BIOSCIENTIST
The Salford Biomedicine Society Magazine

Salford Scientist's Research on Antimicrobial Resistance in *Klebsiella pneumoniae* in Gaza

Dr Joe Latimer In Conversation with Wiktoria Wisniewska

Abstract

We all know that antimicrobial resistance (AMR) is a huge, and very worrying problem. What we might not all be so aware of is that AMR, like too many other awful things in our world, disproportionately affects the world's poorest and most vulnerable people. Dr Latimer works with collaborators around the world to explore how and why the bacteria in resource-poor counties resist antibiotics and what we might be able to do about it.

Currently, Dr Latimer's group is investigating the sensitivity of clinical isolates of *K. pneumoniae* to important antibiotics, and how well-adapted they are to cause severe disease. The results so far are not good – they are resistant to multiple classes of antibiotic. *K. pneumoniae* can cause severe disease such as pneumonia, wound infections, and septicaemia, and is on the WHO priority watchlist of pathogens. The isolates that Dr Latimer is working with were collected from patients from six hospitals throughout Gaza. These strains are now likely spreading within the population, particularly since so many people are displaced, injured and/or suffering from lack of water and food. Medical capacity, of course, is also severely limited, and only one of the six hospitals still stands.

This interview will shed light on this ongoing research and its wider contextual impact on antimicrobial resistance.

Could you tell me about your academic background and what interested you in microbial resistance?

I completed my undergraduate degree in Biological Sciences at Lancaster University, where in my final year I specialised in microbiology and physiology under the supervision of Dr Jackie Parry who got me interested in the microbiology of biofilms. This was when I realised that I need to follow a career in microbiology. So, after travelling for a year, I did my masters in medical and molecular microbiology in the University of Manchester which focused on the diversity of bacteria that cause disease, how they adapt to their environments and how to identify them. My PhD was at the University of Sheffield under Professor Robert Poole, looking at the fundamental nature of biofilms, using a technique called transcriptomics. I then worked in rural Malawi, teaching science, and helping to develop their biomedical science provision. After returning to the UK, I worked for a spin-off company, NeuTec Pharma, developing their antibody therapies for *Clostridium difficile*. Then I went back into academia and worked as a postdoc in oral microbiology focussing on dental plaque. During these five years, I became interested in how microbes interact with human hosts. A senior postdoctoral position came up in Manchester investigating host-microbe interactions in human skin. As the year progressed, I felt that it was time to pursue a lectureship and was encouraged by my boss Dr Cath O'Neill to pursue an independent research career' Here I decided to go down the lectureship route because as much as I love research, I also really enjoy teaching. After securing an interview for a lectureship at Salford, I vividly remember feeling like I would fit in with the team there.

DOI: https://doi.org/10.57898/biosci.193

I have been interested in AMR in resource poor countries for a while. To set the scene, in the UK we have good routine microbiology hospitals reference labs where we can easily track infection and resistance rates. As soon as you start getting to countries with lower incomes, this starts to fall apart, and the central focus becomes treatment rather than surveillance or research. When I was working in Malawi, I was interviewing doctors about the guidelines for prescribing antibiotics for conditions like tuberculosis, malaria, or UTIs, and the most common story was 'if we even have any antibiotics in, we use them.' That is quite a shocking state of affairs because not only can they not keep track of resistance rates, but it is also impossible for them to follow treatment guidelines. The upshot of this is that even in in resource poor countries, even when politically stable, it is difficult to know what is going on. When you add occupation and displacement of dense populations caused by war, it makes the situation even more difficult. I am collaborating with Dr Nabil El Aila, a microbiology professor at Al-Aqsa University in Gaza City, who devotes most of his research to trying to track what is going on. He is particularly worried about the extended spectrum beta lactamases in bacteria. Before the current war, we were conversing about *Klebsiella pneumoniae* which is a Gram-negative pathogen from WHO priority watchlist and how prolific it is. Over a course of a couple months, he took samples from six hospitals and managed to get them over to Salford where we have started to characterise them. The professor came here for a few months for a visit and arrived back at Gaza two days before the war started. He was able to escape to Belgium just before Christmas and because of that we can maintain contact and push this research forward.

Figure 1: Photo of Nabil and his family after escaping from Gaza to Belgium – Jan 2024.

Who is involved in the project and what is the main aim of this research?

Dr Nabil El Aila also has close connections with a group in Paris from South Paris University Hospital. While Dr Nabil is the linchpin of the entire investigation, Dr Tierry Naas and his group provide experience, particularly in the genomic side of things while our work focuses on the phenotypic side. One of our previously undergraduate HBID student Ruby Naylor-Adamson has been working on strengthening our understanding of *Klebsiella* biofilms and its ability to resist antibiotics. The main aim of the investigation as it currently stands is to provide enough information on the infectious pathogens in Gaza. The priority is to obtain a detailed picture of antibiotic susceptibility and share this with organisations such as UN, MSF, Red Cross charities to help them guide operations to treat these infections. I am a strong believer in multidisciplinary team effort and as this project expands, we are going to need to collaborate with experts in environmental sciences to assess what is happening with these bacteria and its resistance in long term and how it relates to air quality for example, to make the impact of the study even more clinically relevant.

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Why is *Klebsiella pneumoniae* the focus of the study?

Klebsiella penumoniae is on the WHO pathogen watchlist alongside *Enterobacteriaceae, P. aeruginosa, Staphylococcus aureus,* etc., addressing great threat to human health. The current literature indicates that *Klebsiella* is starting to overtake these in terms of importance and virulence. The main phenotypes of *Klebsiella* that we find are hyper mucoid or normally virulent and this will be something that we will investigate too. We have 126 isolates as well as samples' origin information and clinical presentation of the patient. These data will help us correlate the clinical results, the infection site, as well as the susceptibility. We understand this may shift slightly once we obtain the genomics work details, but the samples represent a snapshot of demographics and origins.

In developed countries such as the UK, our surveillance would be able to pick this up, however, in resource poor countries, this may not be the case. At some point, we would like to do a similar multicentre study focusing on the situation in different parts of the world to compare the findings. When conducting these studies, it is always important to take into account that the situations in cities is not the same as it is for the majority of the populations that live in rural environments. Interestingly, our academics Prof Chloe James and Prof Richard Birtles are doing work in Uganda where they do not only focus on the capital Kampala but the situation in the rural areas too. When it will become possible, we may consider clinical samples to track the transmission and resistance rates further.

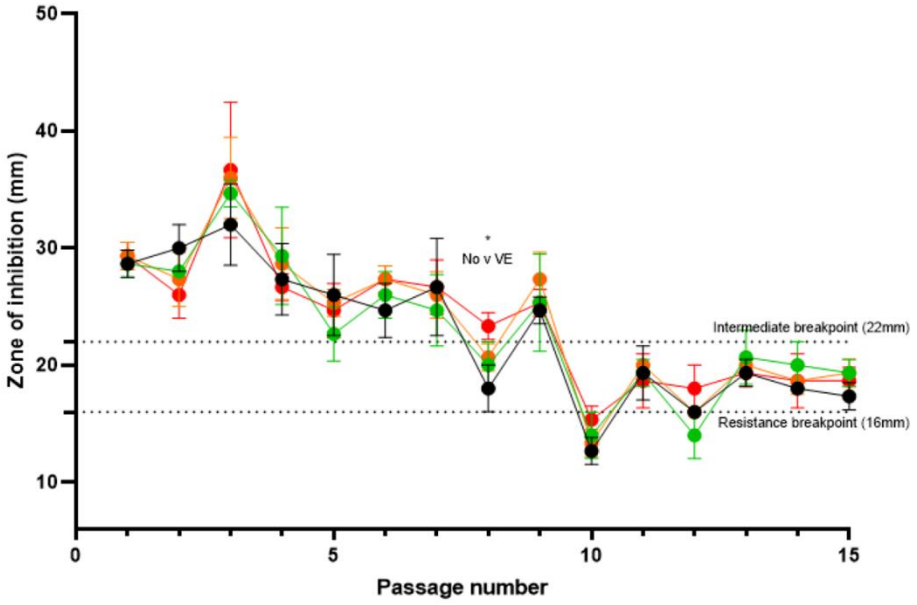

Figure 2: Previous work from Dr Latimer's lab has shown that K. pneumoniae adapts very quickly to last-line antibiotics, becoming resistant after just 10 exposures. This work was done by a previous PhD student, Alex Thompsett in 2019[1].

What were the main challenges in transporting the isolates?

It was horribly difficult. Nabil was able to bring the clinical isolates from Gaza into Egypt and obtained the paperwork and permissions to fly them from Cairo to Paris, which we thought would be the hardest bit. We then tried to get a courier to pick them up from Paris and bring it over here, however, even to organise that ended up being extremely difficult. When we finally got it sorted, the isolates were picked up from Paris and lost! At that point I got all the necessary permissions, settled all the paperwork, got a flight booked and had a very short 24-hour-long holiday to Paris to bring them back!

What about the technical aspects of the experiment?

Genome sequencing will be done in collaboration with Dr Tierry Naas and his group with support of their national databases. We assess the biofilm and planktonic growth dynamics. We used the crystal violet

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method as confirmation which is useful for large scale screening. What we wanted to do that is not commonly done is to look at biofilm formation as relative to overall growth rate as we often see isolates being identified as strong biofilm producer, but it may be possible that this strain just tends to grow faster than the others. This is why we normalise our data with respect to overall growth rate. We will try to assess detailed biofilm growth on Mueller Hinton agar as well as more clinically relevant conditions too, for instance wound or urine medium. We will also aim to look at the concentration of a given antibiotic needed to inhibit or kill the bacteria in both biofilm (via disc diffusion) and planktonic cells. We are also interested in looking at microfluidics and examine the biofilm formation in this environment. We use a wide range of antibiotic classes such as penicillins, tetracyclines, fluoroquinolones, and many more, and we are looking forward to assessing any interesting synergies between their effects.

Are there any more notable interesting methods that will be employed as a part of this study?

We are also very keen to investigate virulence, so we will assay the strains for their ability to produce specific bacterial virulence factors. We will also use an invertebrate virulence model to evaluate and compare overall pathogenicity. This model, which employs waxmoth larvae, is fantastic because it allows us to assess virulence in the presence of host factors. We will also examine whether antibiotic susceptibility varies when the bacteria are in a host environment. There is a lot of work to do, and we are looking forward to taking on more postgraduate research students to continue this research.

Are there any reliability concerns?

As scientists we always need to be careful with our research. As your research experience develops, you become more confident in your ability to ask the right questions. You also tend to become more critical and get better at experimental design with relevant controls and consideration for statistical significance. There are always different test conditions to think about like why was this result anomalous, will it work in a different pH or anaerobically, why is it producing an unexpected pigment, why did the colony morphologies change? These are the things we would consider. The 15 antibiotics that we selected first are based on the EUCAST guidelines from which the data analysis will be based on. To avoid a completely Eurocentric point of view, we will also consider guidelines from other parts of the world to judge the results through different worldview perspectives.

Can this research contribute to the understanding of disease transmission and outbreaks?

As of now, it is impossible to say. No one is allowed in or out of Gaza, so we simply do not know. It is frustrating, it is upsetting, because we would love to look at the geospatial aspect of the problem. Most of the northern Gaza has been demolished with a million people displaced and having to move multiple times. This mass movement and hospital breakdowns make it impossible to control the situation and I am not sure what levels of aid are currently allowed in. Once we can get clinicians and researchers in, we might be able to start building up a picture again, however, I cannot say with confidence that it will be anytime soon. The opportunities to implement this research into public health depends on how the situation develops and if we continue to receive the funding to expand the study. Potentially we may be able to trace infectious diseases as the country begins to rebuild itself. It is always a challenge to find funding, however, we are hoping that once we have published a review explaining what the situation looked like up until the start of the war, this would encourage the readers to engage and then the first and the second paper on the work will start a critical mass thinking and hopefully contribute to the outreach and expansion of the investigation.

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Lastly, is there anything we can do to raise awareness about microbial resistance?

I think the best thing that we can do as scientists is communicate the problem to family, friends, the public, and say it in a way that people will understand. We are much better now at sharing resources and teaching the basics. Antibiotics are absolutely wonderful, and we need to keep them for as long as we can. If you take antibiotics unnecessarily, it increases the chances that when you are 80 years old and get pneumonia, there is nothing to treat the infection with. We are already starting to see strains of *Klebsiella* becoming resistant to certain classes of antibiotics. It is also worth reminding people that when we kill bacteria with antibiotics, we also kill an important part of our own bodies - our microbiome. Through overusing antibiotics or not completing the antibiotic course, the bacteria grow more tolerant to treatment hence become more resistant. Some people tend to use antibiotics for flu which are completely ineffective or using antibiotics from previous prescriptions without realising that different drugs work on different types of bacteria, never mind the variations in dosage and treatment times. Antibiotics will not treat any given infection. There is a finite number of antibiotics as of now with last one being discovered about 40 years ago, while bacteria are mutating all this time winning the arms race. Hopefully, as a society we will be more conscious of this issue. In the future, it is quite possible that we will introduce specific treatment methods that do not necessarily affect the microbiota such as phage therapy or anti-virulence drugs which do not kill the bacteria but stop them from going through an evolutionary pressure to develop resistance.

It is clear that antimicrobial resistance demands our urgent attention. We must recognise our role in this challenge, whether it is being mindful of antibiotic use, supporting research efforts, or advocating for social awareness, every action counts. Hopefully with continued collaboration, we can ensure a more vigilant and proactive approach to combat AMR.

Interested in the study? Dr Latimer is looking to take on a small group of postgraduate students to support this incredible research. If you would like to have a chat or express your interest in getting involved, feel free to reach out to Dr Latimer at j.latimer2@salford.ac.uk.

References

1. Tompsett, A., Ngoc, L. N., Goodhead, I., Withers, S., & Latimer, J. (2019). Towards a clinically relevant model for investigation of host-microbe interactions in ventilator-associated pneumonia. *Access Microbiology*, *1*(1A). https://doi.org/https://doi.org/10.1099/acmi.ac2019.po0422

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