PRESS RELEASE

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NUS Medicine study: Breaking antibiotic-resistant bacteria’s protective shields opens door for immune system response, offers insights for managing pneumococcal diseases

Singapore, 24 March 2025 – Antibiotic-resistant bacteria is a serious public health threat. Understanding the biology of these bacteria—such as how they synthesise their protective capsules—is essential for developing new strategies to counter antibiotic resistance.

Streptococcus pneumoniae is a bacterium commonly found in the upper respiratory tract of humans. While it can exist harmlessly in some individuals, it is also a major pathogen responsible for severe illnesses, particularly in young children, the elderly, and people with weakened immune systems. Diseases caused by this bacterium, such as pneumonia and meningitis, are life-threatening. The bacterium’s ability to evade the immune system and cause disease is largely due to its capsule, which serves as a protective shield. As a result, this capsule is a primary target for vaccine development.

Researchers at the Yong Loo Lin School of Medicine, National University of Singapore (NUS Medicine), have made progress in uncovering how *Streptococcus pneumoniae* constructs its capsule. Their findings reveal that the adaptability of both the capsules and their transport mechanisms may play a crucial role in the bacteria's ability to evolve and diversify, offering insights for managing pneumococcal diseases.

Cellular transporters

The results of their study, published in *Science Advances*, focus on these capsule transporters in this process. These transporters, which belong to the Multidrug/Oligosaccharidyl-lipid/Polysaccharide (MOP) transporter family, help move sugar building blocks from inside the bacteria to the surface, where the capsule is formed. The capsule acts like a shield, protecting the bacteria from the body's immune system. By blocking key immune defences—such as clearing bacteria from the airways or marking them for destruction—the capsule enables the bacteria to survive, multiply, and spread within the body. In addition, the ability to build a capsule that transports a wide range of sugar building blocks has potential applications in glycoengineering, a field that aims to modify sugar structures for various purposes, such as developing new drugs or improving the properties of biomaterials.

The study's lead researcher, Assistant Professor Chris Sham Lok-To, from the Infectious Diseases Translational Research Programme (TRP) and Department of Microbiology and

Immunology, NUS Medicine, highlighted the importance of understanding capsule synthesis for combating pneumococcal infections, “The capsule is critical for pneumococcus to cause disease. By examining how capsule transporters choose their substrates, we hope to open new avenues for research in bacterial evolution, antibiotic resistance, and vaccine development."

Three categories of transporters identified

The researchers developed a large-scale method to study how bacteria transport sugars to build their protective capsules. They tested more than 6,000 combinations of transporters and sugar building blocks by inserting 80 different transporter genes into 79 strains of *Streptococcus pneumoniae*. Asst Prof Chris added, “Each transporter was marked with a unique genetic code (i.e., DNA barcode) for tracking. We then deleted the original transporter in each strain, creating a survival test: only bacteria with a functional replacement transporter could live. By analysing the barcodes of the surviving bacteria, we identified which transporters successfully carried the necessary sugars for capsule formation.”

The study found that transporters could be grouped into three categories based on how selective they were. The first group, strictly specific transporters, only worked with their original sugar building blocks. This ensures accuracy but limits flexibility. The second group, type-specific transporters, could handle sugars with certain common features, like specific chemical structures. These transporters could substitute for others within related capsule types but not beyond that. The third group, relaxed specificity transporters, could handle a variety of different sugars.

Dr Chua Wan Zhen, first author of the study, who is from the Infectious Diseases TRP and Department of Microbiology and Immunology, NUS Medicine, added, “However, this flexibility may sometimes cause problems by transporting incomplete or incorrect sugars, which disrupts bacterial growth. Transporters with relaxed specificity can cause issues because once they move incomplete building blocks across the cell membrane, there are no known mechanisms for the bacteria to send them back.” These unfinished precursors build up and interfere with important processes like cell wall construction, leading to stunted growth or even cell death. This explains why most bacteria have evolved to keep their transporters highly selective, despite the potential benefits of being able to transport a wider variety of sugars.

Key findings indicate that subtle modifications in transporter genes can alter specificity, potentially impacting bacterial adaptability and virulence. Understanding this process can help scientists develop new strategies for treating bacterial infections and explore ways to use these transport systems for engineering beneficial sugar-based materials.

Future research will focus on identifying specific amino acid residues responsible for transporter-substrate interactions and engineering transporters with optimised specificity for potential industrial and healthcare applications.

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Our multidisciplinary and real-world approach to education, research and entrepreneurship enables us to work closely with industry, governments, and academia to address crucial and complex issues relevant to Asia and the world. Researchers in our faculties, research centres of excellence, corporate labs and more than 30 university-level research institutes focus on themes that include energy; environmental and urban sustainability; treatment and prevention of diseases; active ageing; advanced materials; risk management and resilience of financial systems; Asian studies; and Smart Nation capabilities such as artificial intelligence, data science, operations research, and cybersecurity.

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About the NUS Yong Loo Lin School of Medicine (NUS Medicine)

The NUS Yong Loo Lin School of Medicine is Singapore's first and largest medical school. Our enduring mission centres on nurturing highly competent, values-driven, and inspired healthcare professionals to transform the practice of medicine and improve health around the world.

Through a dynamic and future-oriented five-year curriculum that is inter-disciplinary and inter-professional in nature, our students undergo a holistic learning experience that exposes them to multiple facets of healthcare and prepares them to become visionary leaders and compassionate doctors and nurses of tomorrow. Since the School's founding in 1905, more than 12,000 graduates have passed through our doors.

In our pursuit of health for all, our strategic research programmes focus on innovative, cutting-edge biomedical research with collaborators around the world to deliver high impact solutions to benefit human lives.

The School is the oldest institution of higher learning in the National University of Singapore and a founding institutional member of the National University Health System. It is one of the leading medical schools in Asia and ranks among the best in the world (Times Higher Education World University Rankings 2025 by subject and the Quacquarelli Symonds (QS) World University Rankings by subject 2024).

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About the National Medical Research Council (NMRC)

The NMRC was established in 1994 to oversee research funding from the Ministry of Health and support the development and advancement of biomedical research in Singapore, particularly in the public healthcare clusters and medical schools. NMRC engages in research strategy and planning, provides funding to support competitive research grants and core research enablers, and is responsible for the development of clinician scientists through awards and fellowships. The council's work is supported by the NMRC Office which is part of MOH Holdings Pte Ltd. Through its management of the various funding initiatives, NMRC promotes healthcare research in Singapore, for better health and economic outcomes.