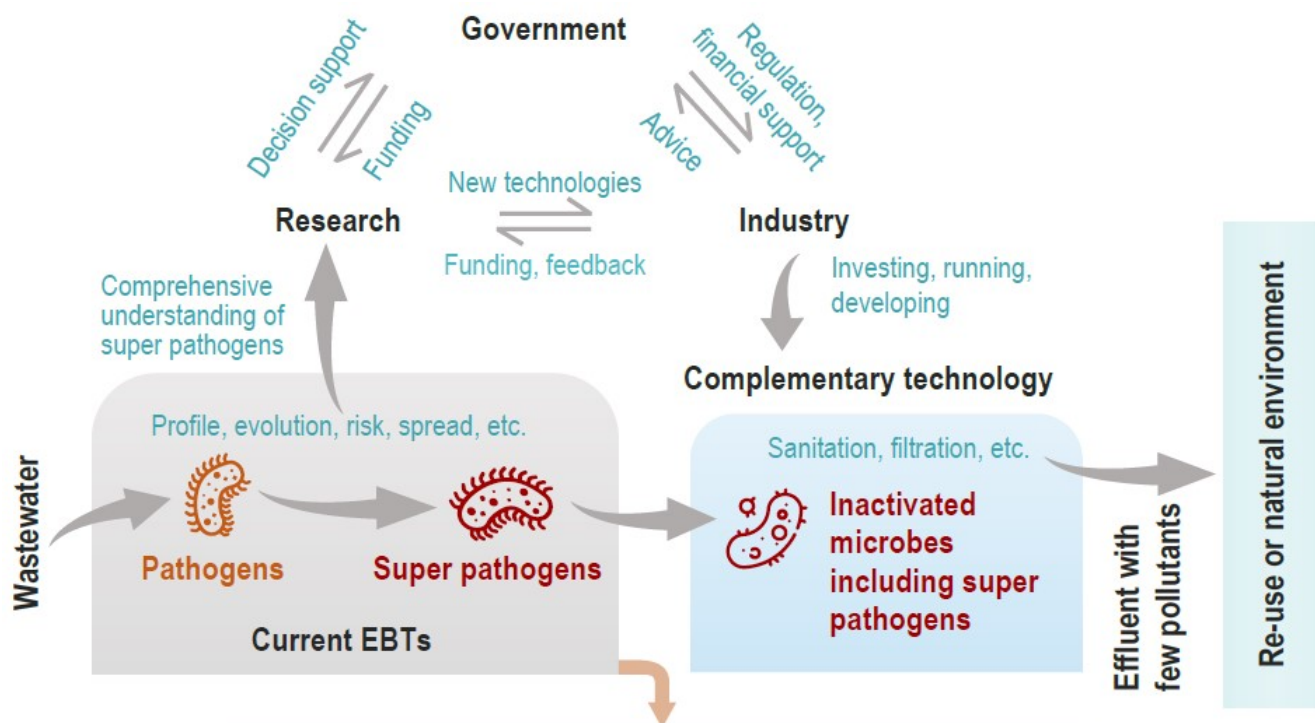
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Conflict of interest statement

The authors declare that they have no conflict of interest.

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Global emission of representative pathogens from EBTs

Species	Cells per liter EBT effluent	Total wastewater per year (L)	Total cells released from EBTs to environment per year
<i>Escherichia coli</i>	10^5 to 10^6	2×10^{14}	10^{19} to 10^{20}
<i>Staphylococcus</i> spp.	10^4 to 10^5		10^{18} to 10^{19}
<i>Pseudomonas aeruginosa</i>	10^4 to 10^5		10^{18} to 10^{19}
<i>Clostridium perfringens</i>	10^4		10^{18}

Figure 1 Collaboration of the research community, industry and government can contribute to therapeutic EBTs for a healthier world. EBTs for removing pollutants are producing and releasing other harmful pollutants, e.g. super pathogens. Huge numbers of pathogenic microbes are now being released from EBTs. See [Supplementary Materials](#) for data sources.