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Rapid point-of-care test for the detection of Chlamydia in individuals at risk of trachoma

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PRIORITISING SUMMARY

REGISTER ID: **000050**

NAME OF TECHNOLOGY: **RAPID POINT-OF-CARE TEST FOR THE DETECTION OF CHLAMYDIA**

PURPOSE AND TARGET GROUP: **INDIVIDUALS AT RISK OF TRACHOMA**

STAGE OF DEVELOPMENT (IN AUSTRALIA):

- ☒ Yet to emerge
- ☐ Experimental
- ☐ Investigational
- ☐ Nearly established
- ☐ Established
- ☐ Established *but* changed indication or modification of technique
- ☐ Should be taken out of use

AUSTRALIAN THERAPEUTIC GOODS ADMINISTRATION APPROVAL

- ☐ Yes — ARTG number
- ☒ No
- ☐ Not applicable

INTERNATIONAL UTILISATION:

COUNTRY	LEVEL OF USE		
	Trials Underway or Completed	Limited Use	Widely Diffused
United Kingdom (study conducted in Tanzania)	✓		
United Kingdom (study conducted in Tanzania, Gambia & Ethiopia)	✓		

IMPACT SUMMARY:

The Diagnostic Development Unit in the Haematology Department of the University of Cambridge (UK) has developed a rapid point-of-care for the detection of infection with *Chlamydia trachomatis*, the leading infectious cause of blindness. The FirstBurst Trachoma test is produced by the company, Diagnostics for the Real World, with The University of Cambridge and the Wellcome Trust as major shareholders. The test has been assigned an International Organization for Standardization number (ISO 13485) and will have approval for European distribution shortly (CE marked) (personal communication University of Cambridge, May 2006).

This technology is not currently available in Australia, but may be a useful tool in the monitoring of *Chlamydia trachomatis* infection in rural and remote Indigenous populations who are at risk of developing trachoma.

BACKGROUND

Trachoma, a chronic keratoconjunctivitis, is caused by repeated episodes of infection with the bacterium *Chlamydia trachomatis* (serotypes A, B, Ba and C). The strain of chlamydia which causes trachoma differs from the genital strain of chlamydia. Trachoma is the second leading cause of blindness in the world (15% of blindness worldwide), but the leading cause of *infectious* blindness, and therefore deemed avoidable. Trachoma is easily spread by human contact, especially amongst children. Routes of transmission include direct eye-to-eye (during play or bed sharing), eye-seeking flies or coughing and sneezing (Communicable Diseases Network Australia 2006; Kasi et al 2004; Wright et al 2006).

Trachoma has three distinct stages (Figure 1). Initial infection results in a mild mucopurulent conjunctivitis after an incubation period of 5-15 days. During infection the conjunctiva (the mucous membrane that lines the surface of the eyelid) becomes red and swollen. Papillae and follicles appear on the tarsal conjunctiva (inner eyelid) during active inflammation which results from repeated or persistent infection. Trachoma at this stage may result in superficial keratitis (inflammation of cornea) which can lead to new vessel growth over the margin of the cornea. Stage two of trachoma, trachomatous scarring, is a result of chronic conjunctivitis caused by repeated infection. Conjunctival scarring is recognised by distinct white bands on the underside of the upper eyelid. Severe scarring may progress to contraction of the eyelid, inturned eyelashes (trachomatous trichiasis) and inturned eyelid margin. The continual abrasive action of the inturned eyelashes is painful and causes corneal scarring and corneal opacities. Once the cornea has become opaque vision loss is irreversible (Communicable Diseases Network Australia 2006; Kasi et al 2004; Wright et al 2006).

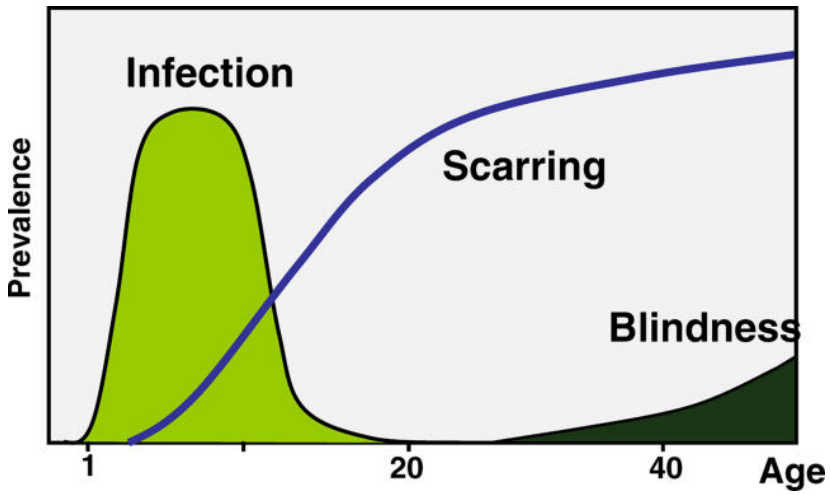

Figure 1 The natural history of trachoma (Printed with permission Wright 2006)

The World Health Organization (WHO) recommends the SAFE strategy (Surgical, Antibiotics, Facial cleanliness and Environmental improvement), which focuses on the prevention of trachoma. Trachomatous trichiasis is associated with an increased risk of blindness and a variety of surgical procedures can relieve the trichiasis, preventing or slowing progression towards blindness. Individuals with active infection are treated with antibiotics; either oral doses of azithromycin or tetracycline eye ointment. If prevalence of trachoma is greater than 10 percent in a community, antibiotics should be provided to the whole, or at least 80 per cent of the community. Antibiotic administration should continue for at least three years and should not stop until prevalence is below five per cent. Clean-face campaigns have been initiated in some communities as children with dirty faces are two to three times more likely to contract trachoma.

Improvements in environmental health include access to clean water, reducing overcrowding by access to adequate housing, waste and fly control (Communicable Diseases Network Australia 2006; Wright et al 2006).

The decision to treat with antibiotics is currently made on the basis of prevalence of trachoma (trachomatous inflammation follicular or TF). Diagnosis of trachoma is based on examination of the eyelid and eye, referring to the WHO trachoma grading classification system (Communicable Diseases Network Australia 2006). However, there is poor correlation between the clinical signs of trachoma and laboratory evidence of infection, especially in areas of low prevalence, as signs of the disease persist longer than the active infection. This may result in the overestimation of active infection and therefore communities may receive unnecessary antibiotic treatment, increasing the possibility of antibiotic-resistant pathogens (Michel et al 2006). The point-of-care FirstBurst Trachoma test has been proposed as a means to quickly and reliably determine active infection, enabling health care workers to make an informed decision on the distribution of antibiotics to the community (Wright & Taylor 2006).

The FirstBurst Trachoma test is a dipstick immunoassay which detects chlamydial lipopolysaccharide and detects all *C trachomatis* serovars and other species of *Chlamydia*. The test can be easily performed in the field with minimal equipment and by local health workers. A swab specimen is taken from the eye and placed in an extraction tube to release the lipopolysaccharide. The resulting extract is removed and placed into a detection tube where the dipstick is placed. In a sample which contains chlamydial lipopolysaccharide a complex is formed, resulting in a colour change on the dipstick indicating a positive sample. The test takes approximately 25 minutes to perform and get a visual result (Michel et al 2006).

CLINICAL NEED AND BURDEN OF DISEASE

Australia appears to be the only developed country where trachoma is endemic, affecting Aboriginal and Torres Strait Islander communities in parts of the Northern Territory, South Australia and Western Australia. Trachoma is highly prevalent in Aboriginal people living in rural and remote locations, in conditions of poverty, over-crowded housing with a lack of access to appropriate eye health care services. Epidemiological data on trachoma is difficult to obtain as each trachoma control programme has its own data collection system. There is no national data collation and trachoma is not a notifiable disease (Mak 2006).

A study conducted in East Arnham in the Northern Territory in 2002, screened 849 children aged 4-15 years fro trachoma using PCR. The overall prevalence was 26 per cent. A 1998 study conducted in communities of Central and Western Australia reported that 40 per cent of children under the age of 13 years had either follicular trachoma or intense trachoma. A survey conducted in the Kimberly region of Western Australia reported trichosis in only 2.9% of individuals over the age of 50 years who had made contact with aged care services. This number is less than what may have been predicted by the high prevalence rates of trachoma reported in young children but may be a reflection on the number of people who contact or have access to aged care.

DIFFUSION

The FirstBurst Trachoma test is not currently available in Australia or New Zealand.

COMPARATORS

The “gold standard” for the detection of *Chlamydia trachomatis* is nucleic acid amplification using polymerase chain reaction (PCR), which is highly sensitive and specific. However, PCR is

costly, requires expensive equipment and would be impossible to perform in field situations (Wright & Taylor 2005). Other laboratory techniques include direct fluorescent antibody cytology, cell culture or enzyme immunoassay, all of which cannot be performed in the field (Wright & Taylor 2005). The WHO trachoma grading system is used in community screening programmes in Australia. Screening is recommended annually in areas where trachoma is endemic, then every three years if the prevalence of active trachoma is less than five per cent.

EFFECTIVENESS AND SAFETY ISSUES

In a good quality study conducted by Michel et al (2006) three groups of children (aged 1-9 years) were enrolled consecutively (level II diagnostic evidence). Two groups were from high prevalence areas (22.7% and 27.5%) and the third group was from a low prevalence area (6.5%). Swabs were taken from either both eyes, or two swabs from the same eye, and randomised for chlamydia detection by either FirstBurst Trachoma test or PCR. The swab collector was blinded to swab allocation. All children enrolled underwent clinical examination and were graded according to the WHO trachoma grading system.

The performance of clinical diagnosis using the WHO clinical grading system and the FirstBurst Trachoma point-of-care test were compared to PCR and the results are described in Table 1. Overall, a total of 128/664 (19%) were confirmed as positive for ocular *Chlamydia trachomatis* infection by PCR. The sensitivity, specificity, positive[1] and negative predictive values were calculated for both clinical grading and First burst and the results are collated in Table 2. FirstBurst had high sensitivity and specificity, 83.6% and 99.4% respectively combined with a good positive predictive value (97.3%) and an excellent negative predictive value (96.2%). The overall agreement between the POC test and PCR, adjusted for groups, was 0.875 [95% CI 0.825, 0.924, p=0.73].

In comparison, clinical diagnosis had much lower values but did have a good negative predictive value of 90.3%, meaning that the majority of children assessed clinically as not having trachoma did not have an active *Chlamydia trachomatis* infection. A lower specificity (80.2%) was recorded due to the high number of children assessed as clinically positive who were in fact negative by PCR. The clinical diagnosis group had poor positive predictive values, which decreased further in Group 3 where the prevalence of trachoma was low

In addition, the authors assessed the inter-observer and intra-observer agreements between four novice health care workers trained in the field for the performance of the point-of-care test (performing swabs and extraction of lipopolysaccharide). Inter-agreement and intra-agreement were 0.988 [95% CI 0.973, 1.0] and 0.950 [95% CI 0.894, 1.0], respectively, indicating excellent reproducibility in the field situation.

[1] Positive predictive value is the percent of individuals who test positive and have the disease. Negative predictive value is the per cent of individuals who actually test negative and don't have the disease.

Table 1 Presence of *Chlamydia trachomatis* DNA assessed by PCR compared to detection by WHO clinical grading and FirstBurst Trachoma test

Group	PCR positive			PCR negative		
	PCR positive	Clinically positive	POC positive	PCR negative	Clinically positive	POC positive
Group 1 n=264 (high prevalence)	60/264 (22.7%)	65%	83%	204/264 (77.3%)	30%	2%
Group 2 n=200 (high prevalence)	55/200 (27.5%)	64%	86%	145/200 (72.5%)	19%	0%
Group 3 n=200 (low prevalence)	13/200 (6.5%)	62%	77%	187/200 (93.5%)	9%	0%
All groups n=664	128/664 (19.3%)	64%	84%	536/664 (80.7%)	20%	1%

PCR = polymerase chain reaction, POC = point-of-care trachoma test

Table 2 Performance of WHO clinical grading and FirstBurst Trachoma test compared to PCR

Positive clinical grading				
Group	Sensitivity % (95% CI)	Specificity % (95% CI)	PPV % (95% CI)	NPV % (95% CI)
Group 1 n=264 (high prevalence)	65.0 (52.9, 71.0)	70.1 (63.8, 76.4)	39.0 (29.4, 48.6)	87.2 (73.9, 92.8)
Group 2 n=200 (high prevalence)	63.6 (50.9, 73.3)	80.7 (74.3, 87.1)	55.6 (43.3, 67.8)	85.4 (79.5, 91.3)
Group 3 n=200 (low prevalence)	61.5 (35.1, 88.0)	90.9 (86.8, 95.0)	32.0 (13.7, 50.3)	97.1 (94.7, 99.6)
All groups n=664	64.1 (55.8, 72.4)	80.2 (76.8, 83.6)	43.6 (36.5, 50.7)	90.3 (87.7, 93.0)
Positive POC assay				
Group 1 n=264 (high prevalence)	83.3 (73.9, 92.8)	98.5 (96.9, 100.0)	94.3 (88.1, 100.6)	95.3 (92.4, 98.1)
Group 2 n=200 (high prevalence)	85.5 (76.1, 94.8)	100.0 (100, 100)	100.0 (94.6, 100.0)	94.8 (91.2, 98.3)
Group 3 n=200 (low prevalence)	76.9 (54.0, 99.8)	100.0 (100, 100)	100.0 (77.2, 100.0)	98.4 (96.6, 100.2)
All groups n=664	83.6 (77.2, 90.0)	99.4 (98.8, 100.0)	97.3 (94.2, 100.3)	96.2 (94.6, 97.8)

PCR = polymerase chain reaction, POC = point-of-care trachoma test, PPV = positive predictive value, NPV= negative predictive value

COST IMPACT

Two item numbers are provided on the Medicare Benefits Schedule for the detection of chlamydia nucleic acid (item number 69364) or exogenous chlamydia antigen (item number 69384), with fees of $28.85 and $15.75, respectively.

Diagnostics for the Real World aim to have a two-tiered price range for the FirstBurst Trachoma test, making it available to developing countries such as Africa for approximately 70 cents per dipstick test. Prices would be higher in Australia (personal communication University of Cambridge, May 2006).

The economic impact of vision impairment was recently evaluated by Taylor et al (2006). Vision disorders ranked seventh in the comparison of direct health costs in Australia during the period 2000-01, ahead of arthritis and ischaemic heart disease. Overall, vision disorders cost $9.85 billion. Direct health system costs were $1.8 billion, with $4.8 billion associated with the loss of well being (years of life lost as a result of disability and premature mortality). The real direct and indirect financial cost of vision loss was estimated to represent $252 for every Australian, or 0.6% of gross domestic product. Although cataracts accounted for 18 per cent of costs, no data were available for the cost of trachoma.

ETHICAL, CULTURAL OR RELIGIOUS CONSIDERATIONS

The delivery of and access to eye care services in rural and remote communities is seriously lacking in Australia. Some indigenous communities are highly mobile, which may undermine strategies such as SAFE to control trachoma (Taylor et al 2003).

OTHER ISSUES

A larger study (n=6,000) is currently being conducted for the detection of Chlamydia in children at risk of trachoma in Gambia, Tanzania and Ethiopia (personal communication University of Cambridge, May 2006).

Two formal clinical trials have been conducted in the United Kingdom using the FirstBurst test for the detection of sexually transmitted chlamydia. The performance was similar to those obtained in the Michel et al (2006) study and will be published soon (personal communication University of Cambridge, May 2006).

CONCLUSION:

Although only one study is included for assessment in this summary, it is a high quality study, indicating that the point-of-care trachoma test is highly accurate in identifying the presence or absence of *Chlamydia trachomatis* infection, when compared to the WHO clinical grading system. Trachoma is endemic in Aboriginal and Torres Strait Islander communities living in rural and remote locations and is a significant cause of blindness in this population. The FirstBurst Trachoma test may be of great benefit for the diagnosis and subsequent treatment for members of these communities.

HEALTHPACT ACTION:

Two large scale trials are currently being conducted in Africa and are due to be completed by the end of 2007. It is therefore recommended that this technology be monitored until these trials are completed.

SOURCES OF FURTHER INFORMATION:

Communicable Diseases Network Australia (2006). *Guidelines for the public health management of Trachoma in Australia*, Department of Health and Ageing, Canberra.

Kasi, P. M., Gilani, A. I. et al (2004). 'Blinding trachoma: a disease of poverty', *PLoS Med*, 1 (2), e44.

Madden, A. C., Simmons, D. et al (2002). 'Eye health in rural Australia', *Clin Experiment Ophthalmol,* 30 (5), 316-321.

Mak, D. B. (2006). 'Better late than never: a national approach to trachoma control', *MJA,* 184 (10), 487-488.

Michel, C. C., Solomon, A. W. et al (2006). 'Field evaluation of a rapid point-of-care assay for targeting antibiotic treatment for trachoma control: a comparative study', *The Lancet,* 367 (9522), 1585.

Solomon, A. W., Foster, A. & Mabey, D. C. (2006). 'Clinical examination versus Chlamydia trachomatis assays to guide antibiotic use in trachoma control programmes', *Lancet Infect Dis,* 6 (1), 5-6; author reply 7-8.

Taylor, H. R. (2001). 'Trachoma in Australia', *Med J Aust,* 175 (7), 371-372.

Taylor, H. R., Pezzullo, M. L. & Keeffe, J. E. (2006). 'The economic impact and cost of visual impairment in Australia', *Br J Ophthalmol,* 90 (3), 272-275.

Taylor, H. R. & Wright, H. R. (2006). 'Dip-stick test for trachoma control programmes', *The Lancet,* 367 (9522), 1553.

Taylor, V., Ewald, D. et al (2003). *Review of the implementation of the national Aboriginal and Torres Strait Islander eye health program,* Centre for Remote Health, Canberra.

Wright, H. R., Keeffe, J. E. & Taylor, H. R. (2006). 'Trachoma and the need for a coordinated community-wide response: a case-based study', *PLoS Med,* 3 (2), e41; quiz e155.

Wright, H. R. & Taylor, H. R. (2005). 'Clinical examination and laboratory tests for estimation of trachoma prevalence in a remote setting: what are they really telling us?' *Lancet Infect Dis,* 5 (5), 313-320.

Wright, H. R., Vu, H. & Taylor, H. R. (2005). 'How to assess the prevalence of trachoma', *Br J Ophthalmol,* 89 (5), 526-527.

LIST OF STUDIES INCLUDED

Total number of studies
Level II diagnostic evidence 1

SEARCH CRITERIA TO BE USED:

Chlamydia trachomatis
Endemic Diseases
Rural Health
Trachoma
Eye Diseases/*epidemiology/therapy
Rural Health Services
Blindness/diagnosis/*epidemiology
Comorbidity