Institution: The University of Edinburgh

Unit of Assessment: 1

Title of case study: D: Preventing deaths from pesticide self-poisoning in rural Asia – pralidoxime is hazardous and banning organophosphorus insecticides is beneficial

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

Impact: Health and welfare; public health studies in Sri Lanka and clinical trials in a cohort of 35,000 pesticide self-poisoning patients have led to the withdrawal of high-dose pralidoxime as a WHO-recommended treatment and bans of three toxic pesticides in Sri Lanka.

Significance: Resultant changes in clinical practice and pesticide regulation have saved 3000 lives in the last four years in Sri Lanka alone; in the rest of Asia many times this as local guidelines and practice have changed.

Beneficiaries: Patients and communities, healthcare providers, policy-makers.

Attribution: Studies designed and led, with international collaborators, by Michael Eddleston, UoE.

Reach: International, particularly Asia, changes in WHO and international guidelines on pesticide use.

2. Underpinning research (indicative maximum 500 words)

Professor Michael Eddleston (Professor of Clinical Toxicology, UoE, 2005–present) has led a series of studies dissecting the roles of specific organophosphates, vehicle components and antidote regimes in deaths following self-poisoning. The work has led to the banning of specific pesticides and changes in World Health Organization (WHO) treatment recommendations.

In 2002, Eddleston, with international collaborators, established in Sri Lanka the first prospective cohort of patients with acute self-poisoning in the developing world. The cohort continues today and now includes over 35,000 patients, with clinical description and, for a sub-sample, laboratory proof of the poison ingested. The quality of this research is evidenced by over 60 peer-reviewed publications by Eddleston's group and twelve peer-reviewed grants (> £9.5M) awarded.

In early research, Eddleston used the cohort to describe, often for the first time, the clinical presentation and outcome of poisoning with many pesticides and the use of the antidote atropine. In particular, in 2005, he described the effects of poisoning with three common organophosphorus (OP) insecticides, dimethoate, chlorpyrifos, and fenthion, showing very different clinical syndromes and case fatality despite all having the same WHO toxicity classification [3.1].

Eddleston was appointed to UoE in 2005, where he performed the research that has led to impact. Two randomised controlled trials (RCTs) were nested into the cohort: one of activated charcoal for all cases of self-poisoning and a second of the antidote pralidoxime in symptomatic OP pesticide poisoning. The former (4632 patients) showed no significant effect of multiple-dose charcoal on death [3.2]. However, it was found to be safe and reduced the need for hazardous gastric lavage, which itself slightly increases case fatality. The second trial, of 235 patients, found pralidoxime to be hazardous for patients (adjusted hazard ratio for death of 1.69, 95% confidence interval 0.88–3.26, $p = 0.12$). Incorporating the baseline amount of acetylcholinesterase and the plasma OP concentration into the analysis increased the hazard ratio for patients receiving pralidoxime to 3.94 (1.25–12.36, $p = 0.02$), decreasing the likelihood that pralidoxime is beneficial [3.3].

Eddleston has also performed further relevant observational and interventional public health studies. For example, in 2007, he showed how transient bans of the most toxic pesticides in Sri Lanka in the 1980–90s were followed by a 50% reduction in the overall suicide rate over 10 years [3.4].

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

3.1 Eddleston M, Eyer P, Worek F, et al. Differences between organophosphorus insecticides in human self-poisoning - a prospective cohort study. Lancet. 2005;366:1452–9. DOI: 10.1016/S0140-6736(05)67598-8.

3.2 Eddleston M, Juszczak E, Buckley N, et al. Multiple dose activated charcoal in acute self-poisoning - a randomised controlled trial. Lancet. 2008;371:579–86. DOI: 10.1016/S0140-6736(08)60270-6.

3.3 Eddleston M, Eyer P, Worek F, et al. Pralidoxime in acute organophosphorus insecticide poisoning - a randomised controlled trial. PLoS Medicine. 2009;6:e1000104. DOI: 10.1371/journal.pmed.1000104.

3.4 Gunnell D, Fernando R, Hewagama M,…Eddleston M. The impact of pesticide regulations on suicide in Sri Lanka. Int J Epidemiol. 2007;36:1235–42. DOI: 10.1093/ije/dym164.

Example Grant:

Wellcome Trust Intermediate Fellowship to M Eddleston. *Title:* Acute organophosphorus pesticide poisoning in Sri Lanka; 2001–7. £699,801.

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

Impact on public policy

Eddleston's work has had a profound impact on WHO policies regarding world pesticide-related poisoning avoidance and treatment. The pralidoxime study led the WHO to exclude pralidoxime from its Essential Drugs List in 2009; high-dose regimens of pralidoxime are no longer recommended [5.1, 5.2]. In addition, 2009 WHO guidance about how to prevent deaths from pesticide poisoning [5.3] was heavily based on Eddleston's work: all six publications cited in its summary were from the Eddleston group. A 2008 WHO meeting led by Eddleston resulted in publication of guidance for triaging and treating patients with acute pesticide poisoning [5.4]. The WHO Mental Health Gap Action Programme (mhGAP) thereafter in 2008 integrated pesticide poisoning into its assessment of patients [5.5].

In addition to the changes in WHO recommendations relating to pralidoxime, Eddleston's work led directly to national bans in Sri Lanka of fenthion, dimethoate and paraquat (2008) [5.6].

These interventions, and particularly the three pesticide bans, have been estimated to save 1000 lives per year in that country alone [5.7].

Impact on clinical practice and guidelines

Guidance concerning treatment of OP-poisoned patients has now changed across Asia (for example, 2010 national guidelines for Indian clinicians [5.8] demonstrate by citation the importance of Eddleston's work).

In summary, based on 250,000 deaths from pesticide self-poisoning across Asia per year, Eddleston and colleagues' findings on the use of atropine, pralidoxime and charcoal, and the bans of three toxic pesticides in Sri Lanka, are estimated to be saving approximately 10,000 lives per year on this continent.

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

5.1 Bevan M, 2009. Proposal for the inclusion of pralidoxime in the WHO model list of essential medicines. http://www.who.int/selection_medicines/committees/expert/17/application/Pralidoxime_web.pdf. *[Systematic review produced for the WHO assessing the evidence for effectiveness of pralidoxime in OP poisoning. Eddleston's pre-publication RCT was presented as the key study.]*

5.2 WHO, 2009. The selection and use of essential medicines. Report of the Expert Committee, 2009 (including the 16th WHO Model List of Essential Medicines and the 2nd WHO

Model List of Essential Medicines for Children). http://whqlibdoc.who.int/trs/WHO_TRS_958_eng.pdf. *[Report of the Expert Committee's decision not to make pralidoxime an Essential Drug, which cited Eddleston's RCT.]*

5.3 WHO, 2009. Guns, knives, and pesticides: reducing access to lethal means. (Series of briefings on violence prevention: the evidence). http://whqlibdoc.who.int/publications/2009/9789241597739_eng.pdf. *[WHO discussion of restricting access to pesticides as a method of suicide prevention, relying heavily on Eddleston and colleagues' work.]*

5.4 WHO, 2008. Clinical management of acute pesticide intoxication: prevention of suicidal behaviours. http://www.who.int/mental_health/prevention/suicide/pesticides_intoxication.pdf. *[Report on WHO meeting led by Eddleston that provided advice on best management of pesticide poisoned patients.]*

5.5 WHO, 2008. mhGAP Intervention guide for mental, neurological and substance use disorders in non-specialized health settings. http://whqlibdoc.who.int/publications/2010/9789241548069_eng.pdf. *[Guide to aid implementation of the WHO mhGAP program in resource-poor developing countries. With Eddleston's guidance, acute pesticide poisoning was integrated into the assessment and management of acutely sick patients.]*

5.6 Minutes of the 44th Meeting of the Sri Lankan Pesticides Technical Advisory Committee held on the 9th November 2007. Point 44.2.2 Use Restriction of Dimethoate and Fenthion in Pollonnaruwa. *[Available on request. Minutes showing discussion of Eddleston's public health intervention study that showed a reduction in case fatality following a ban of fenthion and dimethoate. As a result, the two pesticides were banned for agricultural use in the country in 2008. A further meeting discussed the ban of paraquat.]*

5.7 Dawson A*, Eddleston M*, Senarathna L, et al. Acute human lethal toxicity of agricultural pesticides: a prospective cohort study. PLoS Med. 2010;7:e1000357. DOI: 10.1371/journal.pmed.1000357. (*co-first author). *[Study that estimated the effect of the three Sri Lankan bans based on Eddleston and colleagues' work.]*

5.8 Sundaray N, Kumar R. Organophosphorus poisoning: current management guidelines. In: Rao M, ed. *Medicine Update*, 20 edn. New Delhi, Association of Physicians of India. 2010:420–5. *[Available on request. National guidance to Indian clinicians.]*