Institution: Cardiff University

Unit of Assessment: UoA1

Title of case study: Identification of a novel drug resistance determinant resulting in global change of attitude and policy

1. Summary of the impact

Cardiff Researchers in 2009 discovered the new antibiotic resistance determinant NDM-1 and in 2010/11 characterised its rapid worldwide spread through Gram-negative bacteria (e.g. *Escherichia coli* and *Vibrio cholera*e). NDM-1 redefined how antibiotic resistance can spread locally and internationally and create new extensively-drug resistance (XDR) that severely limits therapeutic options. This discovery has resulted in: 1) new policies for the admission of overseas patients to hospitals in the UK, France, USA, Australia and China, 2) linkage between MDR transmission and poor sewerage treatment, 3) potable water treatment in Southern Asia 4) positioning papers for the World Health Assembly and 5) policy-changes by the World Health Organisation.

2. Underpinning research

The problem of antibiotic resistance is listed as the WHO's key concern for the 21st C – the increasing resistance to the most potent drugs and the lack of new antibiotics being developed is heralding in an era of untreatable infections. These sentiments have been recently echoed by CMO, Prof. Sally Davies. Bacterial enzymes that break down antibiotics such as penicillin are termed β-lactamases and a sub-group, termed carbapenemases break down the latest and most clinically useful group of these antibiotics, carbapenems. The most potent of these enzymes are metallo-β-lactamases (MBL) as there are no clinical inhibitors for these enzymes. In 2008, Timothy Walsh (Head of Microbiology Research, in post since 2006) and Mark Toleman (Research Fellow, in Cardiff since 2007 and now Senior Lecturer) discovered and characterised a novel MBL, called New Delhi Metallo-β-lactamase (NDM-1)[3.1] The hospitalised patient, a native Indian but Swedish resident, had just returned to Stockholm from New Delhi. Collaborative studies in India (Chennai and Haryana) initiated and funded by joint Welcome grant awarded to Walsh and Toleman indicated that the NDM-1 gene was present in approx. 8% of clinical bacterial isolates f in the South and 13% in the north of India. [3.2] NDM-1 is unique in structure, genetic context, clinical epidemiology, and has spread globally more rapidly than any other type of antibiotic resistance. [3.3, 3.4] In September 2010 Walsh collaborated with Channel 4 journalists who were making a documentary on the use of antibiotics in India and obtained water and out-flow seepage samples. This work showed that the Indian environment was significantly contaminated with NDM-1 positive bacteria. [3.5] The work on NDM-1 marked a seminal change in our global understanding of antibiotic resistance. The key findings of the work were:

1. NDM-1 was clearly widespread in the Southern Asian community as well as hospitals making this very different from other types of antibiotic resistance. [3.2,3.5]
2. Genetic context, structure and the aetiology of the NDM-1 gene is unique. [3.5]
3. The success of NDM-1 spreading through diverse bacterial species has been unparalleled in antibiotic resistance and related to their highly promiscuous plasmids. [3.5]
4. Transfer of these plasmids transforms sensitive bacterial strains into extreme drug resistant types only being sensitive to colistin and tigecycline. [3.2,3.5]
5. Global travel and in particular overseas surgery were a high-risk factor in presenting with NDM-1. [3.2,3.6]

All work initially carried out on NDM-1, and 90% of the molecular characterisation in the clinical epidemiology study was performed at Cardiff University. Walsh and Toleman were the first to report NDM-1 in key human pathogens such as *Shigella* spp. and *Vibrio cholerae* (1, 2). These findings have influenced infection control policies in UK hospitals for the isolation of NDM-1 positive pathogens as recently reported in the Lancet. [3.6] They are currently co-ordinating the

biggest clinical trial to date in Southern Asia (Karachi) (funded by Walsh's charitable foundation called **SAARRP**) to assess the clinical significance of NDM-1 positive bacteria. Preliminary data from this trial shows that 31% of patients admitted to public hospitals and 32% on discharge carry NDM-1 bacteria as gut flora. Toleman's work in Bangladesh has also found NDM in 60% of environmental water samples These data when extrapolated to the whole of Southern Asia would suggest that nearly 1 billion people could be carrying NDM-1 positive bacteria.

3. References to the research (indicative maximum of six references)

3.1 Yong, Y., **Toleman, M.A.**, Weeks, J., Giske, C., **Walsh, T.R**. (2009) Characterisation of a new metallo-β-lactamase gene, blaNDM-1, and a novel erythromycin esterase gene carried on a unique genetic structure in *Klebsiella pneumoniae* sequence Type 14 from India. *Antimicrob. Agents and Chemother.* 53, 5046-54. DOI: 10.1128/AAC.00774-09 (cited approx. 100 times).

3.2 Kumarasamy, K.K., **Toleman, M.A.**, **Walsh, T.R.**, I (2010). Emergence of a new antibiotic resistance mechanism in India, Pakistan, and the UK: a molecular, biological, and epidemiological study. *Lancet Infect Dis*. 10, 597-602. DOI: 10.1016/S1473-3099(10)70143-2 (cited >600 times).

3.3 Hammerum, A.M., **Toleman, M.A.**, Hansen, F., Kristensen, B., Lester, C.H., **Walsh, T.R.**, Fuursted, K. (2010). Global spread of New Delhi metallo-β-lactamase1.*Lancet Infect Dis*. 10, 829-30. DOI: 10.1016/S1473-3099(10)70276-0

3.4 **Toleman, M. A.**, Spencer, J., Jones, L., **Walsh, T.R**. (2012**).** *bla*$_{NDM-1}$ is a chimera likely constructed in *Acinetobacter baumannii*. *Antimicrob Agents Chemother*. 56, 2773-6. DOI: 10.1128/AAC.06297-11

3.5 **Walsh, T.R.**, Weeks, J., Livermore, D.M., **Toleman, M.A**. (2011). Dissemination of NDM-1 positive bacteria in the New Delhi environment and its implications for human health: an environmental point prevalence study. *Lancet Infect Dis.* 11, 355-62. DOI: 10.1016/S1473-3099(11)70059-7 (cited >130 times)

3.6 Darley, E., Jones, L., Daniels, V., Wootton, M., MacGowan, A.P., **Walsh, T.R**. (2012). NDM-1 polymicrobial infections including *Vibrio cholerae*. *Lancet.* 380 (9850), 1358. DOI: 10.1016/S0140-6736(12)60911-8

4. Details of the impact

Health Policy Changes: In November 2009, Walsh and Toleman were part of a UK-wide Department of Health (DoH) call alerting all UK hospitals and departments (through the Public Health England Reference Laboratory) to this new type of antibiotic resistance.[5.1] Their NDM-1 studies were used to invoke mandatory screening be conducted for all patients arriving from overseas hospitals – these proposals were fully adopted by the UK DoH. **[5.1]** The ECDC called for greater surveillance and enhanced European-wide infection control measures to contain the threat of NDM-1 – see Table 2 of reference 5.2. In South Africa, the National Institute for Communicable Diseases issued a nationwide alert calling for increased infection control measures due to NDM-1. **[5.3]** In Canada (through governmental agency focusing on practice and policy interventions for Canadian populations), alerts and altered policies have been implemented. **[5.4]**

In August 2010 as a direct response to the first publication, the Ministry of Health and Family Welfare together with the National Centre for Disease Control in India constituted a National Task Force for the containment of Antimicrobial resistance. In March 2011, this task force produced India's first ever national antibiotic policy document entitled "**National Policy for Containment of Antimicrobial Resistance in India" (**http://nicd.nic.in/ab_policy.pdf). In August 2012, all major Indian clinical, academic and research bodies met in Chennai to discuss for the first time implementing 1. Antibiotic stewardship. 2. Infection control and 3. National Surveillance. This document, entitled "**The Chennai Declaration - A Roadmap to**

tackle the Challenge of Antimicrobial Resistance", is a direct response to studies in India, led by Walsh and Toleman that have persuaded the Indian government to acknowledge the very serious antibiotic resistance issues.[5.5] Walsh is advising the authors of the Chennai declaration and the Pakistani health authorities on antibiotic stewardship and infection control issues.
IMPACT: Prevention of the spread of NDM-1 bacteria throughout UK hospital wards as witnessed by the recent example published in the Lancet and International policy changes e.g. India.[5.1-5.5]

Public Behaviour Changes: These studies encouraged the Indian government to take antibiotic resistance more seriously. The work was the catalyst for the Indian government to organise emergency meetings resulting in the publication of the first Indian Government policies on tackling antibiotic resistance. The subsequent Chennai agreement has time lined a road map for implementation of antibiotic stewardship and infection control programs in response to Walsh's description of the issues of multi-drug resistance in India – these are currently being implemented across all of India so their impact is yet to be assessed.[5.5] A secondary behaviour change has resulted from the work because it highlights the threat posed by the growing industry of medical tourism and international cosmetic surgery; this has caused clashes with Indian private hospitals undertaking cosmetic surgery.
IMPACT: As a direct result of the research, stricter control of antibiotic stewardship and national infection control programs are being implemented in India. The research highlighted some of the medical issues, i.e. post-surgical infections, associated with medical tourism.

Public Awareness of a Health Risk: Immediately following publication of the seminal paper in *Lancet Infectious Diseases*, NDM-1 was the fourth biggest story world-wide, the lead story on the BBC 6 o'clock news [5.6] and broadcasted by ABC, CNN, Al-Jazeera, China-TV, India Today, SKY, ITV, Channel 4 and Channel 5. On 11th August, 2010 the NDM-1 story was covered on the front pages of the Telegraph, Independent, Guardian, Mail, Times, Financial Times, Sun and Mirror. [5.6-5.8] Interviews with the Telegraph, Times, Guardian and Independent provided informed editorials in the weekend editions[5.6-5.8] On the web, the NDM-1 feature registered 4.7 million internet hits in 2 days (11th-12th August). Moreover, the follow-up study published in April 2011 was covered widely in India and internationally including by the BBC – this was the first study linking the emergence of "superbugs" to the lack of sanitation in developing countries. This study was covered at the time by a Channel 4 documentary and more recently by BBC Horizon and ABC public awareness programs.[5.9, 5.10]
IMPACT: This global coverage changed the public's perception of "superbugs" and demonstrated that resistance can be readily spread from one bacterium to another – a clear demarcation from MRSA and "*C. difficile*". This perception resulted in international alerts by the Communicable Disease Centre (CDC) (USA), European CDC (ECDC) World Health Organisation (WHO) etc. and resulted in global behavioural and policy changes.

The Control of Diseases has Changed. The follow up study describing the discovery of NDM-1 in the Indian tap-water and environment has directly led to the Indian government issuing chlorine tablets to sanitise tap water for New Delhi residents unable to afford bottled water. [3.6] This practice continues, although control studies have not been undertaken in India to assess the impact of the intervention.
IMPACT: Introduction of potable water treatment in New Delhi.

Impact on National and International Organisations: The impact of NDM-1 has been detailed by many international health organisations including: Individual national governments (China, Korea, France, USA and UK) [5.1-5.5], the European Society of Clinical Microbiology and

Infectious Diseases, (CDC) (USA), WHO, European Parliament, and World Health Assembly. As a result of this international interest, Walsh has been invited to give over 46 international talks (including Australia, Norway, China, USA, Canada, Saudi Arabia, Thailand, Vietnam, Japan, Pakistan and India) and Toleman has given talks in Italy, Switzerland, Austria, USA, Saudi Arabia, and the UK. Walsh has addressed the European parliament with the director of the WHO, Margaret Chan (http://www.who.int/dg/speeches/2012/amr_20120314/en/ available on request from HEI) on NDM-1; Toleman has addressed NATO surgeons at the NATO headquarters in Brussels. Walsh has recently been asked by the WHO and the Chinese CDC to act as a consultant on international antibiotic resistance surveillance and was asked to become a member on the World Health Associated infections forum (http://www.hai-forum.com/ webcast). Walsh has also been asked by the UK government "GoScience" to write a positioning paper predicting resistance rates in 2030 and its impact on human health. .
IMPACT: Mission statements and general alerts on the impact of NDM-1 issued by the above organisations including national screening programs.

Outcomes for Patients have Improved: The research on NDM-1 has altered treatment of individuals presenting with NDM-1 positive infections. The work documenting NDM-1 resistance profiles and prevention measures for spread is known throughout the UK.[5.1] A recent case was of a traveller from India who required emergency admission in at Southmead Hospital, Bristol. Treatment as above prevented further spread of NDM-1 pathogens.[3.6]
IMPACT: Production of guidelines, in collaboration with the HPA, for patient treatment and management. Less harm to patients, limited spread of "superbugs" in UK hospitals and reduced costs.[3.6]

5. Sources to corroborate the impact

5.1 UK: http://www.hpa.org.uk/webc/HPAwebFile/HPAweb_C/1248854045473 (Backs up claim of involvement in UK health policy changes and available on request from HEI)

5.2 Europe-wide: http://www.eurosurveillance.org/ViewArticle.aspx?Articleid=19716 (Backs up claim of involvement in EU health policy changes and available on request from HEI)

5.3 South Africa: National Institute for Communicable Diseases http://www.nhls.ac.za/?page=alerts&id=5&rid=110 (Backs up claim of South African health policy changes and available on request from HEI)

5.4 Canada: http://www.nccid.ca/the-w-5-of-ndm-1 (Backs up claim of involvement in Canadian health policy changes and available on request from HEI).

5.5 Ghafur, A., *et al*. "The Chennai Declaration." *Indian J Cancer* 2012. 49; DOI:10.4103/0019-509X.104065 (backs up claims of Health Policy Changes, Public behaviour changes and public awareness of health risks).

5.6 BBC news. http://www.bbc.co.uk/news/health-10930031) (backs up claims of raising public awareness of a health risk)

5.7 Telegraph (http://www.guardian.co.uk/science/2010/aug/11/antibiotics-efficiency-drug-resistant-bacteria) (backs up claims of raising public awareness of a health risk)

5.8 Guardian (http://www.dailymail.co.uk/health/article-1302358/NDM-1-Were-blame-indestructible-Indian-superbug.html) (backs up claims of raising public awareness of a health risk)

5.9 BBC horizon (www.**bbc**.co.uk/programmes/b01ms5c6 television clips) (backs up claims of raising public awareness of a health risk)

5.10 ABC 7.30 documentary. (http://www.abc.net.au/7.30/content/2013/s3810324.htm) (backs up claims of raising public awareness of a health risk)

All websites, documents etc., are available as .pdfs from the HEI