Institution: University of Leicester

Unit of Assessment: UoA5 Biological Sciences

Title of case study: Reducing the Global Incidence of Contact Lens Related Infections

1. Summary of the impact

There are 125 million contact lens wearers worldwide and most use some form of disinfection system for their safe use, accounting for a $1.5 billion global market per annum. In 2008, an outbreak of infection caused by the amoeba *Acanthamoeba* led to the global recall of the contact lens solution Complete® MoisturePlus®. Dr Kilvington led the root-cause investigation into the outbreak showing, for the first time, that components in contact lens care formulations can cause *Acanthamoeba* to transform into the highly resistant cyst stage. In 2008, he was seconded to the manufacturer of the recalled solution in the USA to develop and launch a new lens care product (AMO RevitaLens®) which has significantly improved antimicrobial properties, notably against *Acanthamoeba*. The outbreak and our subsequent work has had a global impact on the contact lens industry and regulatory bodies, resulting in a greater awareness of the risks from *Acanthamoeba*, development of new test methodologies and safer care solutions in the prevention of blindness.

2. Underpinning research

The presence of pathogenic microbes in the environment presents a constant challenge to the contact lens wearer. Here, microbes can colonise the contact lens storage case, become attached to the contact lens and then be inoculated on to the surface of the cornea to initiate infection (keratitis). Bacteria, fungi and the free-living amoeba *Acanthamoeba* can all cause contact lens related keratitis and, in the untreated state, result in permanent blindness (1). The incidence of microbial keratitis among contact lens wearers is 40:100,000 users: 90% of Acanthamoeba keratitis cases are in contact lens wearers (1,3). *Acanthamoeba* is almost ubiquitous in the environment and can form a dormant cyst stage that is resistant to most disinfectants and antimicrobial agents at working concentrations. Acanthamoeba keratitis is the most difficult ocular infection to manage successfully. Treatment can last over a year and 50% of patients require corneal grafting (keratoplasty) to restore some form of vision (3). However, in about 15% of cases, the infection cannot be controlled and results in permanent blindness (3).

The University of Leicester has established itself as an internationally renowned centre for *Acanthamoeba* research and the prevention of contact lens related microbial infections. The work has led directly to a greater understanding of the cell biology of the organism, the epidemiology of Acanthamoeba keratitis in the UK, and the development of improved therapeutic agents and contact lens care systems (1,2,4-6). Fundamental to this success has been the close collaboration with the eye care industry, researchers and ophthalmologists around the world - notably at Moorfields Eye Hospital, London.

Key achievements that have directly impacted the contact lens care industry and the prevention of infection and blindness worldwide have been:
(a) demonstration that tap water is a major risk source of *Acanthamoeba* in the UK (2004),
(b) development of effective drug treatment for the infection (2009),
(c) root-cause investigation following a global outbreak of Acanthamoeba keratitis (2008),
(d) subsequent development of a new contact lens care solution with potent anti-acanthamoebal activity (2010), and
(e) improved assay methods to determine antimicrobial efficacy against the *Acanthamoeba* (2013) (1-6).

Dr Simon Kilvington has worked on Acanthamoeba since 1980, the past twelve years of which have been at University of Leicester. He was joined by Dr James Lonnen and in 2008 a commercial analytical service laboratory (now named Obrus Microbiology Services) was formed

within the University to meet the needs of the industry in evaluating contact lens care products against *Acanthamoeba* and other corneal pathogens in the development of better care solutions, and to provide a diagnostic service for clinicians.

The impact of our knowledge, key opinion leadership and international recognition for our work is underpinned by over seventy peer reviewed papers in the scientific literature and numerous poster presentations and key-note lecturers at leading international conferences. Significant funding for this research, including PhD studentships, has been obtained over the past ten years from the eye care industry and includes Alcon Laboratories, Bausch and Lomb, Abbott Medical Optics and Menicon.

Key University personnel involved directly in the delivery of these milestones are:
Dr Simon Kilvington, Senior Lecturer 2000 - date.
Dr James Lonnen, Commercial Laboratory Director, 2008 - date. Experimental Officer 2007-2008, Laboratory technician 2002-2003.
Dr Wayne Heaselgrave – Research Associate and Honorary Lecturer in Parasitology 2008 to June 2012. Research Associate 2007-2008. PhD Researcher 2002-2005.
Dr Reanne Hughes, PhD student (2004-2007) funded by Alcon Laboratories, USA.
Dr Kimberley Earland, PhD student (2006-2009) funded by Bausch + Lomb, USA.

3. References to the research

1. **Kilvington, S**. and A. Lam (2013). "Development of standardized methods for assessing biocidal efficacy of contact lens care solutions against acanthamoeba trophozoites and cysts." *Investigative Ophthalmology and Visual Science* **54**(7): 4527-4537.
2. **Kilvington, S**., Huang, L., Kao, E. and Powell, C.H. (2010). Development of a new contact lens multipurpose solution: comparative analysis of microbiological, biological and clinical performance. *Journal of Optometry*. 3:134-142.
3. Dart JK, Saw VP and **Kilvington S**, (2009). Acanthamoeba Keratitis: Diagnosis and Treatment Update 2009, *Am J Ophthalmol*, 148, 487–499
4. **Kilvington, S., W. Heaselgrave**, J. M. Lally, K. Ambrus, and H. Powell. (2008). Encystment of *Acanthamoeba* during incubation in multipurpose contact lens disinfectant solutions and experimental formulations. *Eye Contact Lens* 34:133-9.
5. **Kilvington S**, Gray T, Dart J, Morlet N, Beeching JR, Frazer DG, Matheson M: Acanthamoeba keratitis: the role of domestic tap water contamination in the United Kingdom. *Invest Ophthalmol Vis Sci* 2004, 45(1):165-169.
6. **Kilvington S** and **Lonnen J.** A comparison of regimen methods for the removal and inactivation of bacteria, fungi and *Acanthamoeba* from two types of silicone hydrogel lenses. *Cont Lens Anterior Eye* 2009;32:73-77.

(**bold** type denotes University of Leicester employee at time of publication)

4. Details of the impact

Through applied and translational research, we have impacted directly the understanding of contact lens related eye infections, notably those caused by *Acanthamoeba*, and the measures taken by Industry and regulatory bodies to address the risks. Dr Simon Kilvington and Dr James Lonnen have established an internationally renowned centre in Leicester for *Acanthamoeba* research and the prevention of contact lens related microbial infections. Their work has led directly to a greater understanding of the risks posed to contact lens wearers from *Acanthamoeba*, and how this can be addressed through greater knowledge and the development of improved contact lens care solutions (**B**). Our work impacts the opinion of the eye care industry, regulatory bodies and clinicians worldwide.

Key to the centre's success has been a close collaboration with researchers and ophthalmologists around the world, notably at Moorfields Eye Hospital, London (**E**). In recent years, the centre has also been involved with the pharmaceutical and contact lens industries, where its expertise in

assay methods, therapeutic and disinfectant agent development has been widely sought. Consequently, a commercial analytical service (Obrus Microbiology Services) was formed within the University to meet and develop the commercial aspects of the work and provide a diagnostic service for clinicians (www.le.ac.uk/obrus). This service is headed by Dr James Lonnen and since 2008 has seen significant annual growth in service provision and commercial revenue (£100,000 to £300,000) in demand from the contact lens industry worldwide, particularly in relation to *Acanthamoeba*.

Leicester research not only showed that the reported incidence of Acanthamoeba keratitis in the UK is at least twenty-fold higher than other European countries and the USA, but also revealed why. Uniquely, most homes in the UK have water storage tanks in the loft that supply the bathroom cold taps and are ideal habitats for the growth of *Acanthamoeba* (**C**). Using DNA fingerprinting, researchers showed that strains from keratitis cases were genetically identical to those from the tanks and tap water in patients' homes. The publication confirmed the importance of avoiding tap water in contact lens hygiene procedures and resulted in clearer and more prominent warnings from manufacturers and professional groups.

In addition, when the industry was promoting "No-Rub" lens care solutions, Leicester showed that such an omission would not be effective in removing potential pathogens, including *Acanthamoeba*, from the lenses. As a result, the USA's Food and Drug Administration (FDA) ordered that a separate lens rubbing stage ("Rub and Rinse") be included in all instructions for contact lens solution use (FDA, May 2010):

"We recommend that manufacturers of contact lens multi-purpose solution products that include "no rub" directions remove the "no-rub" from product labeling and emphasize the importance of "rubbing and rinsing" in caring for contact lenses. Our recommendation is consistent with several professional eye organizations."

In 2008 a global recall of a contact lens care solution (AMO Complete MoisturePlus) was implemented following an outbreak of Acanthamoeba keratitis. At the request of the company involved, the University of Leicester led the investigation into the root-cause of the outbreak and Dr Simon Kilvington was invited to present the findings and other aspects of *Acanthamoeba* research at two FDA workshops on contact lens care solution efficacy in 2008 and 2009. We established that the care solution implicated in the outbreak induced *Acanthamoeba* to transform into the resistant cyst stage which is likely to have been a significant factor in the subsequent survival of the organism and initiation of infection (**D**).

As a result of his reputation and scientific excellence at the University of Leicester, Dr Simon Kilvington was seconded in 2008 to work for Abbott Medical Optics (AMO; **A**), California, USA to develop their microbiology R&D capability and lead in the development of a new contact lens care solution, AMO RevitaLens® (**F**), with proven efficacy against *Acanthamoeba*. Key to the solutions potent antimicrobial activity is the use in the formulation of the disinfectant agent alexidine dihydrochloride which had been characterised as a potent anti-acanthamoebal agent by Dr Kilvington's group (Reanne Hughes, PhD thesis University of Leicester, 2004). The product development at AMO was of high priority, as the recall and subsequent loss in investor confidence almost led to the financial collapse of the company before it was bought out by Abbott Laboratories in early 2009. The product was launched in in 2010 and has become one of the global top selling contact lens care solutions, with 10,000,000 bottles sold annually. In recognition for his work at AMO, Dr Simon Kilvington was elected as a Research Fellow to the highly prestigious Abbott Volwiler Society in 2011.

Contact lens care solutions must conform to specified parameters for microbiological efficacy as defined by the International Organization for Standardization (ISO) document 14729. The research and developments in contact lens care have impacted directly the opinions of the industry and regulatory bodies. This has resulted in Dr Simon Kilvington becoming an elected expert member of the ISO committee (2008 to date; International Organization for Standardization; **G**) that examines at all aspects of contact lens microbiology and regulation to ensure the greater global safety of contact lens wearers. Key to this work has been the preparation of a new ISO standard requiring that contact lens care solutions must be tested to demonstrate that they do not induce

Acanthamoeba encystment (ISO/TC 172/SC7/WG9: ISO/NP 19045). Furthermore, the Food and Drug Administration in the USA is revising its guidance regarding microbiological effectiveness for manufacturers seeking approval to market new contact lens care systems ("Premarket Notification (510(k) Guidance Document for Contact Lens Care Products") and this will include efficacy against *Acanthamoeba*, based on methods developed by Dr Kilvington. Accordingly, our work at Leicester has directly impacted the awareness of contact lens safety, the development of improved new contact lens care solutions and, in doing so, contributed to the global prevention of blindness.

5. Sources to corroborate the impact

A. http://www.reuters.com/article/2008/09/23/idUS96982+23-Sep-2008+BW20080923 Details of Dr Kilvington's appointment to lead research at AMO

B. http://www.menicon.fr/pro/lentilles-souples/entretien-des-lentilles-souples/menicare-soft/menicare-soft-notices Menicon, Japan. Company's web page cites results from Acanthamoeba disinfection studies conducted by the University of Leicester and shows the effectiveness of their product.

C. http://www.healio.com/news/print/ocular-surgery-news-europe-asia-edition/%7B88ddca6e-9626-4478-b2f7-45794e436ac0%7D/tap-water-identified-as-source-of-uk-bacterial-keratitis-cases Article cites work from University of Leicester about risk to contact lens wearers from Acanthamoeba in domestic tap water (notably that derived from loft storage tanks which are common in most UK homes).

D. http://www.dailymail.co.uk/health/article-2028226/Why-going-sleep-contact-lenses-blind-you.html Item in national newspaper (2011) quoting work by Dr Kilvington on risk of Acanthamoeba infection from poor contact lens hygiene and promoting need for greater awareness and concerns for their safe use.

E. **Contactable source:** Consultant Ophthalmologist, Moorfields Eye Hospital, London and Honorary Clinical Professor of Ophthalmology at the University College London

F. http://www.amo-inc.com/products/corneal/multi-purpose-solution/revitalens-ocutec-multi-purpose-disinfecting-solution Company's web page cites results from Acanthamoeba disinfection studies conducted by the University of Leicester and shows the effectiveness of their product.

G. **Contactable source:** Professor of Optometry and Vision Science at the University of Alabama at Birmingham and co-member of ISO Committee.