What first sparked your interest in enteric infections?

I was lucky enough to conduct research at the Sanger Centre in Cambridge, UK, during the early days of the genomics era. During this period, I worked on a multitude of projects, but I remember taking a huge interest in typhoid fever relatively quickly. I think this was because of its place in history alongside diseases like the plague and cholera; it is the type of infection that most people think disappeared many years ago and tends to be associated with Dickensian times. It is this which attracted me to trying to improve our understanding of such a complex and widespread disease.

You are currently head of the enteric infections research group based at the Wellcome Trust Major Overseas Programme (WT-MOP) in Vietnam. Could you briefly summarise the overarching goals of this team?

As part of the Programme, we have received considerable support from the Wellcome Trust since it was established in 1991. The WT-MOP incorporates a wide range of research themes, including immunology, host and pathogen genetics, molecular biology, virology, mathematical modelling, bioinformatics, biostatistics and epidemiology, but focuses on clinical questions and samples. We wish to add clinical insight into the infections we work on, focusing on improving patient care, international guidelines, disease treatment and prevention.

In your opinion, what needs to be done to make genome sequences more useful in public health?

Basic science and public health need to be more aligned, and basic science needs to address specific public health issues. Communication is critical and this needs to trickle down through funding organisations as well as policy-making decisions. The will and the science are both there, but integration is currently lacking and needs more attention. Typhoid is a great example; current licenced vaccines do not give long-term protective immunity and diagnostics are unspecific and lack sensitivity. We and other groups are using the *Salmonella enterica* serovar Typhi genome to develop new approaches to treatment, diagnosis and vaccination.

Given the significant threat posed by antibiotic resistance, what research do you have underway to combat bacterial infections?

Prevention is better than cure! We have several projects where we are aiming to develop better ways of controlling disease. In *Shigella*, we are looking for new vaccine targets by using a range of antigens to probe the immune response during early infection.

In typhoid, and generically to prevent other enteric infections, we are looking at introducing household low-maintenance water filters to prevent people drinking contaminated water. The international community could do more to eliminate bacterial infections usually caused by poor sanitation and unclean water supplies in low- and middle-income countries. Whilst it is not an easy target, more could be done to reduce these risks. I would like to see more stringent regulations for water quality, and international aid and charities ensuring that more money is directed in establishing clean water supplies.

Do you collaborate with any other researchers or institutes? How is a multidisciplinary approach important to the future success of your research?

We work with many national and international researchers and institutions. We have ongoing projects with provincial hospitals in Vietnam, Nepal and other locations across Asia. Collaboration and multidisciplinary approaches are fundamental to the group’s research, so we work with other researchers in the UK, USA, Europe, Australia and Africa. At the moment, we rely on different collaborations in a range of institutions across the world for a number of techniques that we do not perform in Vietnam or Nepal. I hope that we can continue to develop the infrastructure and local capacity, in the form of well-trained scientists, to perform more technologically driven science that is specifically related to the diseases that are important in these locations.
ACCORDING TO THE World Health Organization (WHO), antimicrobial resistance threatens a global return to the pre-antibiotic era, with the risk of many infectious diseases becoming untreatable and uncontrollable. Without effective antimicrobials for care and prevention of infections, the success of life-saving treatments will be compromised. This potentially devastating situation threatens the health security of countries all over the world, and damages trade and economies. WHO states that whilst the emergence of new resistance mechanisms is a natural phenomenon, the misuse of antimicrobial medicines has rapidly accelerated this evolutionary process and is now making the latest generation of antibiotics virtually ineffective.

In this context, detailed studies into the ability of pathogens to survive exposure to a wide array of antibiotics and the consequent immune responses have been underway at the Oxford University Clinical Research Unit (OUCRU) through the Wellcome Trust Major Overseas Programme (WT-MOP) for a number of years now. In particular, this group has been looking at reduced susceptibility to fluoroquinolones, which lessen clinical efficacy, and are becoming far more pervasive.

EXPLORING TYPHOID

Dr Stephen Baker – Head of the enteric infections research group at the Unit, a Sir Henry Dale Fellow and a senior lecturer at the London School of Hygiene and Tropical Medicine – has been specifically focusing on understanding more about Salmonella enterica serovar Typhi; the bacterium that causes typhoid fever. His team has been studying the implications of using fluoroquinolones in typhoid patients who are infected with isolates of S. Typhi that have increasing resistance to fluoroquinolones.

Baker points out that typhoid continues to be a major issue in cities with poor sanitation and hygiene, and the problem is growing: “Typhoid remains a major public health concern as cities with poor infrastructure are increasing in size and organisms are developing resistance to antimicrobials. It is a disease that can be tackled, but the window of opportunity may be closing.”

GENOMIC SEQUENCING

Back in 2001, Baker was part of a team that successfully sequenced the genome of S. Typhi. This represented a significant step forward in understanding of the evolution, population dynamics, antimicrobial susceptibility and transmission of S. Typhi, as well as genomic comparison with other members of the Salmonella family. “In addition, we have been able to learn far more about the role of specific genes and gene islands in disease, gene regulation and expression, building public health capabilities

As antimicrobial resistance becomes an evermore pressing major global challenge, a team of scientists at the Oxford University Clinical Research Unit in Vietnam is developing novel tools to combat this growing healthcare crisis.
and how the immune system sees various cellular structures during early infection."

The ongoing research in Baker's group utilises a range of molecular, microbiological and immunological methods. One of the more innovative approaches currently being developed by the researchers will enable them to analyse the ways in which S. Typhi activates the immune response during early infection. They are also developing and validating new microbiological methods, which will help to isolate and study how the organism interacts within the environment.

Their latest investigation into S. Typhi revealed that epistasis, the action of one gene upon another, might be crucial in its evolution. Through this work, the researchers have learnt that antibiotic-resistant strains of S. Typhi can outcompete drug-sensitive strains when grown in the laboratory, even in the absence of antibiotics. They also found that drug-resistant isolates had the ability to outcompete their drug-sensitive parent strains. "This is important because the control of typhoid across Asia and Africa currently relies on treatment with fluoroquinolones but resistance is rising," explains Baker. "Withdrawing or restricting the use of this class of antibiotics is one approach to try and combat the spread of resistance." The results further indicate a need to develop better control strategies, as resistance to antibiotics is highly likely to persist and escalate, even if these kinds of strategies are implemented.

TACKLING SHIGELLA IN SOUTHEAST ASIA

The work underway at OUCRU also involves investigating the evolution and epidemiology of Shigella in Southeast Asia. Baker's team is keen to understand more about the way S. sonnei has rapidly emerged in industrialising countries by building a more robust knowledge base about disease distribution, incidence and exposure. "We also want to gather further information about the effect of uncontrolled antimicrobial usage on the international spread and dynamics of pathogens like Shigella," he adds. To do so, the team, in corroboration with the Wellcome Trust Sanger Institute, is using newly available high-throughput sequencing technology to study how the bacterial populations are changing and evolving in real time. Their work looking at strain evolution both globally and in Vietnam has uncovered some valuable insights into bacterial dysentery and its evolution and spread in the human population.

Baker explains that the four species of the Gram-negative bacterial genus Shigella (boydi, dysenteriae, flexneri and sonnei), are amongst the most common causes of dysenteric diarrhoea, with more than 164 million infections worldwide annually. Interestingly, there is a clear geographical variance between the species that are most prevalent: in developing countries it is S. flexneri, whereas in developed countries it is S. sonnei. More recent observations have indicated that S. sonnei is increasingly replacing S. flexneri as the primary agent of dysentery in many countries, often depending upon a country's economic status. "Our work in Ho Chi Minh City, Vietnam, has reaffirmed this association, demonstrating a transition from S. flexneri to S. sonnei over the past 15 years," Baker reveals. "Now more than 99 per cent of Shigella infections in this city are S. sonnei, making it the principal bacterial agent of hospitalised diarrhoea." Patients appearing at hospitals with such aggressive infections will generally need antimicrobial treatments, but there is increasing resistance to available medications and, as a result, their efficacy is rapidly decreasing.

MULTIDRUG RESISTANCE

One of the most significant findings is that a key factor in the spread of S. sonnei has been a rise in multidrug resistance. "Because S. sonnei is easily transmitted and has high levels of drug resistance, we suggested that drug treatment alone would not be sufficient for controlling the disease," recalls Baker. "Vaccine development is therefore crucial for disease control in the mid to long-term."

Their investigations looking at the pathogen in Vietnam highlighted four genetic bottlenecks where mutations in S. sonnei developed in a small subset of strains and rapidly became common. Baker’s team has been able to link these genetic bottlenecks to the development of different resistances to common oral antibiotics: "Because each of the bottlenecks coincided with increased infection rates, we argued that these events helped to confer antimicrobial resistance or some other competitive advantage on S. sonnei."

The increasing challenge for the healthcare industry is to take a global approach to the rising crisis of antimicrobial resistance, and Baker's work is instrumental in linking understanding about the ways that new antimicrobial-resistant strains of pathogens establish and how novel medicines can be developed to combat this evolution.

INTERRINGENCE

ENTERIC INFECTIONS RESEARCH AT OXFORD UNIVERSITY CLINICAL RESEARCH UNIT, HO CHI MINH CITY, VIETNAM

OBJECTIVES

To add clinical insights into typhoid fever and Shigella, focusing on improving patient care, international guidelines, disease treatment and prevention.

KEY PARTNERS

The Hospital for Tropical Diseases, Ho Chi Minh City, Vietnam • Patan Hospital, Kathmandu, Nepal • Wellcome Trust Sanger Institute, Hinxton, Cambridge, UK • Armed Forces Research Institute of Medical Sciences (AFRIMS), Bangkok, Thailand • University of Melbourne, Australia • University of Cambridge, UK • University of Oxford, UK • London School of Hygiene and Tropical Medicine, UK • Novartis Vaccines for Global Health (NVGH), Siena, Italy • University of California Irvine, USA

FUNDING

Wellcome Trust, UK • The Royal Society, UK • Li Ka Shing Foundation, China • Bill & Melinda Gates Foundation

CONTACT

Dr Stephen Baker
Head of enteric infections
The Hospital for Tropical Diseases
Oxford University Clinical Research Unit
764 Vo Van Kiet
Quan 5
Ho Chi Minh City
Vietnam
T +84 839 237 954
E sbaker@oucru.org
www.ndm.ox.ac.uk/principal-investigators/researcher/stephen-baker

DR STEPHEN BAKER is Head of the enteric infections research group and a member of the faculty and strategic committee at the Wellcome Trust Major Overseas Programme, Oxford University Clinical Research Unit, Ho Chi Minh City, Vietnam. Currently, he holds a research lecturer’s position at the University of Oxford and a senior lecturer’s position at the London School of Hygiene and Tropical Medicine, UK. As group head, Baker is responsible for the structure, publications, funding, scientific direction and general management of enteric infections research. Prior to this, he received a PhD from Imperial College London in 2005, investigating the genome diversity in Salmonella, and undertook postdoctoral training at the Wellcome Trust Sanger Institute in Cambridge, UK, until 2007.