Institution: The University of Edinburgh

Unit of Assessment: 1

Title of case study: R: Community-directed delivery of doxycycline in Cameroon demonstrates effectiveness as a treatment for onchocerciasis (river blindness) in Africa that avoids adverse effects associated with ivermectin

1. Summary of the impact (indicative maximum 100 words)

Impact: Health and welfare and public healthcare policy; demonstrating that community-directed treatment of onchocerciasis with doxycycline is effective where ivermectin is contra-indicated.

Significance: 12,936 onchocerciasis patients were treated safely and protected for at least 4 years. The treatment regime has been adopted by the US Centers for Disease Control and Prevention, the World Health Organization and governments.

Beneficiaries: Patients with onchocerciasis; governments and policy-makers.

Attribution: Studies performed by a long-standing African-European partnership formed and led by Taylor (UoE).

Reach: International; up to 8 million people in the Congo basin; onchocerciasis patients in Africa where ivermectin is not appropriate plus those in South America participating in focal eradication campaigns.

2. Underpinning research (indicative maximum 500 words)

Professor David Taylor (Professor of Tropical Animal Health, UoE, 1994–present), demonstrated for the first time that doxycycline was an effective treatment for onchocerciasis. This work led to the adoption of the doxycycline treatment regime by the US Centers for Disease Control and Prevention (CDC) and other international agencies, replacing ivermectin as the first-line mass treatment.

Onchocerciasis (river blindness), caused by the filarial nematode *Onchocerca volvulus*, is the second most common infectious blinding disease of the developing world, afflicting 31 million people, 95% of whom live in West or Central Africa. Seventy percent of patients experience severe and debilitating skin disease that has major economic and social consequences including poor school performance, low productivity, low income, higher health-related costs, and extreme social stigmatization, especially among women.

Ivermectin has long been used in mass treatment campaigns to control onchocerciasis. However, when these treatment programmes were extended to Cameroon, where a proportion of the target population is co-infected with the eye worm *Loa loa*, there was an unacceptable number of severe, sometimes fatal, adverse reactions including encephalopathy. Ivermectin is no longer considered safe for mass treatment programmes where *O volvulus* and *L loa* are co-endemic.

Taylor has led an African-European partnership, funded by six successive European Framework contracts, to improve treatment and control of onchocerciasis. Human epidemiological and immunological studies in Cameroon, Ghana and Togo were combined with immunological studies in animal models, and with parasite proteomics and genomics. Infections with *O volvulus* cannot be established in mice, but Bain (Paris) and Taylor demonstrated that the filariae *Litomosoides sigmodonitis* could produce potent infections in mice and that the parasitological presentations replicated those of the human parasites [3.1], leading the way for detailed immunological investigations [e.g., 3.2, 3.3]. In parallel, the partnership developed a bovine model using *O ochengi* [3.4]. Both models were pivotal to the work underpinning and leading to the trial of doxycycline.

In 2000, it was identified that *O volvulus* harbours the endosymbiotic Gram-negative bacteria

Wolbachia. This opened the possibility of therapy with antibiotics, led directly to consortium partners demonstrating the efficacy of tetracyclines in the *O ochengi* bovine model [3.4] and, crucially, human studies in the field that demonstrated similar efficacy [3.5].

These results took on far greater significance when it was discovered that *L loa* does not possess *Wolbachia*. This raised the prospect of using doxycycline to selectively target *O volvulus* in patients co-infected with *L loa* previously at risk of ivermectin-induced side effects.

Doxycycline treatment requires administration of the drug three times a day for 6 weeks, which is difficult to achieve conventionally in remote regions of developing countries. To overcome this, Taylor and colleagues conducted a community-directed treatment trial of doxycycline in five hyper-endemic areas of Cameroon [3.6]. The study communities identified trusted individuals whom the group subsequently trained to diagnose infection, dispense drugs and record treatment and any side effects (carried out under the supervision of the Ministry of Health, Cameroon). 21,000 people were recruited and 12,936 individuals were treated with doxycycline, giving a therapeutic coverage of the eligible population of 73.8% and a compliance rate of 97.5% at the end of six weeks. No serious side effects were registered.

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

3.1 Maréchal P, Le Goff L, Hoffman W,…Taylor D, et al. Immune response to the filaria Litomosoides sigmodontis in susceptible and resistant mice. Parasite Immunol. 1997;19:273–9. DOI: 10.1046/j.1365-3024.1997.d01-209.x.

3.2 Le Goff L, Loke P, Ali H,… Taylor D, Allen J. Interleukin-5 is essential for vaccine-mediated immunity but not innate resistance to a filarial parasite. Infect Immun. 2000;68:2513–7. DOI: 10.1128/IAI.68.5.2513-2517.2000.

3.3 van der Werf N, Redpath S, Azuma M, Yagita H, Taylor M. Th2 cell-intrinsic hypo-responsiveness determines susceptibility to helminth infection. PLoS Pathog. 2013;9:e1003215. DOI: 10.1371/journal.ppat.1003215.

3.4 Langworthy S, Renz A, Mackenstedt U, et al. Macrofilaricidal activity of tetracycline against the filarial nematode, Onchocerca ochengi: elimination of Wolbachia proceeds worm death and suggests a dependent relationship. Proc Biol Sci. 2000;267:1063–9. DOI: 10.1098/rspb.2000.1110.

3.5 Hoerauf A, Spechts S, Marfo-Debrekyi Y, et al. Efficacy of 5 week doxycycline treatment on adult Onchocerca volvulus. Parasitol Res. 2009;104:437–47. DOI: 10.1007/s00436-008-1217-8.

3.6 Wanji S, Tendongfor N, Nji T,…Taylor D. Community-directed delivery of doxycycline for the treatment of onchocerciasis in areas of co-endemicity with loiasis in Cameroon. Parasit Vectors. 2009;2:39. DOI: 10.1186/1756-3305-2-39.

4. Details of the impact (indicative maximum 750 words)

The WHO and its subsidiary African Programme for Onchocerciasis Control (APOC) have reduced morbidity in many parts of west Africa and eliminated onchocerciasis from some isolated foci in South America [5.1]. Onchocerciasis is now identified as a target for elimination from Africa by 2020.

Because ivermectin is not suitable for use in children under 5 years or in those co-infected with *L Loa*, and drug resistance is emerging, it is unsuitable for mass treatment programmes in over 8 million Africans. The work described above in Cameroon [5.2] demonstrated that doxycycline could overcome the problem of *L loa* co-infection, provided attention is paid to ensure community involvement in drug administration.

Impact on practitioners and services

Doxycycline is now defined as one of only two treatments effective for onchocerciasis by the CDC [5.3]. CDC also notes that the alternative (ivermectin) may cause dangerous side effects in the presence of *L Loa* co-infection.

The Cameroon Academy of Sciences has recommended the use of doxycycline for the treatment of river blindness to the Cameroon Government (2013) [5.4]; the Government is now revising the national onchocerciasis control strategy in accordance with these recommendations. Furthermore, in South America, doxycycline is being used to treat residual cases and foci where eradication rather than control is being targeted [5.5].

Impact on public policy
The Cameroon study's very high compliance rate of over 97.5% was attributed to detailed training of health workers recruited directly from the study community and the involvement of social scientists to ensure local traditions were not compromised. Since the study, WHO/APOC has advocated greater use of community-directed treatment programmes [5.1]. This approach is more expensive than traditional mass treatment programmes but, as demonstrated, effective use of doxycycline would protect the community for at least 4 years [5.2] and therefore be cost-effective.

Impact on the economy
A 2004 WHO study concluded that the disease burden of onchocerciasis was about 884,000 disability-adjusted life years. This can be interpreted as a loss of 15% gross national product in areas of high endemicity. Such losses are being reduced through the adoption of doxycycline in mass treatment campaigns.

Impact on health and welfare
The Cameroon study showed that, when empowered, community health workers can successfully deliver doxycycline for six weeks for the treatment of onchocerciasis. It paves the way for the initiation of control programmes for 8 million people across Cameroon, DR Congo and the Central African Republic.

At the end of the 6-week course of treatment with doxycycline, the community as a whole reported both immediate and long-term benefits [3.6]. Relief from itching and the regression of nodules were indicative of clearance of *O volvulus*. More rapid wound healing and reduction of secondary bacterial infections were reported together with increased appetite and sexual desire. The positive feedback from community members who took part in the first phase of treatment motivated reluctant individuals to adhere to treatment.

Resolution and prevention of skin disease is particularly important for women as this avoids the major social stigma and societal exclusion (including no marriage) that is associated with onchocerciasis.

5. Sources to corroborate the impact (indicative maximum of 10 references)

5.1 World Health Organization, African Programme for Onchocerciasis Control (APOC), 2012. Achievements of community-directed treatment with ivermectin (CDTI). http://www.who.int/apoc/cdti/achievements/en/.

5.2 Tamarozzi F, Tendongfor N, Enyong P, et al. Long term impact of large scale community-directed delivery of doxycycline for the treatment of onchocerciasis. Parasit Vectors. 2012;5:53. DOI: 10.1186/1756-3305-5-53.

5.3 CDC Resources for Health Professionals, Parasites - Onchocerciasis (also known as River Blindness), 2013. http://www.cdc.gov/parasites/onchocerciasis/health_professionals/.

5.4 Cameroon Academy of Sciences, 2013. Recent advances in onchocerciasis research and implications for control. *[Available on request.]*

5.5 Gustavsen K, Hopkins A, Sauerbrey M. Onchocerciasis in the Americas: from arrival to (near) elimination. Parasit Vectors. 2011;4:205. DOI: 10.1186/1756-3305-4-205.