A strategy for hope in the face of death…

It was quarter past midnight, when I was standing in the intensive care unit (ICU) for a 400-bed secondary referral hospital enjoying some momentary air-conditioned respite from the outside tropical heat. After an evening of trawling the medical wards checking on patients in clinical studies, and supervising research assistants who carried out the data collection, the ICU was my last stop before retiring for the night. Out of the 6 ventilated beds in the unit, 3 were occupied by intubated and mechanically ventilated organophosphorus (OP) poisoned patients who had ingested pesticides through a variety of impulsive acts.

The first patient was a 40 year-old female who had recovered from 3 cardiac arrests within the preceding 2 hours, and was on an infusion of inotropes (cardiovascular drugs) that seemed to be helping her maintain a blood pressure enough to keep her alive. I asked the doctor, who was about 3 years out of medical school in seniority, whether this particular patient would be receiving oxime therapy. Oximes are an antidote whose use is controversial in the management of OP poisoning. His answer was that it depended upon the Consultant who was looking after the patient because there were no clear protocols on its use, and no means to measure its effectiveness.

This patient had been admitted on a day where she would get oximes, and I wondered to myself, "was it going to be important in this patient? Would it make a difference? Will the inotrope infusion make a difference to her survival? Or will she arrest again no matter what we do?"

"Perhaps an acetylcholinesterase (AChE) level, if available, could be helpful in guiding this difficult decision", I quietly thought to myself as I watched this motionless lady lie helplessly connected to an artificial ventilator through a breathing tube. AChE is a biomarker that can

give an indication of both the levels of poisoning and the effectiveness of oxime therapy, and the portable field kit that I had chosen to study could measure it.

In the next bed lay another intubated patient, a 26 year-old male, who was bare-chested, and donning a sarong for cover of his bottom half. His attire was entirely appropriate as ICU was still not "cold" despite being cooler due to the air conditioned, a welcome change from the humid heat that was present outside and in the regular ward setting. This man had been in the ICU for 2 weeks and was being treated for aspiration pneumonia rather than the direct toxic effect of the poison, which had long since left his body.

I found out about the circumstance of this patient's admission, upon further inquiry from my ICU night doctor friend, and learned that he was transferred from a peripheral hospital with an unprotected airway, despite having a stomach full of pesticides and alcohol. He was close to having a respiratory arrest upon arrival in the secondary referral hospital. This junior ICU doctor was quite frustrated when explaining this scenario to me. He said he often received patients from peripheral hospitals, who had travelled for up to 2 hours in the back of an ambulance without nurse or paramedic, and that it was common for the patients to have not received the adequate initial advanced life support and airway protection prior to transfer.

It was easy to be critical of the doctors in the periphery but I wondered if the problem was more complex than it seemed on the surface? I had learned from a colleague's local research that primary care doctors in the peripheral hospitals were professionally isolated and found it hard to access training. I had observed a lack of training in resuscitation for junior doctors even in the larger referral centres, and thought resuscitation education must be even more scarce in the periphery.

"Surely, there must be something that can be done to address this problem?" I reflected, wondering about a research intervention that could provide resuscitation training to the

peripheral hospital doctor population, but that hopeful thought would have to wait for another day as at that moment I still had a ward round to complete.

Finally, the last patient whose observations were collected on my routine ICU visit, was a 20 year-old female who had been distressed about a relationship that had ended, providing her with an additional stressor that contributed to her drinking poison that night. She was resuscitated in the ward and had come to ICU intubated like the other two patients.

"What would be her fate?" I wondered, whilst my mind slowed a little, already full of a heap of unanswered clinical questions about improving health care systems that could perhaps lead to improved care in these critically ill poisoned patients. "Would she also receive oxime therapy?", I continued to ponder, "And if so, is there evidence to distinguish whether this was the best therapy for her right now?", "If she arrested again, what would be the best treatment for her in that moment – do we even know?".

Such questions kept rapidly appearing, but the strategies to find some of the answers would form much more slowly, over the months, and even years to come. All I knew at that moment was that this patient was too young to die; and if something was possible make a positive difference in some small way, then we had to at least try…

The following thesis is dedicated to the pesticide poisoned patients and their families, and to the medical staff that have been entrusted with their care.

Preface – Introduction and aims of thesis

Self-poisoning is a major worldwide public health problem, resulting in over 300,000 deaths annually. Organophosphorus (OP) pesticides are the most common agents accounting for approximately 200,000 deaths each year in Asia(1-3). Case fatality is between 15-30% with current best practice, but there has been limited research dedicated to reducing the mortality and morbidity of this condition.

The high case fatality is multifactorial and has been linked to several factors including the toxicity of the pesticide, the quality of medical treatment and a lack of resources in the region where the practice of self poisoning is prevalent(4). Early medical management that includes effective resuscitation and targeted antidote therapy is often lacking(5). My research aimed to demonstrate that health services research and training were two important vehicles that could act to close the evidence to practice gap and thereby improve the medical management of OP poisoning.

I used the conceptual framework of translational research, also known as “knowledge translation”(6), to link together two streams of research that addressed the topic of OP poisoning management, which may otherwise appear unrelated. These streams consisted of research investigating the use of AChE in guiding clinical management, and research that measured the effectiveness of resuscitation training in a rural setting. Both streams tested strategies focused on improving medical management of a single condition, OP poisoning, with an overarching goal of reducing mortality and morbidity.

The different studies operate at different stages of the continuum in the translation of evidence into practice, as summarized in Figure 1. This diagram also highlights how both research topics, AChE and Resuscitation, represent more than one of the three component’s that have been described as integral to the process of knowledge

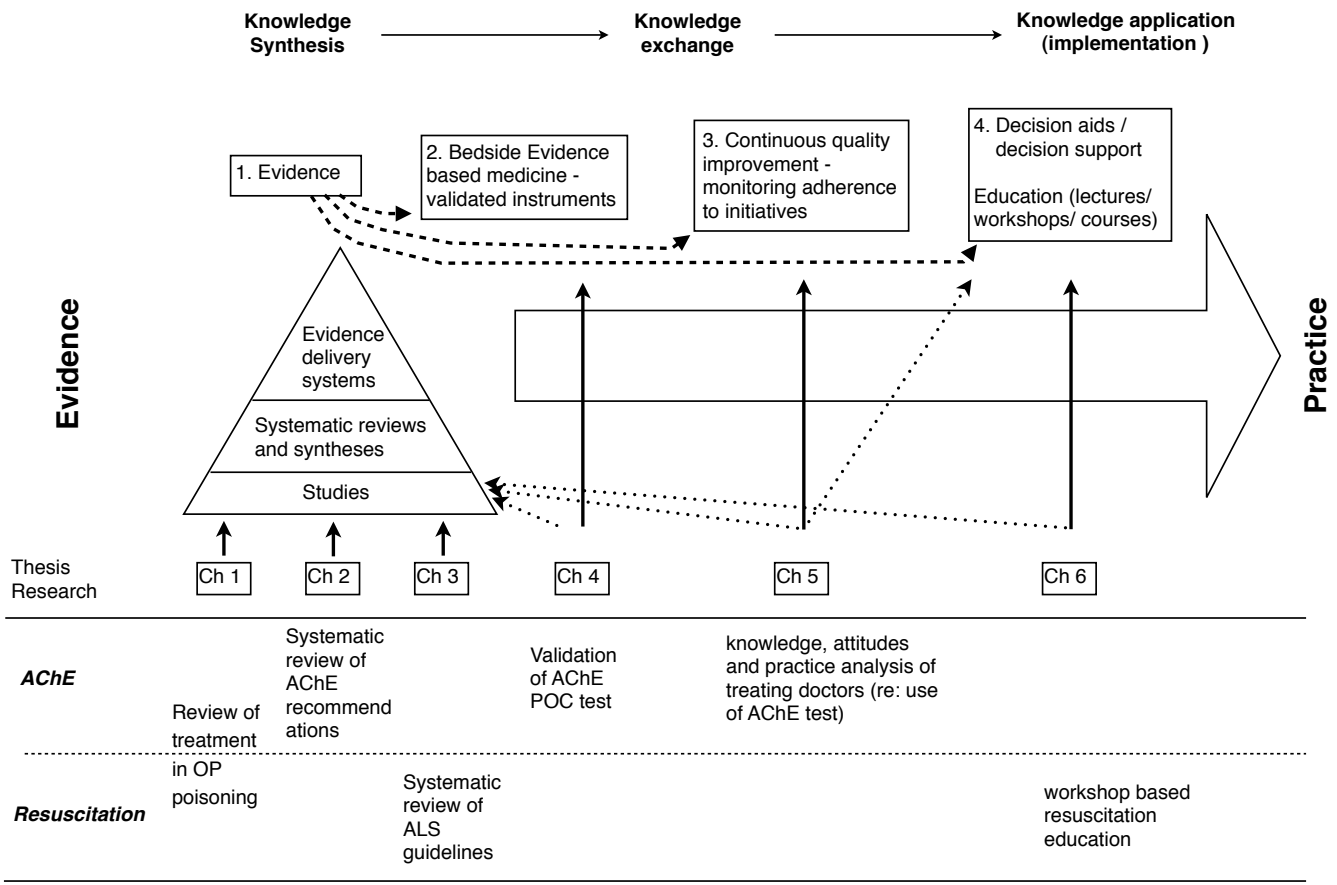


Figure 1 Schema of a translational research model for closing the evidence-to-practice gap.

Shows the contribution of individual chapters to different steps in the process of evidence being translated into practice. Schema based on a figure by Lang et al.(8) and adapted according to Arnold et al.(6).

Translation; knowledge synthesis, exchange and application (6, 7).

Peripheral hospitals are frequently the first point of contact with health services for OP poisoned patients. Half of my research focused on exploring an educational strategy in this setting, and the other half addressed a deficiency in laboratory facilities at secondary referral hospitals by providing biomarkers of OP poisoning through point-of-care (POC) testing. Specifically, I evaluated the effectiveness of a train-the-trainer (TTT) model of resuscitation education for peripheral hospital doctors, and I studied the validity of an acetylcholinesterase (AChE) POC test in acute OP poisoning, as well as the effect its results have on the knowledge, attitudes and practice of treating clinicians at secondary referral hospitals.

Both projects address a gap in the translation of existing knowledge, and recommendations into practice, and each targets aspects of an underdeveloped emergency and critical care service for acutely poisoned OP patients in resource limited rural hospital settings.

Origin of research projects and details of fieldwork

Before I embarked on the path of higher degree research through the Australian National University, I was an Emergency Medicine specialist-in-training working in an urban emergency department in Wellington, New Zealand. I had an interest in medical education and research, and this background combined with my discovery of specific on-the-ground deficiencies in the Sri Lankan rural health services led me to the current research projects. The South Asian Clinical Toxicology Research Collaboration (SACTRC; www.sactrc.org) is a research collaboration whose objective is to reduce mortality from poisoning through capacity building research that utilises a range of strategies. Working through SACTRC's infrastructure I conducted my research entirely

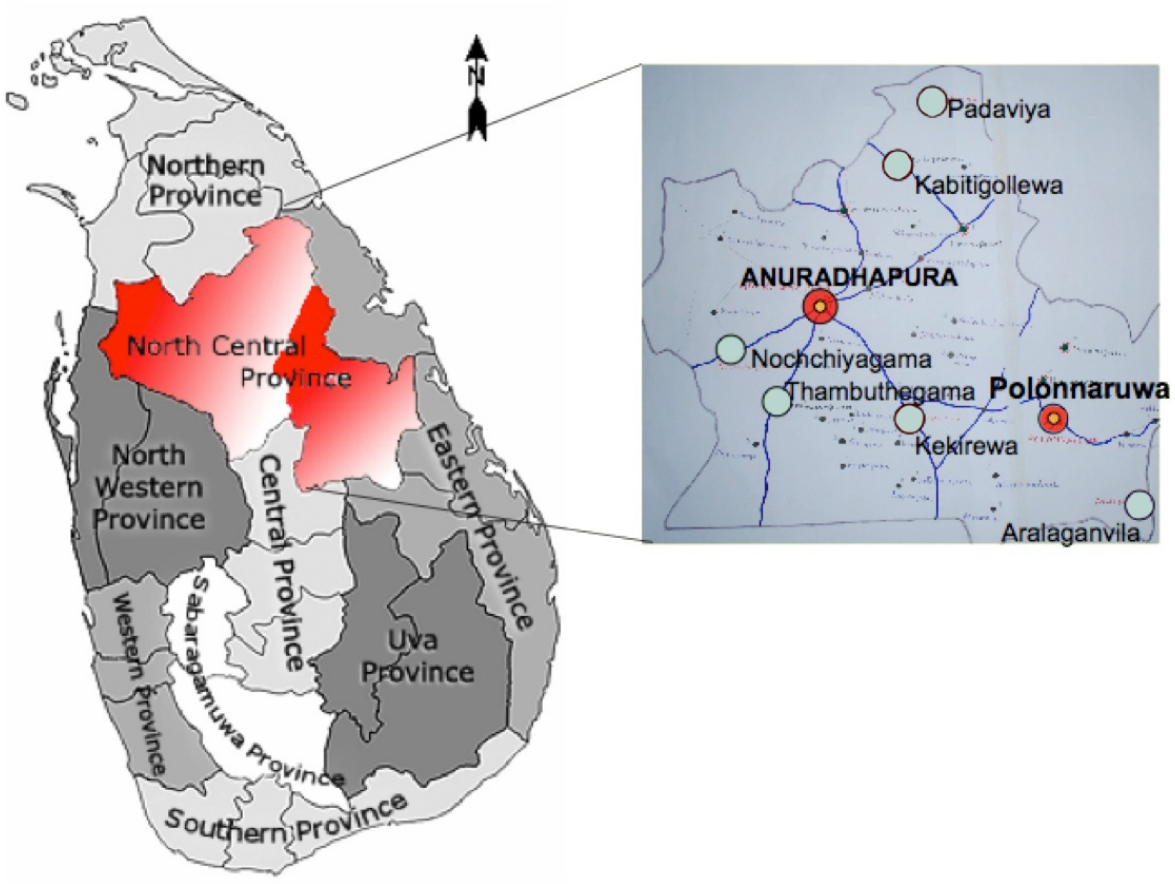
in Sri Lanka owing to the high prevalence of OP poisoning and consequent burden of disease.

The clinical research was conducted at hospitals in the North Central Province, the largest province in Sri Lanka. Employment is largely in agriculture and consequently agrochemicals such as OP pesticides are widely available. The POC testing research was based at the two larger referral hospitals located in the cities of Anuradhapura and town of Polonnaruwa, (Figure 2), and the resuscitation training work was conducted at smaller peripheral hospitals throughout the province. For the purpose of the argument presented in this thesis, these two referral hospitals were both considered as central "rural" hospitals because their health services shared similar resource constraints, in terms of resuscitation and laboratory facilities, when compared to the larger cities located in Sri Lanka's commercial centres such as Kandy or Colombo. The research office was in a collaborating local university, University of Peradeniya, which was located close to Kandy, the second largest city in Sri Lanka.

My aim whilst working with SACTRC in Sri Lanka was to find practical ways of addressing the challenge of improving the medical management of OP poisoning and to participate in organizational change whilst conducting research. Thus the research strategy I employed could be considered a form of participatory action research(9, 10). At the same time both the introduction of the POC test, and study of the TTT education model had characteristics of complex interventions(11); such as engagement with the local health service, and having more than one phase of development and evaluation for some interventions.

The research methodology I used was adapted to the health care setting where my fieldwork took place. At these hospitals there was a general lack of research culture, a paucity of methodical note taking or audit, and lack of familiarity or acceptance of the benefits of coordinated research such as randomized studies. These rural hospitals are

Figure 2 Map of Sri Lanka showing the location of central and peripheral hospitals in the north central province(12).



Sri Lanka is an Island nation of 64,000 square kilometers, and a population of 21 million people. It is a low to middle income country with an annual income of USD $5,500 per capita, and life expectancy of 71 years for men and 78 years for women(13). The figure highlights the North Central Province, and the inset shows the distribution of central and peripheral hospitals. The two central referral hospitals are marked with shaded circles and inner dot. The remaining hospitals vary in size from larger peripheral hospitals (marked with a shaded circle), to small peripheral hospitals and peripheral units (shown as black dots).

focused on delivering clinical care to very high volumes of patients with limited infrastructure.

Gap in emergency and critical care training in rural hospitals

The Postgraduate Institute of Medicine (PGIM) coordinates postgraduate training in all accredited specialties in Sri Lanka (including medicine, surgery, paediatrics and obstetrics and gynaecology). At the time I embarked on my fieldwork in 2006 there were no dedicated qualifications for intensivists or emergency physicians. This left a void in the provision of critical care, and particularly in the realm of resuscitation training and supervision. This situation is compounded by the fact that only a low proportion (less than 20%) of medical graduates undertake any postgraduate training, and these people are concentrated in urban hospitals. There are very few, or no, doctors undergoing postgraduate specialist training in peripheral rural hospitals where pesticide poisoned patients generally first present. From 2006 to 2010, during which time my fieldwork was conducted, no national resuscitation training programs or ad hoc resuscitation training was available in the peripheral hospitals. Since then Sri Lanka has experienced advances in the nationwide Emergency Medicine strategy that includes an active Emergency Medicine specialist training program, which was launched in 2013(14). These developments would suggest an increased access to resuscitation training for the small number of doctors who were training in Emergency Medicine, in the large urban centres where specialist training occurs. However, despite such advances in the large urban centres where specialist training occurs, a national resuscitation training program was still absent for the peripheral hospitals at the time this thesis was published.

Resource limitations in emergency and critical care service provision

Resource limitations in rural areas have a strong impact on the emergency care of OP poisoned patients. In referral hospitals, laboratory tests are not commonly used. Patients are diagnosed and managed largely based on clinical findings. Access to

basic tests (biochemistry, haematology) is very limited. There is no laboratory accreditation enforcement so the quality of results can be unreliable.

There are limited numbers of intensive care beds, with the largest (1600 bed) secondary referral hospitals only having 8-10 ventilated beds within their medical intensive care unit (ICU).

Nurse and doctor to patient ratios are much lower than in western countries. It is not uncommon for a large referral hospital to only have two consultant physicians managing up to 200 patients each. Furthermore, the same consultant physicians are in charge of the medical ICU and the care of ventilated patients. Most of the middle tier doctors, senior house officers (SHO's), who are responsible for delivery of patient care and supervising intern doctors are between 3-4 years post graduation. They also all have heavy clinical loads. Primary hospitals range in size from central dispensary units without inpatient facilities that are manned by a single doctor, to larger base hospitals with more than ten doctors. Such hospitals do not have specialist-trained doctors, and there is a limited infrastructure for training. Often the nearest training may occur several hours away and an inability for doctors at these locations to obtain leave from clinical duties leads to professional isolation(15).

'Participatory action research' - framework for methods used

This research also has many features of participatory action research (PAR) which involves collective, self reflective inquiry that researchers and participants undertake, so that they can understand and improve upon the practices in which they participate (9, 16). The reflective process is directly linked to action, influenced by the understanding of history, culture, and local context and is embedded in social relationships. The process of PAR should be empowering and lead to people having increased control over their lives(9). PAR is a growing field that is noted to be of

particular value in the problems affecting low income countries, and in addressing the 10:90 gap, a term highlighting that only 10% of research funds are addressing 90% of the global disease burden(9, 16-18). Another term for PAR that is seen in the literature is community based participatory research (CBPR)(16).

The studies I carried out were reflective of this approach on many levels including the conduct of research through collaboration and development of partnerships with local authorities, development of sustaining and trusting community-researcher relationships, the assessment of barriers to achieving better health, and the dissemination of findings to practice and policy. Reflections on the use of these type of methods will be addressed in the final chapter.

Chapter outline

The challenge of improving the medical management of OP poisoning in a resource limited rural setting is evaluated through interventional studies, and systematic reviews that form the chapters of this thesis. The chapters have been conventionally ordered with the background and systematic reviews at the beginning, followed by the description of experimental work. However, the research was undertaken in a different order, which is outlined below.

The thesis starts with a review of the management of OP poisoning (Chapter 1) which describes how effective resuscitation, and targeted antidote therapy, are the accepted cornerstones of acute management in the incidence of severe OP poisoning. Improvements in these two aspects of medical management are the basis for the two streams of intervention, acetylcholinesterase (AChE) POC testing, and rural resuscitation training, which is the focus of the remainder of the thesis.

The first half of the research assesses the introduction of an acetylcholinesterase POC test (Test-mate ChE 460) designed in North America for occupational use in the surveillance of agricultural workers rather than for use in the setting of severe OP self-poisoning. The POC Test-mate machine is first validated in this population (Chapter 4). Thereafter the change in knowledge, attitude and practice of clinicians with exposure to seeing AChE test results was studied, with the expectation that the introduction of this widely recommended test may improve all three (Chapter 5). It became clear after the analysis of this study that interpretation of AChE results was not straightforward. Thus, I conducted a detailed systematic review of the literature on the range of specific recommendations for the use of AChE in the management of OP poisoning, and the degree such recommendations were backed up by evidence (Chapter 2).

The second stream of research was related to advance life support (ALS). I observed preventable poor outcomes in OP poisoned patients that were largely due to poor resuscitation. Frequently such results were observed in transferred patients who had been inadequately resuscitated at the peripheral hospitals where they first presented. I also observed a lack of practical training and supervision in resuscitation. This motivated me to carry out some pilot training work using mannequins, video technology and scenarios that led to shifts in ALS knowledge and skills. This pilot work is what inspired my study that evaluated the effectiveness of a train-the-trainer (TTT) model of resuscitation in peripheral hospital doctors (Chapter 6). It also addressed the shortage of specialist trainers through the use of peripheral hospital doctors to run peer-led resuscitation education workshops.

In the context of doing general advanced life support training, it became apparent that specific OP ALS guidelines might more directly address the challenge of resuscitation in the context of OP poisoning. Thus, I conducted a systematic review (Chapter 3) that identifies which components are broadly accepted, and the sequence in which antidotes should be recommended, and this was incorporated into an OP specific ALS guideline. The TTT study described in Chapter 6 did not test the proposed guideline because the first step was to find out whether a “model” of training for rural hospitals was feasible and effective in teaching a previously validated guideline such as standard ALS.

Chapter 7 summarizes the contributions, strengths and weaknesses of the thesis and outlines suggestions for future research and policy changes relating to AChE POC testing, and resuscitation training for OP poisoned patients.