Proceedings of ICMMGH 2026 Symposium: Cell and Molecular Biology: Understanding Immune Cell Functions
DOI: 10.54254/2753-8818/2026.PJ29392

From the Black Death to the Age of Superbugs: Lessons from History for the Antimicrobial Resistance Crisis

Xinyi Liu

Xi'an Jiaotong-Liverpool University, Suzhou, China
Xinyi.Liu320@outlook.com

Abstract. Antimicrobial resistance has become one of the most severe global health threats, challenging the foundations of modern medicine. The article outlines the historical trajectory between humans and bacterial infections, from the devastating Black Death of the 14th century to the revolutionary discovery of antibiotics in the 20th century, and now to the crisis exacerbated by "superbugs." Combining historical analysis with contemporary epidemiological data, this study explores how past uncontrolled bacterial outbreaks can provide insights for current drug resistance management. The research methodology relies on historical literature, reports from the World Health Organization and the Centers for Disease Control and Prevention in the United States, as well as the latest findings on resistance mechanisms and control measures. The research question focuses on how historical experience can provide insights for current and future drug resistance strategies. Results indicate that alleviating drug resistance requires a combination of multiple approaches, including rational antibiotic management, enhanced infection prevention, and exploration of alternative therapies. These experiences are of decisive significance in preventing humanity from returning to the era before the emergence of antibiotics.

Keywords: Black Death, Antibiotic Resistance, Superbugs, Public Health History, Antimicrobial Stewardship

1. Introduction

Throughout history, bacterial infections have profoundly impacted human survival, social structures, and the development of medicine. The Black Death alone claimed the lives of approximately 25 million people in Europe between 1347 and 1351, dramatically reshaping demographic, economic, and cultural patterns of the time. Similarly, before the emergence of antibiotics, diseases such as cholera and tuberculosis caused multiple global crises, highlighting the limited capacity of early societies to control bacterial threats. The discovery of penicillin in 1928 and its large-scale production during World War II became a turning point in medicine, bringing unprecedented progress. The excessive and improper use of antibiotics has given rise to drug resistance, with pathogens such as methicillin-resistant Staphylococcus aureus (MRSA) and drug-resistant tuberculosis causing millions of deaths every year. This study traces the process from bacterial pandemics before the emergence of antibiotics to the current resistance crisis, emphasizing the lessons learned from history. The research relies on historical literature, reports from global health

© 2026 The Authors. This is an open access article distributed under the terms of the Creative Commons Attribution License 4.0 (https://creativecommons.org/licenses/by/4.0/).

DOI: 10.54254/2753-8818/2026.PJ29392

institutions, and contemporary scientific achievements to propose feasible strategies for addressing drug resistance. The core question is: what experiences can be gained from past pandemics and antibiotic development history to guide contemporary drug resistance policies and innovation? Mastering these experiences is crucial for maintaining antibiotic efficacy and safeguarding global health.

2. Historical bacterial pandemics

2.1. The Black Death: origins, transmission, and impact

The Black Death, which swept across Europe from 1347 to 1351, was one of the most devastating plagues in human history. The cause is Yersinia pestis, transmitted by fleas carried on black rats, spreading rapidly along trade networks that connected Asia, the Middle East, and Europe. It is estimated that about one-third of the European population died within four years, with a death toll approaching 25 million. Beyond its high mortality rates, the epidemic profoundly shaped social structures. The disintegration of serfdom, labor shortage, and peasant uprisings all followed the population shock. Religious life also underwent drastic changes, with many interpreting the epidemics as divine punishment, which led to intensified worship and triggered scapegoating attacks on Jewish communities.

The epidemic highlights the weakness of pre-modern medicine. Doctors relied on fluid theory, bloodletting, and herbal therapy, but these methods were ineffective. In 1377, Venice implemented the first systematic quarantine, reflecting an early recognition of infectivity despite the absence of microbial knowledge. The Black Death demonstrated the fragility of society without effective treatments and showed that epidemics could reshape economies, politics, and culture. This experience still has enlightening significance for today's era of antimicrobial resistance.

2.2. Cholera in the 19th century

In the 19th century, cholera became a global pandemic, spreading from the Indian subcontinent to Asia, Europe, and the Americas. Unlike the sudden outbreak of the Black Death, cholera recurred in six major waves between 1817 and 1923. Industrialization and poor sanitation conditions provided ideal conditions for transmission, making cities particularly vulnerable. The case of Havana is particularly typical, as the popularity in the 19th century influenced funeral customs, urban planning, and public health measures, revealing the social dimension of diseases [1].

The epidemic also drove significant changes in medical knowledge and public health. During the 1854 London outbreak, John Snow demonstrated the link between cholera and contaminated water, overturning the miasma theory and laying the foundation for modern epidemiology. Governments responded with large-scale investments in sewers, clean water supplies, and waste management, establishing public health as a state responsibility.

Medical treatment remained limited to fluid replacement and supportive care, and mortality rates in severe epidemics often exceeded 50%. Without effective therapeutics, prevention and sanitation were the only effective tools. Cholera revealed the limitations of 19th-century medicine and demonstrated the enormous potential of public health intervention. This experience is particularly enlightening for the current issue of antimicrobial resistance, where prevention and hygiene remain at the core beyond treatment.

DOI: 10.54254/2753-8818/2026.PJ29392

2.3. Tuberculosis in the pre-antibiotic era

Tuberculosis (TB) emerged as the leading killer of the 19th and early 20th centuries, earning the grim nickname “the White Plague.” Caused by Mycobacterium tuberculosis, the disease spread insidiously through respiratory droplets, flourishing in crowded industrial cities. At its peak, TB accounted for up to 25% of all deaths in Europe, devastating both working-class and middle-class families alike [2].

TB shaped not only medicine but also social and cultural life. Romantic literature of the 19th century often portrayed it as a disease of sensitivity and genius, further stigmatizing sufferers. Public health responses emphasized isolation in sanatoria, where patients were prescribed fresh air, rest, and nutritious diets. While some improved temporarily, these measures rarely cured the infection. For most, TB was a slow death sentence.

The discovery of the tubercle bacillus by Robert Koch in 1882 marked a milestone in bacteriology, but TB remained untreatable until 1944 with the arrival of streptomycin. Before antibiotics, TB exposed medicine’s helplessness against bacterial infections. Its cultural and epidemiological impact underscores the urgency of preserving antibiotic efficacy today, since multidrug-resistant TB once again threatens global health.

2.4. Public health measures before modern medicine

Before antibiotics, societies relied almost exclusively on preventive measures to manage bacterial epidemics. Quarantine was the most important innovation, first institutionalized in Venice in the 14th century in response to plague. Similar measures were later used in ports across the Mediterranean to limit contagion. In the 19th century, cholera outbreaks spurred the construction of modern sanitation systems, including London’s sewer network, which protected water supplies from contamination.

During TB epidemics, governments emphasized public health education, urging citizens not to spit in public and to observe better hygiene. Sanatoria represented an attempt at medicalized public health, separating infected individuals from the healthy population. These approaches highlight that before antibiotics, societies placed their hopes in prevention, sanitation, and social reform.

Military history also underscores this vulnerability. The Ottoman Third Army in 1915, for instance, suffered devastating infectious disease outbreaks during World War I, demonstrating how infections could cripple armies as effectively as combat [3]. These lessons remind people of the severe limitations of medicine before the antibiotic era.

3. The antibiotic revolution

3.1. The discovery of penicillin and its wartime impact

The modern era of antibiotics began with Fleming's discovery of penicillin in 1928, building upon Duchenne’s earlier but overlooked 1897 observation of fungi’s antibacterial potential [4]. The real turning point occurred during World War II, when British and American scientists developed large-scale production methods. Penicillin was widely used to treat sepsis and pneumonia on the battlefield, saving countless lives and demonstrating that bacterial infections were not invincible. This success also highlighted the potential of international cooperation, as scientific innovation combined with policy support to address global health threats.

DOI: 10.54254/2753-8818/2026.PJ29392

3.2. Expansion of antibiotic classes (1940s–1980s)

The 1940s to 1980s are often referred to as the "golden age" of antibiotics, during which multiple new classes of drugs emerged. After penicillin, streptomycin was discovered in 1944 and became the first effective treatment for tuberculosis. Subsequently, tetracycline, chloramphenicol, and erythromycin appeared, each with different mechanisms of action. Cephalosporins, aminoglycosides, and fluoroquinolones further expanded treatment options. These antibiotics target different bacterial pathways: β-lactams interfere with cell wall synthesis, aminoglycosides and tetracyclines inhibit protein synthesis, and fluoroquinolones block DNA replication. The diversification of mechanisms reduced reliance on a single drug and significantly expanded the scope of treatable infections [5].

Clinically, this led to an unprecedented decline in mortality from pneumonia, sepsis, and surgical infections, which had once been fatal. However, early signs of resistance emerged, as antibiotics were frequently prescribed and often misused, laying the groundwork for future resistance crises.

3.3. Transformation of medical practice

The medical revolution brought about by antibiotics extended far beyond infectious disease treatment. In surgery, antibiotics significantly reduce postoperative infection risks, enabling complex and invasive operations. Cancer chemotherapy and organ transplantation also became feasible, as opportunistic infections in immunocompromised patients could be effectively managed.

On the public health front, antibiotics changed social expectations: infectious diseases, once seen as unavoidable, were gradually recognized as solvable. Yet, the increasing dependence of medicine on antibiotics also made modern medicine vulnerable, as antimicrobial resistance threatens not only infection control but also the foundation of the entire advanced medical system.

4. The rise of antimicrobial resistance

4.1. Early signs of resistance in the 1940s

The success of penicillin in the 1940s was quickly weakened by bacterial adaptability. In 1942, clinical cases of drug-resistant Staphylococcus aureus appeared, shaking the optimism that antibiotics could permanently defeat infectious diseases. Resistance arises through spontaneous mutations or horizontal gene transfer. For penicillin, bacteria produce β-lactase, which can break down the β-lactam ring of drugs, rendering them inactive [6]. Streptomycin, the first effective drug against tuberculosis, also faced resistance within a few years of clinical use, often forcing doctors to adopt combination therapies. These early experiences showed that resistance was not an anomaly but an inevitable result of antibiotic exposure.

Beyond hospitals, the postwar expansion of antibiotics into antibiotics into agriculture accelerated the spread of resistance genes. The routine use of antibiotics in animal husbandry to promote growth is a notable example, foreshadowing the wide prevalence of drug-resistant infections in later decades.

4.2. Mechanisms of resistance

Bacteria employ various biochemical and genetic strategies to evade antibiotics, including enzymatic drug degradation, modification of drug targets, decreased cell permeability, and active efflux. β-lactase degradation is one of the most important clinical mechanisms. Equally critical are

DOI: 10.54254/2753-8818/2026.PJ29392

alterations in binding sites: under macrolides or aminoglycosides, ribosomal modifications prevent antibiotics from inhibiting protein synthesis [7].

Horizontal gene transfer via plasmids, transposons, and integrons promotes the flow of resistance genes across species. Multidrug resistance often results when a single strain accumulates multiple mechanisms. Carbapenem-resistant Escherichia coli is a typical example, as they possess carbapenemase, efflux pumps, and porin mutations simultaneously, making clinical treatment almost impossible. These mechanisms highlight the evolutionary nature of bacteria, making antimicrobial resistance a systemic threat across all pathogens and treatment contexts.

4.3. Global epidemiology of AMR today

By the early 21st century, antimicrobial resistance (AMR) had developed into a global crisis. The World Health Organization estimates that at least 1.27 million people die directly from drug-resistant infections each year, with many more deaths indirectly linked. Multidrug-resistant tuberculosis remains the main killer, and methicillin-resistant Staphylococcus aureus continues to cause severe hospital infections. The emergence of carbapenem-resistant Escherichia coli is particularly concerning, as carbapenem has long been regarded as the last life-saving drug.

The burden of AMR falls disproportionately on low- and middle-income countries. Their resources in new antibiotics, diagnostic capabilities, and infection control systems are limited. Globalization has intensified the crisis, and drug-resistant pathogens rely on travel, trade, and food supply chains to spread across borders. Beyond health outcomes, AMR poses a serious economic threat. More than 60,000 annual deaths are attributed to AMR in Europe and the United States, and projections suggest up to 10 million global deaths by 2050 if current trends persist [9]. AMR is thus not only a biomedical problem but also a challenge for global development and security. Epidemiological evidence highlights the need for urgent, coordinated action to prevent a return to pre-antibiotic vulnerability.

5. Historical lessons for controlling AMR

5.1. Parallels between pre- and post-antibiotic threats

The Black Death, cholera, and tuberculosis all demonstrated the devastating effects of uncontrolled bacterial infections. The plague of the 14th century destroyed Europe, and cholera in the 19th century paralyzed rapidly expanding cities. Both relied on prevention due to the lack of curative therapies. The rise of multidrug-resistant pathogens poses a similar threat to modern healthcare. The parallel lies in the sense of powerlessness: in the past, people relied on isolation and hygiene measures, and today, if antibiotics fail, clinicians may once again be forced to rely on non-therapeutic methods. Recognizing this similarity indicates that antimicrobial resistance is not unprecedented but rather a part of the long-term struggle between humans and microorganisms.

5.2. The importance of early intervention and prevention

History reminds us that quick and decisive intervention has significant value. The evidence of cholera in London suggests that delayed health reforms worsened cholera outbreaks, while early water safety measures reduced mortality. The isolation of tuberculosis patients in sanatoria also reflected a preventive logic, even without a cure. The lesson today is clear: establishing comprehensive surveillance to detect resistant pathogens early can prevent uncontrolled spread. For example, rapid identification of carbapenem-resistant Escherichia coli in hospitals and immediate

DOI: 10.54254/2753-8818/2026.PJ29392

infection control could contain transmission. These cases highlight the enduring significance of early prevention and containment.

5.3. Public health education and policy lessons

Education has consistently shaped epidemic outcomes. In tuberculosis prevention, campaigns against public spitting reduced transmission risk, while cholera prompted governments to promote hygiene and cleanliness awareness. These examples show that changes in public behavior have the same impact as medical innovation. In the AMR era, educating the public to avoid unnecessary antibiotic use plays a similar role. The policy framework is equally crucial. In the 19th century, governments of various countries legislated to ensure hygiene and water safety, while current governments must regulate the use of antibiotics in agriculture and implement drug management in clinical practice. When there is a lack of effective policies, social behavior often tends to prioritize short-term convenience over long-term protection.

5.4. Global cooperation as a historical warning

History reveals that infectious diseases have always transcended national borders. From Venice's quarantine measures to the 19th-century international Cholera Conferences and the wartime cooperation in mass penicillin production, the importance of cooperation has been evident. In today's globalized world, drug-resistant pathogens spread even faster through travel, trade, and food supply chains, making unilateral policies ineffective. Combating AMR requires coordinated international collaboration: WHO action plans, cross-border research funding support, and a global monitoring network. History also shows that the crisis of drug resistance cannot be addressed solely by science. In the past, society needed to combine prevention, education, and cooperation in epidemic prevention, while the current response must integrate biomedical, social, and political strategies. The past is not a distant relic but a mirror reflecting the urgency of current actions.

6. Strategies to combat antimicrobial resistance

Antibiotic stewardship programs seek to optimize the use of antibiotics and preserve their effectiveness. Evidence shows that inappropriate prescribing is a major driver of resistance: for example, up to 30% of outpatient antibiotic prescriptions in the United States are unnecessary. Stewardship includes strict prescribing guidelines, rapid diagnostics to distinguish bacterial from viral infections, and hospital-based monitoring of resistance trends. Lessons from streptomycin-treated tuberculosis patients show that monotherapy accelerates resistance; thus, combination therapy is required for chronic infections; therefore, combination therapy is required for chronic infections.

Prevention has always been a cornerstone of public health, from plague quarantines to cholera sanitation. In the AMR era, hospital infection control plays a critical role. Strategies include rigorous hand hygiene, sterilization of equipment, isolation of resistant cases, and vaccination programs to reduce bacterial circulation. In low- and middle-income countries, investments in clean water and sanitation remain essential, since poor infrastructure amplifies both infection rates and resistance transmission. These approaches highlight a historical lesson: when treatments fail, prevention saves lives [8].

Antimicrobial resistance is not only a political and economic issue but also a biomedical challenge. Policies need to regulate antibiotic use in agriculture, where misuse contributes

DOI: 10.54254/2753-8818/2026.PJ29392

significantly to resistance. The pharmaceutical industry requires economic incentives, as limited profits from antibiotic research and development compared to chronic disease drugs result in insufficient investment. Global frameworks, such as the World Health Organization's Global Action Plan, propose monitoring, education, and research cooperation, but the level of implementation varies. Fair access is equally crucial, as low-income countries need effective antibiotics and participation in global norms of drug use and management. Lack of inclusive policies will only exacerbate inequality, leading to inadequate treatment and promoting the continued spread of drug resistance [9].

7. Conclusion

The historical trajectory from the Black Death to the current crisis of antimicrobial resistance highlights the cyclical nature of the struggle between humans and bacteria. Plague, cholera, and tuberculosis exposed the catastrophic consequences of uncontrolled infections before the emergence of antibiotics, revealing the irreplaceable value of effective treatments. The discovery of antibiotics in the 20th century brought a turning point, making previously fatal infections treatable and enabling advances in surgery, oncology, and transplant medicine. However, the rapid emergence and global spread of drug resistance indicate that without careful management and long-term planning, scientific achievements are easily eroded.

History provides clear insights for addressing current crises. Early and coordinated intervention is crucial in preventing local epidemics from evolving into global threats. Public health education is also significant. From tuberculosis prevention campaigns in the 19th century to contemporary initiatives aimed at reducing antibiotic abuse, evidence shows that behavior change can reduce transmission and drug resistance pressures. Innovation must also be seen as a continuous process. The antibiotic revolution of the 20th century reshaped modern medicine, and in the 21st century, sustained investment in alternative therapies, diagnostic tools, and infection prevention strategies is essential to preserve these gains.

Without decisive action, humanity may enter a “post-antibiotic era,” where minor injuries or routine surgeries once again threaten life. The existing global health framework, such as the initiatives of the World Health Organization and the action plans of various countries, provides a foundation but requires further strengthening. Policy design should draw on historical experience while integrating modern scientific research to build sustainable solutions. Future research should combine historical epidemiology with contemporary models of drug resistance evolution to provide predictive insights and help prevent large-scale crises. Only by learning from the past and taking decisive action in the present can humanity safeguard the future of medicine.

References

[1] Wade, B.M. (2022) Death in the time of cholera: pandemics, public health, and burial in 19th-century Havana, Mortality, 27(4): 395–409. doi: 10.1080/13576275.2022.2141419.
[2] Chakraborty, A., Jayawickrama, J., & Zhang, Y. A. (2025). A Brief Social History of Tuberculosis: Key Challenges to Global Health (p. 110). Taylor & Francis.
[3] Erdem, H. et al. (2011) War and infection in the pre-antibiotic era: The Third Ottoman Army in 1915, Scandinavian Journal of Infectious Diseases, 43(9): 690–695. doi: 10.3109/00365548.2011.577801.
[4] Abarzúa, C.G.O. (2024) About Ernest Duchesne and the discovery of penicillin, Revista Chilena de Infectologia, 41(6): 772-776–776. doi: 10.4067/s0716-10182024000600165.
[5] Aminov, R.I. (2010) A brief history of the antibiotic era: lessons learned and challenges for the future, Frontiers in Microbiology, 1. doi: 10.3389/fmicb.2010.00134.

DOI: 10.54254/2753-8818/2026.PJ29392

[6] Coates, A.R.M. (ed.) (2012) Antibiotic Resistance. 1st ed. 2012. Springer Berlin Heidelberg (Handbook of Experimental Pharmacology: 211). Available at: https: //search.ebscohost.com/login.aspx?direct=true& db=cat01010a& AN=xjtlu.0001529506& site=eds-live& scope=site (Accessed: 30 August 2025).
[7] Džidić, S., Šušković, J. and Kos, B. (2008) Antibiotic Resistance Mechanisms in Bacteria: Biochemical and Genetic Aspects, Food Technology & Biotechnology, 46(1): 11–21.
[8] Capuozzo, M. et al. (2024) Optimizing Antibiotic Use: Addressing Resistance Through Effective Strategies and Health Policies, Antibiotics (2079-6382), 13(12): 1112. doi: 10.3390/antibiotics13121112.
[9] Rabi, M. (2024) The global (health) governance of antimicrobial resistance, Globalizations, 21(8): 1518–1538. doi: 10.1080/14747731.2024.2375455.