Institution:
UNIVERSITY OF LIVERPOOL and LIVERPOOL SCHOOL OF TROPICAL MEDICINE

Unit of Assessment:
UOA1 - Clinical Medicine

Title of case study:
Improving Meningococcal Disease Diagnosis

1. Summary of the impact

Meningococcal disease (MCD) is a major cause of morbidity and mortality worldwide. Underpinning research by Dr Carrol and colleagues at the University of Liverpool (1997-1999), has led to improved diagnosis and case confirmation, establishing Polymerase Chain Reaction (PCR) of meningococcal DNA as a gold standard test for diagnosis. The result is better management and therefore, impact on health and welfare of patients, and on practitioners. The work was conducted in collaboration with the Meningococcal Reference Unit, which provides a national diagnosis and surveillance service. The test was recommended in NICE guidelines in 2010, thereby impacting public policy.

2. Underpinning research

The University of Liverpool (UoL) research group led by Professor Hart between 1977 and 2007 was one of only two groups in the UK and one of four worldwide conducting research into MCD in children. Between 1997-1999, Dr Enitan Carrol (then Clinical research fellow at the UoL) in collaboration with the Meningococcal Reference Unit, which provides a national diagnosis and surveillance service, evaluated the impact of meningococcal DNA detection in blood or cerebrospinal fluid by PCR.

The research achieved three things:

1. Demonstrated the feasibility of whole blood PCR testing for MCD diagnosis, a significant step forward. The research showed that meningococcal DNA detection in blood or cerebrospinal fluid by PCR is a useful method of diagnosis of MCD, and improves case confirmation.

2. Developed a test method or assay that could be used in clinical settings and laboratories that significantly increased the diagnostic confirmation rate. This was done by modifying the above test using whole blood which significantly improved the diagnostic confirmation rate from 31% (before introduction of meningococcal PCR into routine testing) to 88% in 2002, establishing this test as the gold standard for confirming cases of MCD [1,2].

3. The utility of this test in clinical settings, with its superior diagnostic confirmation rates and sufficiently rapidity to be clinically useful, was demonstrated in a real-life clinical setting. It showed a dramatic fall in serogroup C cases following introduction of the meningococcal C vaccine in 1999. Improved case confirmation allows better public health surveillance and assessment of the impact of introducing new vaccines.

Dr Enitan Carrol collated all the data collected from the Hart group between 1977 and 2007, which comprised 1157 children with MCD, 730 of these were recruited between 1993 and 2007. The analysis described the impact of introduction of the meningococcal C vaccine, and examined the association with social deprivation. This is one of the largest single-centre studies of MCD (from 1997 to 2007) and also supports the association between social deprivation and MCD [3]

The patients recruited by Dr Enitan Carrol between 1997 and 1999 were included in a multi-centre study which conducted the first whole genome screening of confirmed MCD. Liverpool contributed 25% of the patients in the initial Genome Wide Association study (GWAS) [4]. This study demonstrated the importance of host genetic variation in the regulation of complement activation. Genetic variation in complement factor H (CFH) and CFH-related protein 3 (CFHR3) play a role in determining the occurrence of invasive disease versus asymptomatic colonization by *Neisseria meningitidis.*

3. References to the research

1. **Carrol ED**, **Thomson AP**, **Shears P**, Gray SJ, Kaczmarski EB, **Hart CA**: Performance characteristics of the polymerase chain reaction assay to confirm clinical meningococcal disease. Arch Dis Child 2000, 83(3):271-273. Citations: 36 Impact Factor: 3.051

2. **Hackett SJ**, **Carrol ED**, Guiver M, Marsh J, **Sills JA**, **Thomson AP**, Kaczmarski EB, **Hart CA**: Improved case confirmation in meningococcal disease with whole blood Taqman PCR. Arch Dis Child 2002, 86(6):449-452. Citations: 22 Impact Factor: 3.051

3. Stanton MC, **Taylor-Robinson D**, **Harris D**, **Paize F**, **Makwana N**, **Hackett SJ**, **Baines PB**, **Riordan FA**, **Marzouk O**, **Thomson AP** et al: Meningococcal disease in children in Merseyside, England: a 31 year descriptive study. PLoS One 2011, 6(10):e25957. Citations: 2 Impact Factor: 3.730

4. Davila S, Wright VJ, Khor CC, Sim KS, Binder A, Breunis WB, Inwald D, Nadel S, Betts H, **Carrol ED** et al: Genome-wide association study identifies variants in the CFH region associated with host susceptibility to meningococcal disease. Nat Genet 2010, 42(9):772-776. Citations: 80 Impact Factor: 35.209

Key Research Grants

2004-2006. **Johanne Holly Meningitis Fund, RLCH NHS Trust**. The role of neuropeptides in the pathophysiology of meningococcal disease, £80,480, **ED Carrol**, N Makwana, APJ Thomson, PB Baines, B Flanagan, **CA Hart** (PI).

2004- 2006. **Meningitis Merseyside**. The role of neuropeptides in the pathophysiology of meningococcal disease. £36,080, **ED Carrol (PI)**, N Makwana, APJ Thomson, PB Baines, B Flanagan, CA Hart.

2006-2009. **Meningitis Research Foundation**. The Role Of The Microcirculation in the Pathophysiology of Meningococcal Disease, £154,561, N Makwana, APJ Thomson, **ED Carrol**, PB Baines, R Sarginson, **CA Hart** (PI).

4. Details of the impact

The research on the meningococcal PCR was done in conjunction with the Meningococcal Reference Unit at the Health Protection Agency (HPA), now Health Protection England. The HPA's advice, information and services are underpinned by evidence-based research. The UoL research provided evidence that PCR offered advantages over blood culture in real life settings and was directly used to improve diagnosis nationally, thereby ensuring that patients received more appropriate and earlier treatment than they would otherwise have done. The assay and primer sequences used by HPA are published in journals with a wide circulation, allowing others to develop their own in-house PCR assays, thereby increasing global impact; the partnership with HPA increased the reach and impact of the research. Meningococcal PCR is recommended as the gold standard in the 2010 NICE Clinical Guideline CG102 [5]. The research is also influencing the formulation of child specific NICE guidelines through work started in 2010 [6].

These organisations fund research to prevent meningitis and septicaemia, and improve survival rates and outcomes. They also promote education and awareness to reduce death and disability, and give support to people affected. As a result of the close collaboration between Professor Hart's group and these patient organisations (Meningitis Merseyside, Meningitis UK, Meningitis Research Foundation), results from the programme were disseminated directly to patient organisations and through conferences and literature to scientists and clinicians. The close links with patient groups provided societal benefit by contributing to increased knowledge of the disease being shared with members of the public. Key findings from research funded by Meningitis Research Foundation are

published on their website. Publications in medium to high impact publications also helped to give international recognition to this work.

The guidelines derived from the UoL research are being implemented and are impacting patients. For example, an HPA population-level assessment published in 2013 of the added value of PCR testing for MCD to augment traditional culture confirmation concluded that PCR-testing has a crucial role in the confirmation of MCD in England [7]. A total of 57% of all confirmed MCD cases were confirmed by PCR only, indicating high case ascertainment for national surveillance. The sensitivity of PCR in the recent HPA study is 97-99% [7].

The beneficiaries are 1) patients and patient groups through faster and more accurate diagnosis and therefore more effective treatment, and 2) healthcare providers who can more effectively use their resources. In England, in 2009 and 2010 there were 1924 reported MCD cases, 1099 (57.1%) were confirmed by PCR only, 432 (22.5%) by culture only and 393 (20.4%) by both tests. This means that, on average about 500 additional patients per year receive an accurate diagnosis and appropriate therapy as a result of this test.

The researchers have also engaged patient groups, the Meningitis Research Foundation and Meningitis UK. The beneficiaries are the public through increased awareness and access to knowledge.

The research has achieved international prominence and is now being applied in Europe. For example, in Barcelona 39% of 118 MCD were only detected by PCR [8]. MenB is the leading cause of meningitis and septicaemia in Ireland, with an average of 170 average cases per year. The study by Drew [9] reports that 63% of cases were diagnosed by PCR alone, which equates to about 107 extra cases /year in Ireland.

4. Sources to corroborate the impact

Each source listed below provides evidence for the corresponding numbered claim made in section 4 (details of the impact).

5. National Institute for Health and Clinical Excellence. Clinical guideline no. 102: Bacterial meningitis and meningococcal septicaemia (CG102). 2010. http://guidance.nice.org.uk/CG102

6. Bacterial meningitis and meningococcal septicaemia in children. (2010). http://guidance.nice.org.uk/CG/Wave11/3

7. Heinsbroek E, Ladhani S, Gray S, Guiver M, Kaczmarski E, Borrow R, Ramsay M: **Added value of PCR-testing for confirmation of invasive meningococcal disease in England**. *J Infect* 2013, **67**(5):385-390.

8. Munoz-Almagro C, Rodriguez-Plata MT, Marin S, Esteva C, Esteban E, Gene A, Gelabert G, Jordan I. Polymerase chain reaction for diagnosis and serogrouping of meningococcal disease in children. Diagn Microbiol Infect Dis. 2009 Feb;63(2):148-54

9. Drew RJ, Ó Maoldomhnaigh C, Gavin PJ, O' Sullivan N, Butler KM, Cafferkey M. The impact of meningococcal polymerase chain reaction testing on laboratory confirmation of invasive meningococcal disease. Pediatr Infect Dis J. 2012 Mar;31(3):316-8.