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- Predicting bladder cancer death amongst Australian Veterans
- Army Malaria Institute – its Evolution and Achievements
- Rabies post-exposure prophylaxis in Australian Defence Force

The Journal of the Australasian Military Medicine Association

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Journal of Military and Veterans' Health

Australasian Military Medicine Association

STATEMENT OF OBJECTIVES

The Australasian Military Association is an independent, professional scientific organisation of health professionals with the objectives of:

- Promoting the study of military medicine
- Bringing together those with an interest in military medicine
- Disseminating knowledge of military medicine
- Publishing and distributing a journal in military medicine
- Promoting research in military medicine

Membership of the Association is open to doctors, dentists, nurses, pharmacists, paramedics and anyone with a professional interest in any of the disciplines of military medicine. The Association is totally independent of the Australian Defence Force.

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Inside this edition

As we move into 2015, we have a unique opportunity to look back to the origins of Australian Defence Force health services 100 years ago, the changes in Defence healthcare in the intervening years and where we might expect to go into the future. The fundamentals of conflicts and wars themselves have changed – from the set piece battles and trench warfare of the Great War to the highly mobile conflicts of the 21st century. The establishment of the No. 1 Australian General Hospital (No. 1 AGH) is a case in point. First sanctioned by the Commonwealth Defence Department in August 1914, the unit left Australia as a General Hospital of 520 beds on board the S.S. Kyarra on 21 November 1914. Arriving in Egypt on 14 January 1915, the No.1 AGH was set up in the Heliopolis Palace Hotel. By June 1915, this 520 bed hospital and surrounding buildings held nearly 2500 patients, cared for by only 150 nurses. Needless to say, hospital equipment and supplies were totally inadequate. (1) The sheer scale is daunting and, arguably, way beyond the worst nightmares of today's Defence health planners. The resilience of the medical, nursing and health support staff, the innovation in difficult situations and the dedication to support the broader military forces continues on. Ian McPhedran's description of the life-saving health care provided by RAAF and other ADF health staff after the Bali Bombing, in his recent book "Air Force", (2) highlights both this continued dedication and the appreciation of these efforts by other non-health ADF personnel. How we apply these lessons in years to come will be of great interest.

Some of the more perceptive of our readers may have noticed that we did not publish a 4th issue in 2014. This was to allow us to realign our publication dates and to get the first issue out early in 2015. Our first issue has a tropical medicine theme, with excellent articles on rabies and the more recent history of the Army Malaria Institute. We also continue looking at cancer cases in serving members and veterans with a review of bladder cancer deaths among veterans. This issue also looks at the nurse practitioners' role in facilitating treatment in post-traumatic stress disorder. Finally, this issue includes all the abstracts from our recent AMMA Conference in Sydney in October 2014.

We continue to get a good range of articles, but other military and veterans' health articles are always very welcome and we would encourage all our readers to consider writing on their areas of military or veterans' health interest.

Dr Andy Robertson, CSC

Editor-in-Chief

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1. Bassett J. Guns and Brooches: Australian Army Nursing from the Boer War to the Gulf War. Oxford; Melbourne: 1992.
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Predicting bladder cancer death amongst Australian Veterans

Sophie Plagakis, Sheryl Edwards, Michael O'Callaghan, Darren Foreman

Abstract

Background The purpose of this study was to compare the veteran and non-veteran cohorts of patients diagnosed with bladder cancer in order to determine if veterans have a worse clinical outcome, as has previously been demonstrated in prostate cancer.

Methods Using the Bladder Cancer Outcomes Database at the Repatriation General Hospital, South Australia, all bladder cancer cases between January 1984 and December 2011 were identified. This data was used to identify independent predictors of death in these populations and to contrast their five year bladder cancer-specific and overall survival. A subgroup of muscle-invasive bladder cancer was also analysed. There were a total of 1177 patients studied.

Results Overall, there was no significant difference in bladder cancer specific outcomes for veteran compared to non-veteran subjects. In both groups, the staging of disease at diagnosis was the strongest independent predictor of outcome, followed by the patient's age at diagnosis. Veterans were generally older at diagnosis than non-veterans, and they did demonstrate worse all cause mortality outcomes.

In the muscle invasive bladder cancer subgroup, outcomes were similar between veterans and non-veterans but veterans were more likely to be treated with radiotherapy.

Conclusion The independent predictors of outcome and bladder cancer specific survival rates in our South Australian cohort were similar to those described in the international literature and do not demonstrate poorer outcomes in our veteran population. All cause mortality was worse in the veteran population, however, which may be related to their older age at diagnosis and different treatments they may be offered as a consequence.

Keywords Bladder cancer, veteran, muscle invasive, survival

Introduction

Bladder cancer is the tenth most common malignancy diagnosed in Australia and has an annual incidence of 2.0% among all newly diagnosed cancers.[1] It is the seventh highest cause of cancer related death in the veteran population of the United States.[2] It is predominantly diagnosed in older, male patients with almost 80% of patients being over 65 years of age at the time of diagnosis. Since 1984, there has been a decrease observed in the age-standardised incidence of bladder cancer in both male and female Australians, and there has been a corresponding increase in mortality of those who have been diagnosed.[3]

There is a strong causal link with bladder cancer and tobacco smoking.[2-4] A study in 2011 found the risk of bladder cancer to be four times higher in smokers, compared with non-smokers[5], and Kuper et al. estimates a decrease of up to 60% in the risk of bladder cancer following cessation of smoking.[6] In the United States, it has been shown that the veteran population has a higher prevalence of smoking than the non-veteran population.[7] International studies have also demonstrated higher rates of bladder cancer in veterans from the USA and the United Kingdom ; however there are no studies published reporting the incidence of bladder cancer in Australian veterans.[2,8]

Analyses of the South Australian Prostate Cancer Outcomes Database have demonstrated that veterans have worse clinical disease profiles than non-veterans with prostate cancer, and significantly lower prostate cancer-specific survival rates.[9] This study was designed to determine whether a similar relationship exists with Australian veterans and bladder cancer.

A further sub-group of patients with muscle-invasive bladder cancer at diagnosis were identified within the veteran population. Their characteristics, treatment decisions and survival outcomes were compared against a non-veteran population.

Materials and Methods

Ethics approval for this project was obtained from the Southern Adelaide Clinical Human Research Ethics Committee.

The Bladder Cancer Outcomes Database has been maintained at the Repatriation General Hospital in South Australia since 1984, and contains almost 1500 patients. The database records all bladder cancer diagnoses that have been treated at a single public hospital, which caters for both veteran and non-veteran patients within a large catchment area in South Australia. Data is collected prospectively and includes age, gender, disease stage and grade, treatment received, cytotoxic agent use, veteran status and cause of death. The database was originally conceived as a specialist nurse record of patients' treatment to assist with the administration of intravesical therapy and tracking ongoing surveillance. It has since been approved for research activity.

The Bladder Cancer Outcomes Database was used to identify patients who had been diagnosed between January 1984 and December 2011. Patient data extracted for this study included gender, age at diagnosis, stage and grade at diagnosis, and cause of death. Veterans were defined as patients who held a Department of Veteran's Affairs Gold Card at the time of diagnosis. Gold Card holders include ex-servicemen and women, and also include war widows and widowers and dependents of servicemen who were killed in the course of duty.[10]

A subgroup of patient with muscle-invasive bladder cancer were analysed separately using the additional data of American Society of Anaesthesiologists (ASA) score and treatment modality. Comparisons between veteran and non-veteran groups were made. Distribution was compared with Kruskal Wallis tests or a Chi-squared test (Fisher's exact test where cell counts were low). Means were compared using a t-test. Independent predictors of survival were analysed using a Cox proportional hazards model and five and ten year survival rates were obtained from a Kaplan-Meier curve.

Results

The Bladder Cancer Outcomes Database identified 1466 patients, however only 1176 had veteran status identified and were included in the study. There were

Table 1: Patient characteristics in overall bladder cancer group and muscle-invasive bladder cancer sub-group

Descriptors and Outcomes		Veteran status		Totals	Significance p value
		Yes (%)	No (%)		
Gender	Male	231	671	902	
	Female	26	248	274	
Mean Age at Diagnosis		77 years	70 years		<0.001
Median Follow Up		61 months	49 months		
Five year bladder cancer specific survival (%)		82	85		
Ten year bladder cancer specific survival (%)		75	72		
Stage at Diagnosis	Ta	90 (52)	390 (56)	480	0.74†
	T1	56 (33)	197 (28)	253	
	T2	19 (11)	84 (12)	103	
	T3	5 (3)	15 (2)	20	
	T4	2 (1)	12 (2)	14	
	Totals	172 (100)	698 (100)	870	
Survival Outcomes	Alive	79 (31)	568 (62)	647	Reference
	Death – bladder cancer	47 (18)	127 (13)	174	< 0.001
	Death – other cause	127 (50)	220 (24)	347	< 0.001
	Lost to follow up	0 (0)	2 (0.2)	2	-
	Totals	253 (100)	917 (100)	1170	
Overall Total		257	919		
Muscle-Invasive Bladder Cancer subgroup					
Proportion of cohort		28	124	152	
Average Age at Diagnosis		82	74		<0.001*
Treatment modality	Surgery	5 (18)	52 (43)		0.002‡
	Radiation	17 (61)	24 (19)		
	Palliative	5 (18)	35 (28)		
	Missing	1 (3)	13 (10)		
	Totals	28 (100)	124 (100)		
ASA status	1	0	1		0.002†
	2	2	33		
	3	18	77		
	4	8	13		

**t-test; † Kruskal-Wallis test; ‡ Chi squared test.*

257 veterans and 919 non-veterans. The mean follow up time was 49 months for non-veterans (95% CI 43-54) and 61 months for veterans (95% CI 49-72).

In total, 76.7% of the patient group were male, with a higher proportion of males when comparing the veteran group with non-veterans (90% compared with 73%).

Mean age at diagnosis for veterans was 77 years compared with 70 years for non-veterans (p value <0.001). Almost 80% of veterans were diagnosed between the ages of 70 and 89, whilst the majority of non-veterans were diagnosed from 60 to 79 years of age.

Outcomes recorded in the database for all patients were: Alive, Dead from Bladder Cancer, Dead from Other Cause and Lost to Follow Up. Non-veterans were more likely to be alive. Veterans were more likely to have died from other cause compared with non-veterans (50% compared with 24%, p <0.001). A higher proportion of veterans died from bladder cancer (18% compared with 13%, p <0.001).

Tumour stage at diagnosis was assigned by pathological assessment as Ta, T1, T2, T3 and T4. The tumour stage at diagnosis was similarly distributed between both groups, with no significant differences between the groups. Tumour grade was also evenly spread between the groups, and the p value between the groups was insignificant (p=0.75).

Independent predictors of survival were analysed in a multivariable model and included age at diagnosis, gender, veteran status, stage and grade of disease at diagnosis. Veteran status was not a statistically significant predictor of death from bladder cancer (p = 0.96). However, age, gender and stage at diagnosis were all significant predictors of death from bladder cancer. Increasing stage at diagnosis was associated with increasingly worse outcomes. The hazard ratio for death from bladder cancer was 27.5 (95% CI 9.4-80.5) for T4 disease compared to 5.8 (95% CI 2.9-11.8) for T1 disease.

Bladder cancer specific survival was not significantly different between veteran and non-veteran patients (p = 0.58). The longest a veteran lived post diagnosis was 423 months, and the longest a non-veteran lived was for 364 months. Overall survival was significantly worse among veterans compared with non-veterans (p<0.001)

Muscle-invasive Bladder Cancer subgroup

A subgroup of patients with muscle-invasive bladder cancer was analysed. One hundred and fifty two patients were identified (28 veterans, 124 non-veterans, p = 0.33), and the average age at diagnosis

Table 2: Cox proportional hazards model of survival from the time of diagnosis for bladder cancer patients and a subgroup of patients with muscle invasive disease

Variable	Hazard ratio (95% Confidence Interval)	P value
All Cases – bladder cancer specific survival		
Age at Diagnosis	1.05 (1.03-1.07)	<0.001
Gender	1.95 (1.32-2.9)	<0.001
Veteran Status	1.01 (0.67-1.6)	0.96
Cancer Stage		
Ta	-	-
T1	5.8 (2.9-11.8)	<0.001
T2	14.8 (6.8-32.1)	<0.001
T3	49.5 (20.1-122.1)	<0.001
T4	27.5 (9.4-80.5)	<0.001
Cancer Grade		
1	-	-
2	1.2 (0.4-3.3)	0.76
3	2.14 (0.7-6.2)	0.16
Muscle-Invasive Bladder Cancer subgroup – overall survival		
Age	0.98 (0.97-1.01)	0.21
Veteran status	1.36 (0.82-2.26)	0.23
Gender	0.61 (0.39-0.93)	0.02
Treatment Group		
Surgery	-	-
Radiation	3.54 (1.96-6.41)	<0.001
Palliative	7.01 (3.86-12.76)	<0.001
Missing	1.33 (0.53-3.33)	0.53

Figure 1a

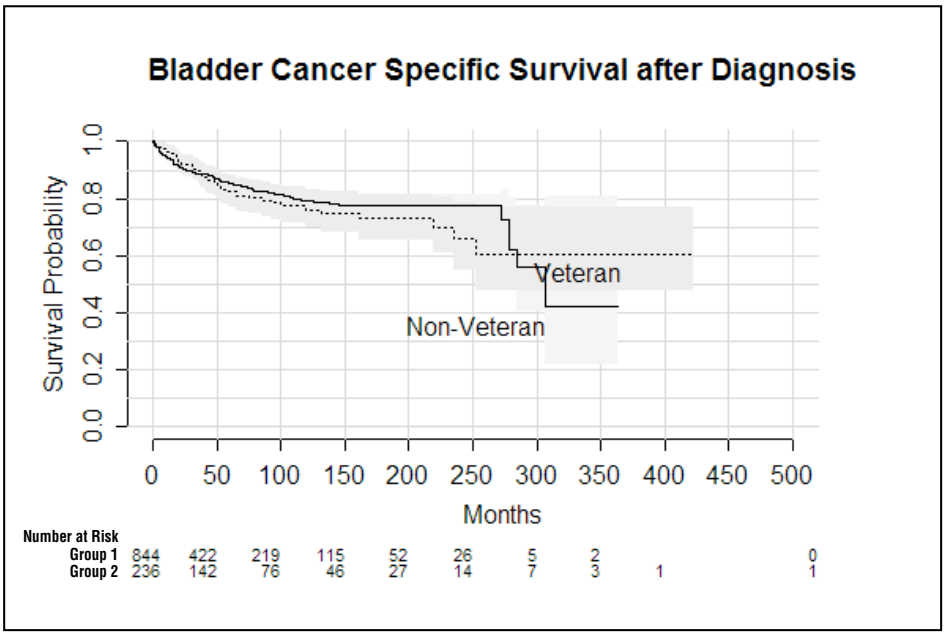
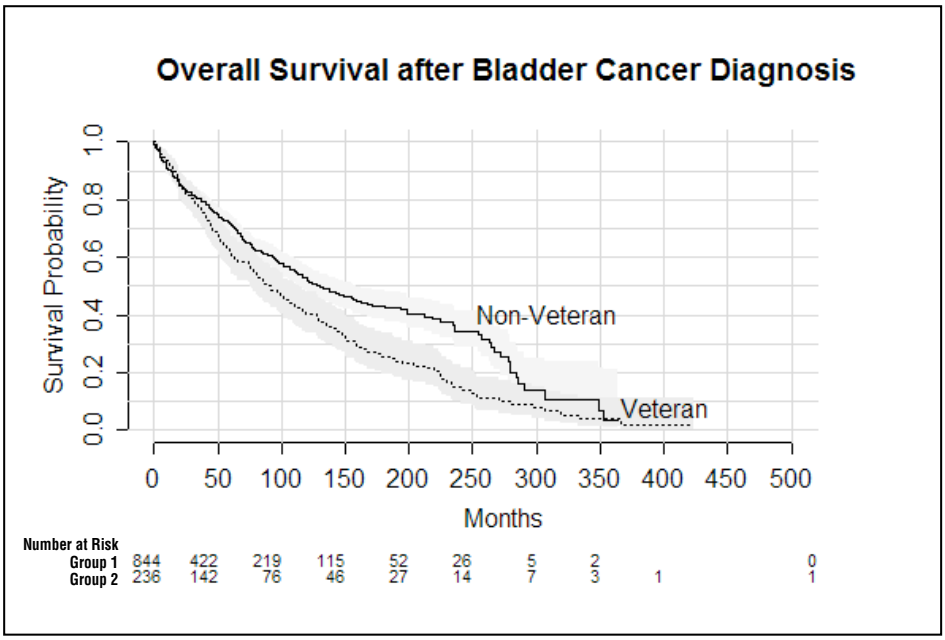


Figure 1b



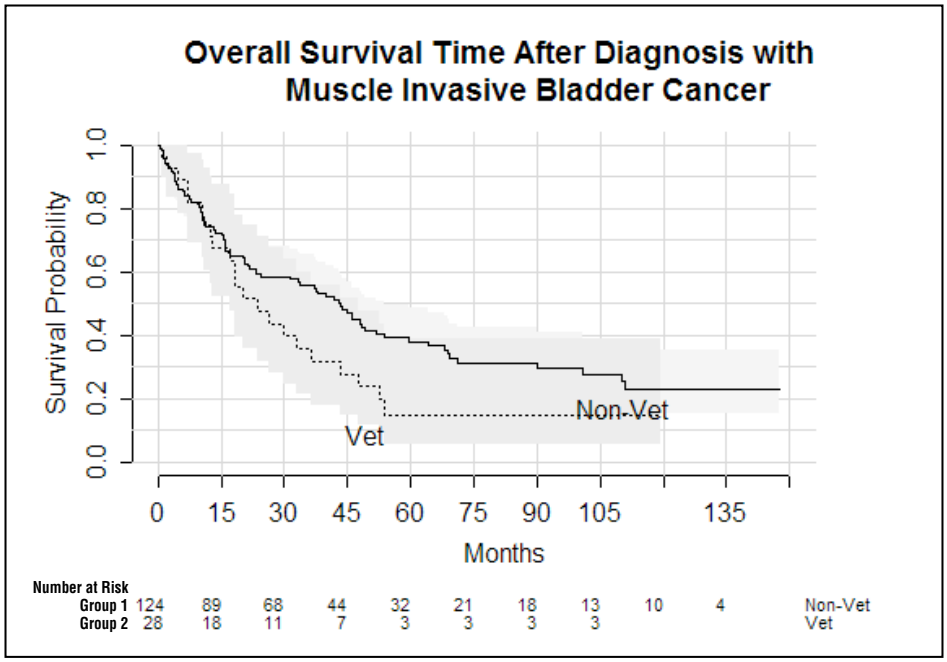
was 82 years for the veteran group and 74 years for the non-veteran group, which was significantly different ($p < 0.001$). Veterans undergoing surgery had a higher median age than non-veteran patients (78 versus 68.5, $p = 0.13$). There were a higher proportion of male patients in the veteran group.

Veterans were three times more likely to have their muscle-invasive bladder cancer managed with radiotherapy ($p < 0.001$), and were four times less likely to have surgical excision of their bladder compared to the non-veteran group (Table 1). This is most likely reflective of their older age at diagnosis. A similar proportion in each group was managed with palliative intent.

The American Society of Anaesthesiologists (ASA) uses a physical status classification to record patient fitness for an anaesthetic, which ranges from ASA 1, which is assigned to a healthy person, to ASA 4 which is severe systemic disease that is a constant threat to life. The veteran group contained a higher proportion of patients with ASA 3 and 4 ($p = 0.02$).

There was no statistically significant difference in survival outcome of muscle-invasive bladder cancer patients between the two patient groups ($p = 0.1$). Neither age, veteran status nor gender were statistically significant predictors of death in the muscle-invasive subgroup.

Figure 2



Discussion

In this South Australian population, we found that the clinical descriptors of veteran and non-veteran patients with bladder cancer to be similar. The most marked differences occurred in age at diagnosis and gender. The gender difference between the groups was expected, due to the high male proportion within the veteran population.

Smoking history was not reliably recorded in the Bladder Cancer Outcomes Database and was not used for analysis.

Using the DVA Gold Card as the main identifier for Veteran Status does mean that war widows and dependents have been included in our veteran population, however it was not possible to scrutinise their details after de-identification of data. We do acknowledge this as a weakness in our analysis.

Bladder tumour grade was reported by our pathologists according to Mostofi in 1973.[11] Modifications to grade occurred in 1998[12] and 2004,[13] and these were also reported to allow for consistent comparison between tumours within the database.

The stage and grade at diagnosis was comparable between the groups. Considering the older age at diagnosis, the equivalent pathological stage suggests that there was no significant delay in diagnosis within the veteran group. The older age at diagnosis may account for the higher proportion of death from other causes in the veteran group. This contrasts with recent studies that demonstrate worse cancer-specific mortality in patients diagnosed at an older age, both because they are diagnosed with higher-risk tumours and are less likely to undergo aggressive treatment.[14] We were not able to determine why veterans were diagnosed at an older age than non-veterans.

Female patients in our overall bladder cancer cohort did demonstrate poorer outcomes than male patients. This trend is consistent with international literature.[14-15] The reason for poorer outcomes in females requires further investigation, and hypotheses include challenges staging disease within the female pelvis, and delayed diagnosis due to symptoms being attributed to urinary tract infection or overactive bladder. It has also been suggested that women respond less effectively to intravesical treatments, but this is unsubstantiated by evidence.[14]

Veterans with muscle-invasive bladder cancer were more likely to be treated with radiotherapy than non-veterans, and this is most likely due to older age at diagnosis and poorer anaesthetic fitness. There was no statistical difference between the groups in survival, although the sample size was small.

In conclusion, this South Australian veteran population did not demonstrate a worse clinical disease profile than the non-veteran population. Our cohort was predominantly male and diagnosed at an older age. However there was no statistically significant difference in bladder cancer specific survival, including the muscle-invasive disease

subgroup, compared to the non-veteran group. Veterans did however have worse all cause mortality outcomes. The most significant independent predictor of outcome in all patients is the stage of disease at diagnosis, and this is consistent with the international literature.

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Army Malaria Institute - its evolution and achievements. Fourth decade (2nd half): 2000-2005

Karl H. Rieckmann, Qin Cheng, Stephen P. Frances, Scott J. Kitchener, Robert D. Cooper, Alyson Auliff, Michael D. Edstein

Abstract

The 2000-2005 quinquennium saw a marked drop in the number of Australian Defence Force (ADF) personnel suffering from malaria following the deployment of an Australian Army Malaria Institute (AMI) outbreak investigation team to Timor Leste and improved compliance with various prevention measures. The field evaluation of novel drug regimens using currently registered and new drugs also contributed to the reduced number of malaria cases overseas and after return to Australia. The main purpose of some of these studies was to determine the tolerability and effectiveness of more user friendly drug regimens, such as shorter courses of primaquine and 3-day courses of tafenoquine for post-exposure prophylaxis against vivax malaria. Clinical/field studies were also conducted with atovaquone/proguanil (Malarone®), loading doses of mefloquine, and a new artemisinin drug – artemisone. All of these investigations yielded positive results. Another landmark study – the first Phase III study in which weekly tafenoquine was taken for six months by non-immune individuals – showed that Australian soldiers could be protected against both falciparum and vivax malaria while in Timor Leste without having to take a post-exposure primaquine eradication course upon return to Australia.

In addition to documenting increasing drug resistance of malaria parasites in various parts of the Asia/Pacific region, molecular markers and changes associated with parasite resistance to antimalarial drugs were identified. An *in vitro* field test for assessing the drug susceptibility of *Plasmodium vivax* was also developed and, for the first time, successful transfection of *P. vivax* genes to continuously cultured *P. falciparum* enabled antifolate drugs to be screened *in vitro* for their activity against *P. vivax.* Furthermore, various laboratory/epidemiological studies and mathematical models were developed to investigate factors involved in the evolution and spread of drug resistance, such as mutation patterns, antigenic variation, loss of fitness, and inappropriate treatment.

In ongoing efforts to improve protection against mosquito bites, the effectiveness of various repellents/insecticides applied to skin, clothing and tents were evaluated in military training areas in Queensland and the Northern Territory. Mosquito control measures, including the use of newly-developed tools, were instrumental in controlling the outbreak of both malaria and dengue fever in Timor Leste. Furthermore, investigations in Australia, Vietnam and China indicated the potential value of novel molecular-based and other tests for identifying and controlling the spread of mosquitoes transmitting malaria, dengue and Japanese encephalitis. In view of the ADF's increasing exposure to arboviral diseases, further clinical studies were conducted to assess the tolerability and immunogenicity of dengue and Japanese encephalitis vaccines and prelicensure studies were started to determine the effectiveness of new vaccines.

Background

In 1943, an impressive medical and scientific group was assembled by Brigadier Neil H. Fairley in response to the devastating effects of malaria being experienced by allied soldiers deployed to the South Pacific. In just three years (1943-1946), the 'high priority' Land Headquarters Malaria Research Unit, based at Cairns in North Queensland, obtained considerable new information about the activity of drugs such as proguanil (Paludrine®) against different stages of the human malaria parasite and was able to protect soldiers remarkably well against malaria infections.[1]

By the mid-1960s, there were renewed concerns regarding the ability of antimalarial drugs to provide adequate protection against malaria. In 1965, Professor Robert H. Black, Army Consultant in Tropical Medicine and a previous investigator at the Cairns Unit, proposed that the Army should conduct malaria studies to address the growing drug resistance problem in Southeast Asia.[2] As a result, a small research unit comprising two scientists and a few technicians was established at the University of Sydney in 1966. Although additional positions were established later, research activities were hampered by frequent staff changes and cramped facilities.

The relocation of the unit to more spacious pre-fabricated quarters behind 2nd Military Hospital at Ingleburn, Sydney in 1974 led to a gradual improvement in the scope and significance of research activities at the Army Malaria Research Unit (AMRU), receiving a special boost when the number of unit staff positions was increased from 13 to 24 in 1982.[3] Commencing in the mid-1980s the pace of research activities gathered momentum and greater emphasis was placed on practical problems facing Australian Defence Force (ADF) personnel deployed to malarious areas.[4,5]

The unit continued to operate out of Sydney until late 1996 when it was relocated to a new purpose built laboratory complex at Gallipoli Barracks, Enoggera, Brisbane and known as the Australian Army Malaria Institute (AMI).[6] The establishment of the Institute enabled the ADF to play a key global role in the fight against malaria and other vector-borne diseases (VBDs). Enhanced collaboration with Australian and overseas institutions empowered AMI to make evermore significant contributions to the more effective control of VBDs. This was further facilitated by increased funding from non-Defence Health Service sources.

Commencing in 1997, AMI deployed outbreak management teams to Bougainville, and later to Timor Leste (formerly known as East Timor), in response to scores of soldiers developing malaria while on deployment to these areas.[6] Without daily doxycycline prophylaxis, there is ample evidence that up to one thousand soldiers would have been incapacitated by malaria, most of them infected with potentially fatal falciparum malaria.[6] Apart from causing personal distress, this would have compromised operational capability, placed severe strain on the health services and may even have jeopardised the successful outcome of the peace-keeping missions. Despite the prescribed 14-day post-exposure primaquine course, several hundred soldiers experienced their first attack of vivax malaria after returning to Australia. Furthermore, about one-fifth of them proceeded to have one to four relapses for up to a year after their initial attack. This course of events was a rather sobering reminder that malaria continued to be a serious threat to the well being and fitness of military personnel deployed to malarious areas. In addition to highlighting the importance of adhering to prescribed antimalarial measures, it emphasised the need for more effective and user friendly tools to counter the ever increasing problem of drug resistance.

AMI had earlier on pioneered the use of doxycycline for mass chemoprophylaxis and demonstrated its effectiveness during ADF deployments overseas.[5] More recently it had shown that daily atovaquone/proguanil (Malarone®) could be used as an alternative to doxycycline if required.[6] Studies by AMI had also demonstrated that tafenoquine, a long-acting 8-aminoquinoline drug, might ultimately play a very useful role in malaria prophylaxis and possibly replace primaquine for prevention of vivax malaria.[6] Although higher doses appeared to be more effective,[6] the very short elimination half-life of primaquine and its toxicity (e.g. gastro-intestional disturbances) would always remain a problem. With the growing threat of drug resistance, significant progress was made in the non-clinical assessment of various potential antimalarial drugs, including the artemisinins, Mannich bases, and third generation antifolate compounds.

The establishment of a molecular parasitology laboratory broadened the scope of investigations in malaria diagnosis and drug resistance.[6] Early results using DNA technology identified molecular markers for atovaquone resistance. These procedures also complemented various investigations with already established *in vitro* and *in vivo* procedures and enhanced AMI's fundamental commitment to improve malaria diagnosis and to monitor the evolution and spread of drug resistance.

In the continuing quest for improved personal protection against mosquito bites, field studies included the evaluation of two novel topical mosquito repellents and a self-erecting, low profile bednet.[6] The extensive survey of anopheline mosquitoes in 10 provinces of PNG, started in 1992, was completed in 2000.[6] Detailed analysis of collected specimens, using DNA-based technology and monoclonal antibodies, revealed many hereto unknown facts of significant benefit to malaria control activities. One of these was groundbreaking information on the vectorial capacity of various genotypes and taxons of *Anopheles farauti*.

AMI became involved with other mosquito-borne diseases following its relocation to Brisbane.[6] After identifying Ross River virus in mosquitoes at the Shoalwater Bay Training Area in Queensland during 1998, further observations highlighted the importance of collecting serum specimens for IgG and IgM analysis during both acute and convalescent phases of the illness. In 1999/2000, AMI identified 160 cases of dengue (mostly serotype 3) among ADF personnel in Timor Leste and virus containment was successfully managed, when nine of them were medically evacuated to Townsville. In response to the shortage and cost of Japanese encephalitis (JE) vaccine (Biken) in Australia, a series of studies was undertaken which revealed that low dose

intradermal injections (one-fifth of the dose of the usual regimen) were able to provide good protection, thereby extending the life of the vaccine stockpile.

By 2000, AMI had evolved from its humble beginnings in the mid-1960s to become a world centre of excellence for malaria research.

Mission, Organisation and Staff

AMI continued its mission to ensure that ADF personnel were able to have the best possible protection against malaria and other VBDs. This mission had become more important than ever with the increased deployment of military personnel to areas overseas with a high prevalence of VBDs. Recent deployments to Bougainville, Papua New Guinea, and Timor Leste had demonstrated the importance of adequate protection against these diseases for optimum performance under adverse conditions.

During the 2000-2005 quinquennium, Professor Karl Rieckmann continued to lead AMI's activities. In late 2002, Lieutenant Colonel Michael Edstein retired from full-time military service, and his position as Deputy Director and Commanding Officer was filled by Lieutenant Colonel Robert Cooper. Both scientists were long-standing members of AMRU/AMI and they continued to remain actively involved in various laboratory and field activities throughout this quinquennium.

Effective control of malaria parasites, arboviruses, and their mosquito vectors relied heavily on an improved understanding of the biology and epidemiology of these organisms. For example, the ever-changing susceptibility of malaria parasites to drugs could be tackled more effectively by a better insight into the mechanisms of drug resistance and by developing better surveillance techniques. In addition to devising novel regimens and approaches to improving the effectiveness of currently available agents, AMI was actively involved in the development and/or evaluation of new antimalarial drugs, vaccines and personal protection measures. Although these investigations were generally tailored to meet the requirements of the military sector, many of them were of benefit for controlling malaria and other VBDs in civilian populations.

Objectives at AMI were primarily achieved through the activities of its five departments: Drug Resistance and Diagnostics (DRD), Drug Evaluation (DE), Clinical Studies and Surveillance (CSS), Vector Surveillance and Control (VSC), and Arbovirology (AV). Each department head had either a military or civilian appointment within the Australian Defence Organisation. Some department heads also had adjunct academic appointments with the Faculty of Health Sciences of the Unversity of Queensland. Departmental activities were supported by an Administrative/Logistics section, a Quality Assurance section, and various committees, such as Biosafety and Animal Ethics. All human studies were reviewed by the Australian Defence Human Research Ethics Committee.

Drug Resistance and Diagnostics (DRD). Dr Qin Cheng was the Head of the department. Members of her staff included Dr Nanhua Chen, Captain Alyson Auliff, Captain Bruce Russell (up to 2002), Lieutenant Joanne Baker, and Lieutenant (Army Reserve) Michael Korsinczky.

Key functions of the department were (1) to monitor drug susceptibility of malaria parasites in the field; (2) to better understand how and why parasites develop drug resistance; (3) to determine host, parasite and environmental factors that might enhance or hinder the development and spread of drug resistance; and (4) to improve the reliability and performance of malaria diagnosis.

Responding to a call for applications by the National Institutes of Health, USA, a research proposal by Dr Qin Cheng and Prof Allan Saul (QIMR) entitled "Evolution of drug resistance in *Plasmodium falciparum*" was submitted and subsequently funded for three years commencing in March 2000. The project aimed to develop computer models, based on laboratory experiments and mathematical modelling, which would mimic both the growth of malaria parasites in people and the transmission of parasites within communities. The models would then be used to investigate factors underlying the development and spread of drug resistance, thereby helping to design better strategies for extending the life of existing antimalarial drugs and for protecting future drugs. Following the departure of Prof Saul a few months after initiation of the project, Dr Cheng became the Principal Investigator, assisted by Dr Michelle Gatton (mathematical modeller), Dr Beth Fowler (molecular geneticist), and Mrs Jenny Peters (molecular biologist). At the end of this first NIH grant funding period, a competitive renewal application entitled "Antigenic variation and drug resistance in *P. falciparum*" was prepared and submitted to NIH by Dr Qin Cheng (Principal Investigator) and Drs Michelle Gatton, Nanhua Chen and Dennis Kyle (Co-Investigators). Based on results obtained during the first grant, NIH provided support for a further three years (2004-2007). Dr Darren Krause joned the research efforts in 2004.

Drug Evaluation (DE). Dr Michael Edstein was the Head of the department. Members of his staff included Dr

Barbara Kotecka, Dr Marina Chavchich (from 2003), Sergeant Kerryn Rowcliffe, Mr Thomas Travers, Mr Wayne Lyons, and Sergeant Hamish Barbour (from 2003). Veterinarians at the Institute's animal facility were: Major Ivor Harris, Captain (Army Reserve) Clair Nussey (until 2001), Captain (Army Reserve) Narelle Peach (until 2003), Captain (Army Reserve) Joanne Beckett (from 2002), and Captain (Army Reserve) Amanda Perry (from 2004). Animal technicians included Mr Zbigniew Kotecki and Mrs Julie Staley (until 2003).

Key functions of the department were (1) to optimise drug regimens for malaria prophylaxis and treatment by pharmacokinetic and pharmacodynamic studies; (2) to support new antimalarial drug discovery progams; (3) to assess the antimalaria activity of promising candidate drugs using various parasitological tools and animal models; and (4) to manage the animal facility.

Dr Edstein was intimately involved with the establishment of the Vietnam Australia Defence Malaria Project (VADMP) and assumed primary responsibility for operational administration of the Australian component of the project. He also played a leading role in contributing to the successful outcome of many of the clinical and field studies in Vietnam and in organising the exchange visits by Vietnamese and Australian personnel.

Clinical Studies and Surveillance (CSS). Lieutenant Colonel Peter Nasveld continued to be closely involved in operations of several departments of the Institute, having been posted as Senior Medical Officer of the Third Brigade to the forward area of operations in Timor Leste at the beginning of this period. Major Scott Kitchener (1999-2002) carried on Lieutenant Colonel Nasveld's work as department head from late 1999 before being replaced by Lieutenant Commander Sonya Bennett (2002-2004). Following his departure and appointment as Lieutenant Colonel (Army Reserve), he became involved with the development of chimeric arborviral vaccines at Acambis Research (ACR) and provided a link for their subsequent clinical evaluation by AMI. Valuable support was also provided by Major (Army Reserve) Nathan Elmes (from 2003), Captain (Army Reserve) Anne Jensen (from 2001), and Captain (Army Reserve) Tracy Carthew (from 2002). Other members included Warrant Officer John Staley (until 2003), Warrant Officer Derek Davis (from 2004) and Sergeant (Army Reserve) Christine Atkins (from 2004).

Key functions of the department were (1) to conduct clinical evaluations of antimalarial drugs and vaccines against VBDs; (2) to protect ADF personnel against VBDs by monitoring their occurrence and prevalence; (3) to provide clinical advice on VBDs to ADF personnel; and (4) to maintain the ADF Central Malaria Register.

Vector Surveillance and Control (VSC). Major Stephen Frances replaced Major Robert Cooper as Head of the department in 2002 following Major Cooper's promotion to Commanding Officer. In addition to both of these long-serving entomologists, other members of the department included Miss Cassie Jansen (until 2004), Lieutenant Robert Marlow (from 2004), Sergeant Stephen Mcleod-Robertson, Corporal Brooke Wilson (2001-2002), Corporal Raethea Huggins (2002-2005).

Key functions of the department were (1) to conduct risk assessment of exposure to VBDs by mosquito surveys; (2) to provide field commanders with the best possible assessment of risk from VBDs and optimum vector protection measures; (3) to identify potential mosquito vectors of VBDs by using molecular-based technology; (4) to determine environmental factors affecting the distribution patterns of anopheline mosquitoes; (5) to evaluate personal protection measures against VBDs used by ADF personnel under field conditions, especially topical mosquito repellents, impregnated military clothing and bednets; and (6) to evaluate the use of pyrethroid insecticides in military fabrics for protection against nuisance and vector mosquitoes.

Arbovirology (AV). Major Stephen Frances was Head of the department until 2002 when he relinquished the position to direct VSC activities. His position was assumed by Major (Army Reserve)/Professor John Aaskov, an experienced virologist at QUT, who had joined AMI in 2000. Members of his staff included Captain Mark Reid, Lieutenant Michael Reid (until 2003), Cadet Lisa Baade, Sergeant Kerry Somerscales (2002-2003), Corporal Natalie Lehmann (2003), and Corporal Andrew Baron (from 2004).

Key functions of the department were to improve the capacity of the ADF to detect, diagnose and prevent diseases caused by mosquito-borne viruses. During this period, Captain Reid helped accredit AMI with the Office of the Gene Technology Regulator and manage the Physical Containment Level 3 arbovirus laboratory.

Administrative/Logistic Section. Major Ivor Harris was the Head of the section except during his absence in Antarctica during 2003 when his duties were performed by Major Robin Gregory. Other members included Major (Army Reserve) Chrisopher McCormack (from 2003), Sergeant (Army Reserve) John Humphries, Corporal Anna Davis (until 2002) and Mr Kevin Anderson (from 2002) in Administration,

and Corporal John Ross (until 2003) and Corporal Cameron Redman (from 2003) in Logistics.

Key functions of the section were (1) to provide personnel management, training and security support; (2) to manage internal and external financial affairs; (3) to prepare staff for courses, overseas visits and overseas deployments; (4) to manage the day-to-day administration of overseas visitors engaged in research activities at AMI; and (5) to order and account for equipment and supplies required by the departments and coordinate the maintenance and repair of equipment. During this period, the section maintained a considerable operational tempo of personnel movement and support for extended periods in several overseas operations.

Quality Management Section. Mr Ken Lilley was the Head of the section and was assisted by Major (Army Reserve) Robin Gregory.

Key functions of the section were (1) to ensure that laboratory equipment and procedures were maintained at the highest standard to produce data with the greatest accuracy and validity; (2) to implement and maintain accreditation and certification with national and international authorities such as National Association of Testing Authorities/Royal College of Pathologists of Australasia. (NATA/RCPA) and ISO 9001:2000; to conform to the relevant requirements of the Office of the Gene Technology Regulator (OGTR), the Australian Quarantine and Inspection Service (AQIS), and the animal use requirements of the Commmonwealth Scientific and Industrial Research Organisation (CSIRO) and Queensland Department of Primary Industries (DPI); and (3) to promote a culture of continuous improvement in the pursuit of excellence.

Walter Reed Army Institute of Research (WRAIR) Laboratory

The WRAIR laboratory was established at AMI in 2001 with the arrival of Lieutenant Colonel Dennis Kyle from WRAIR. He was part of the Engineer and Scientist Exchange Program (ESEP) between the Australia Defence Organisation and the United States Department of Defence. Just before his departure in 2004, Major Michael O'Neil replaced him for a further 3-year assignment by WRAIR to AMI. They were assisted in their investigations by Dr Marina Chavchich (from 2003), Mrs Jennifer Peters (from 2004) and Ms Karryn Grestey (from 2005).

Key functions of the laboratory were (1) to support the discovery of new antimalarial drugs; (2) to study drug resistance; and (3) to develop tools for controlling drug-resistant malaria more effectively. Most of their activities were closely integrated with work being carried out by the DRD and DE departments.

Figure 1: Visit to AMI by US Army Surgeon General, July 2002. (L to R): Dr Q. Cheng, Lieutenant Colonel R.D. Cooper, Lieutenant Colonel M.D. Edstein, Commander S. Bennett, Professor K. H. Rieckmann, Lieutenant General J. B. Peake, Lieutenant Colonel D. E. Kyle, Lieutenant Colonel S. Boos, Captain M. G. Reid, Major S. P. Frances, Colonel P. Alexander.

Collaboration and engagement with military and civilian organisations

Apart from close collaboration with medical research establishments within the US Army, as evidenced by the establishment of the WRAIR Laboratory at AMI, collaboration and engagement with various military and civilian organisations, both in Australia and overseas,[5,6] was maintained and expanded during this quinquennium. This was of paramount importance in achieving AMI's objectives to improve the control of malaria and other VBDs.

Vietnam Australia Defence Malaria Project (VADMP)

Following several years of consultation, a vitally important relationship was established between the ADF and the Vietnam People's Army (VPA) with the signing of a Memorandum of Understanding (MOU) in Hanoi in March 2000.[6] This marked the start of the Vietnam Australia Defence Malaria Project (VADMP) which not only served to enhance malaria control activities within the defence forces of Vietnam and Australia but also contributed to developing overall closer defence cooperation between both countries.[6] This long-term collaborative project between AMI and the VPA Military Medicine Department (MMD) had a strong and comprehensive focus on training, technological transfer, capacity building,

developing effective antimalarial drug regimens and characterising malaria transmission.

The principal collaborating institutions in Vietnam were the Military Institute of Hygiene and Epidemiology (MIHE) and the Central Military Hospital 108 in Hanoi, and the Military Preventative Medical Centre and Military Hospital 175 in Ho Chi Minh City. During this quinquennium six Vietnamese officers spent 2 to 6 months at AMI. Among them was Colonel Vu Quoc Binh, Deputy Director of MIHE, and later to become the Director of MMD and the Surgeon-General of VPA, and Lieutenant Colonel Le Nogc Anh, Secretary of the Project Management Unit of VADMP in Vietnam. On 12 August 2002, the VADMP Laboratories were officially opened at MIHE, the ceremonies being attended by the Australian Ambassador to Vietnam and other dignitaries. Following the establishment of the Laboratories, successful laboratory and field studies were conducted, with some results being presented at the 14th and 15th Asia Pacific Military Medicine Conferences held in Brisbane (2004) and Hanoi (2005), respectively.

World Health Organization (WHO) Collaborating Centre for Malaria

Professor Rieckmann continued to serve as Director of the WHO Collaborating Centre for Malaria and, at the end of the quinquennium, completed his 32-year service as Member of the WHO Expert Advisory Panel on Malaria. Between 9-11 December, AMI hosted the "13th South-West Pacific Malaria Meeting – Roll Back Malaria in the Pacific". This meeting brought together nine national representatives from Governments in the region, eleven Who staff members, five temporary advisers, and six observers from national and international funding organisations to discuss many different aspects of malaria control in the region. AMI was also visited by several WHO staff during 2000-2005, including several visits by Dr David Bell and Dr Jeffrey Hii.

Throughout this period, many AMI staff members continued to contribute to, and benefit from, participation in WHO activities. Dr Qin Cheng served as Temporary Adviser at WHO Workshops/ Consultations in Shanghai and Manila, and was the recipient of two WHO grants relating to rapid diagnostic tests (RDTs) for malaria. She was also a collaborating partner on a WHO funded project to eliminate malaria from the Hainan Province in China. Ms Joanne Baker participated in WHO-sponsored field and laboratory evaluations of RDTs in the Philippines. Dr Robert Cooper, in collaboration with Professor Gao Qi (JIPD) and Dr Nigel Beebe (UTS), received a WHO grant to study the potential malaria vectors of the Hyrcanus group of mosquitoes in central and southern China. Mr Ken Lilley acted as Rapporteur at a WHO Multiregional Workshop on "Quality Assurance of Malaria Light Microscopy" held in Malaysia, in addition to conducting WHO-sponsored malaria microscopy courses in the Philippines, Cambodia, Indonesia and the Solomon Islands. The purpose of these courses was to assesss the proficiency of provincial microscopists, to identify qualified personnel as national trainers, and to review draft quality assurance (QA) programs and procedures for malaria microscopy and RDTs at country peripheral levels.

Figure 2: Inauguration of Vietnam Australia Defence Malaria Project laboratories, Hanoi, August 2002.

Wide network of partnerships

Interaction with other experts at national and international meetings continued to enhance AMIs ability to achieve its objectives. For example, following the outbreak of vivax malaria in ADF personnel returning to Australia, AMI co-sponsored the first-ever international conference on vivax malaria research organised by the US-based Multilateral Initiative on Malaria (MIM). This 2002 conference in Bangkok provided AMI staff with the opportunity to interact with others who were also concerned with the prevention of vivax malaria after leaving endemic areas. The second international conference - "Vivax Malaria Research: 2005 and beyond" was held in Washington DC, USA, with Dr Cheng being a member of the organising committee.

All departments were involved in continuing and expanding their collaboration with other institutions. These institutions included:

(1) AFRIMS - Armed Forces Research Institute of Medical Sciences, Bangkok, Thailand.

(2) AP - Aventis Pasteur, France

(3) ACR - Acambis Research, UK
(4) BAY - Bayer AG, Germany
(5) CDC - Center for Disease Control, USA
(6) GMI - Gorgas Memorial Institute of Health Studies, Panama
(7) JPC - Jacobus Pharmaceutical Company, USA
(8) JIPD - Jiangsu Institute of Parasitic Diseases, China
(9) MAH - Mahidol University, Thailand
(10) MERLIN - Medical Emergency Relief International, UK
(11) MMV - Medicines for Malaria Venture, Switzerland
(12) MSHR - Menzies School of Health Research, Australia
(13) NAMRU-2 -) US Naval Medical Research Unit No. 2, Indonesia
(14) NIH - Laboratory of Parasitic Diseases, National Institutes of Health, USA
(15) NIHRD - National Institute of Health Research and Development, Indonesia
(16) QH - Queensland State Health, Tropical Public Health Program, Australia
(17) QIMR - Queensland Institute of Medical Research, Australia
(18) QUT - Queensland University of Technology
(19) PNGIMR - Papua New Guinea Institute of Medical Research, PNG
(20) RITM - Research Institute of Tropical Medicine, Philippines
(21) SMRU - Shoklo Malaria Research Unit, Thailand
(22 UQ - University of Queensland, Department of Parasitology, Australia
(23) UTS - University of Technology Sydney, Australia
(24) VBDCU - Vanuatu Malaria and Other Vector Borne Diseases Control Unit, Vanuatu
(25) VADMP - Vietnam Australia Defence Malaria Project, Vietnam
(26) WEHI - Walter and Eliza Hall Institute, Australia
(27) WHO - World Health Organization, Switzerland
(28) WHO/WPRO - World Health Organization, Western Pacific Regional Office, Philippines
(29) WRAIR - Walter Reed Army Institute of Research, Experimental Therapeutics Division, USA
(30) WRL - Wellcome Research Laboratories, Thailand

Activities

Many of the objectives at AMI were achieved by joint efforts between two or more departments. Because of this, outcomes and achievements of each department are not presented under department headings. Rather, they are presented according to key objectives pursued by AMI during this quinquennium.

1. MALARIA PREVALENCE AND SURVEILLANCE

Regular six-monthly updates on the malaria situation in the ADF were issued during this quinquennium.[7-9] They were based primarily on the analysis of data provided by health personnel to the ADF Central Malaria Register maintained at AMI.[10] Malaria notifications in the ADF declined from almost 400 cases in 2000 to 75 in 2001, and then to fewer than 20 per year over the next four years.[11] As described previously,[6] most of the malaria cases in 2000 were observed in soldiers who experienced their first acute attack of malaria in Australia because doxycycline had effectively suppressed their vivax infections while they were on peacekeeping duties in Timor Leste. However, because more than 60 soldiers developed malaria (two-thirds of them falciparum malaria) soon after arrival in the forward area of operations,[12] an AMI disease outbreak investigation and management team was deployed to Timor Leste at the beginning of 2000.[13]

Major risk factors were poor compliance with doxycycline prophylaxis, involvement in night operations, lack of preventive medicine support and higher risk locations selected by platoons. Following initial field assessments, the malaria outbreak was brought under control by instituting various epidemiological surveillance and operational activities (in collaboration with preventive medicine personnel) and fostering improved compliance with personal protection and chemoprophylactic measures.[13-15] In addition, new tools were assessed for improved prevention and control of malaria (see below). The marked reduction in the number of malaria cases was achieved despite a significant level of malaria transmission in the local villages.[16] Apart from being infected with *P. falciparum* and *P. vivax*, a few villagers were infected with *P. malariae*, possibly the first report of the presence of this Plasmodial species on the island of Timor Leste.[17]

2. PROPHYLAXIS AND TREATMENT OF BLOOD STAGE MALARIA PARASITES

AMI continued its investigations to identify better tools for countering the threat posed by drug-resistant malaria. More than a decade ago AMI had pioneered the daily use of doxycycline for military contingents deployed to malarious areas. This tetracycline

antibiotic continued to be effective against the blood stages of drug-resistant parasites and was the first-line drug for protecting ADF personnel against malaria while they were overseas. Atovaquone/proguanil (Malarone®), a drug combination which had been investigated intensively at AMI for many years, had recently been approved for daily use by soldiers who were unable to take doxycycline. However, under certain field conditions, better drug compliance might be achieved by using ADF's second-line drug, mefloquine, which had to be taken only once a week. Although mefloquine was being used widely overseas as a first-line drug for malaria prophylaxis, further information regarding mefloquine's tolerability, safety and pharmacokinetics seemed desirable.

Most drugs used for prophylaxis were also being used to treat drug-resistant malaria infections. But, increasingly, they were being used in combination with artemisinin drugs, a group of semi-synthetic compounds derived from *Artemisia annua*. Apart from an extremely rapid clinical response to treatment, artemisinin-based combination therapy (ACT) was far more effective than mono-drug therapy in curing falciparum infections and reduced the likelihood of the emergence of drug-resistant parasites. During the previous decade, AMI had developed *in vitro* tests and bioassays to assist in the pharmacokinetic evaluation of various artemisinin and antifolate compounds.[5,6] Investigations were now broadened to determine the pharmacokinetics of atovaquone/proguanil, mefloquine and other compounds used in ACTs. Furthermore, studies were carried out to assess the effects that pregnancy, gender or food might have on the absorption and/or disposition of these drugs, because they might ultimately affect their bioavailability and effectiveness. In view of the increasing role of artemisinin drugs in the treatment of drug-resistant malaria, further studies were carried out with artemisone, a potent new drug with little or no neuro- or cyto-toxicity.

Atovaquone/proguanil (Malarone®) pharmacokinetics during pregnancy

Atovaquone/proguanil/artesunate was a well tolerated and highly effective ACT that was being investigated for the treatment of falciparum malaria. Earlier studies in collaboration with WRL had shown that the pharmacokinetics of individual components of this ACT were not altered when given in combination with one another.[6] As few antimalarial drugs could be recommended during pregnancy, the SMRU on the western border of Thailand approached AMI in 2001 to assess the pharmacokinetics of the proguanil and atovaquone components of this ACT during pregnancy. This was especially important in view of the well known heightened vulnerability of pregnant women to malaria infections, higher risk of developing severe malaria, and the fact that no information was available on the extent to which the extensive physiological changes during pregnancy might affect the pharmacokinetics of this drug combination.

The first study, carried out in healthy Karen women during the second and third trimesters of pregnancy, showed that plasma concentrations of cycloguanil, the active triazine metabolite of proguanil, were reduced by approximately 50% when proguanil was administered alone.[18] This suggested that late pregnancy was associated with reduced biotransformation of proguanil. Although pregnancy did not affect the rate of proguanil absorption, it did increase plasma clearance and apparent volume of distribution of the drug, suggesting that pregnant women might need to receive a higher dose of proguanil. In the second study, serial plasma concentrations of atovaquone, proguanil and cycloguanil were measured in 24 malaria infected pregnant Karen women after completing a 3-day treatment regimen consisting of atovaquone (20 mg/kg/day), proguanil (8 mg/kg/day) and artesunate (4 mg/kg/day).[19] This ACT was well tolerated with no adverse effects in the pregnant women, birth outcomes, and other clinical and laboratory parameters. Compared with previously reported blood maximum drug concentrations (Cmax) and area under the drug concentration versus time curve (AUC) values of atovaquone, proguanil and cycloguanil in healthy women from the same population group, pregnancy caused a 50% reduction in the Cmax and AUC values, suggesting that the dose of atovaquone-proguanil might need to be increased for malaria treatment during pregnancy.

Prolonged persistence of atovaquone after administration of atovaquone/proguanil (Malarone®)

Further information on the pharmacokinetics of atovaquone was obtained by determining plasma atovaquone concentrations collected from three Caucasian volunteers after they had been treated for three days with atovaquone/proguanil during malaria investigations at QIMR.[20] The average elimination half-life of atovaquone in the volunteers was much longer than expected at 5.9 days by high performance liquid chromatographic (HPLC) analysis and 4.9 days by bioassay, and atovaquone was still present 35 days after treatment. These half-lives were about twice as long as those obtained previously in African and Asian patients treated with atovaquone. Since proguanil has a half-life of less than one day, proguanil would not be present to potentiate the

antimalarial activity of atovaquone for about a month after treatment. Although the prolonged persistence of atovaquone would be of little consequence when used by short-term travellers, it could lead to the rapid selection of atovaquone-resistant parasites if used widely by residents living in endemic areas

Effectiveness, tolerability and pharmacokinetics of mefloquine for malaria prophylaxis in Timor Leste

Poor compliance by some soldiers with daily doxycycline prophylaxis led to an appraisal of the wider use of mefloquine for ADF personnel because it had to be taken only once a week.[21,22] Although mefloquine prophylaxis had been well tolerated by British, Dutch, Indonesian, Italian and US soldiers during two to five month deployments to malarious areas, parasite resistance to mefloquine had been encountered in Cambodia and Indonesia. Furthermore, there were isolated reports of severe neuropsychiatric side-effects associated with the use of mefloquine. Following a field study in Timor Leste during which no severe adverse events were observed in the 162 Australian soldiers receiving mefloquine for six months,[23] a large field study was undertaken in Timor Leste to determine whether a loading dose of mefloquine would (1) help to identify individuals who might not tolerate the drug, and (2) allow "steady-state" blood mefloquine concentrations to be reached right at the start rather than several weeks after commencing weekly medication.

Figure 3: Captain B. Russell and Major S. Kitchener taking off from Komoro airfield in Timor Leste to carry out field investigations.

In two successive contingents, 1,155 male soldiers received a loading dose of one 250 mg tablet of mefloquine every other day on three occasions, followed by one tablet a week for six months.[24] Seventy-five soldiers (6.5%) experienced adverse responses to the drug and completed their deployments on doxycycline prophylaxis. The three soldiers who experienced serious adverse events of a neuropsychiatric nature, all revealed prior episodes of either depression, hallucinations or epilepsy. All soldiers were protected against malaria while in Timor Leste and 94% of them indicated that they would use mefloquine again. Clinical assessment after the loading dose was found to be both positively and negatively predictive of side effects associated with mefloquine, simplifying its use for malaria chemoprophylaxis. Pharmacokinetic studies also provided much useful information relating to the use of this drug under operational conditions.[25] After determining plasma mefloquine concentrations by HPLC at various times during prophylaxis, the pharmacokinetics of mefloquine could best be described as a two-compartment model: low plasma clearance (CL/F, 2.1 L/h) and a high central volume of distribution (V1/F, 528 L), with an elimination half-life of 14.0 days. Body weight had a positive influence on central volume but was insufficient to warrant adjustments to the drug regimen.

Clinical studies in Vietnam on the influence of food on mefloquine and piperaquine pharmacokinetics

Food had been reported to increase the bioavailability of mefloquine in healthy Caucasian volunteers, but it was unclear whether this was also the case in malaria patients. As part of a VADMP project, the pharmacokinetics of mefloquine was determined in Vietnamese malaria patients treated with mefloquine in the fasting and fed state.[26] Blood mefloquine concentrations were compared in two cohorts of six malaria patients treated with mefloquine (15 mg/kg) and artesunate (8 mg/kg) and given either a low-fat (approximately 3 g fat) or high-fat (approximately 30 g fat) meal. The results showed no statistical differences ($P<0.05$) in the Cmax and AUC of mefloquine between these two groups of patients. These findings suggested that a high-fatty meal does not increase the bioavailability of mefloquine in malaria patients and should therefore not affect their response to treatment. This was not the case for piperaquine, another drug being considered as a partner with dihydroartemisinin for ACT in Vietnam and other countries of Southeast Asia. When 26 healthy Vietnamese soldiers were administered 0.5 or 1.0 g of piperaquine, the bioavailability of the drug was increased by 41% after eating a moderately fatty meal (about 17 g of fat).[27]

Artemisone - a new artemisinin compound for clinical evaluation

Artemisinin derivatives had by now been acknowleged to be the most rapidly acting drugs for the treatment of falciparum infections. However, infections were

not being cured by 3-day courses of treatment due to the short pharmacological elimination half-lives of the artemisinins. Since patient compliance with longer courses of treatment was poor, especially in malarious areas with limited health facilities, various slower-acting but longer-lasting drugs (see above) were being investigated for use as partner drugs for ACT. Recently artemisone, a new semi-synthetic drug, had been developed which was relatively cheap to synthesise, and, unlike some other artemisinins, displayed negligible neuro- and cytotoxicity. Early *ex vivo* investigations with artemisone at AMI had also indicated that the degree and duration of its activity against multidrug-resistant *P. falciparum* was significantly greater than that of artesunate following drug administration to non-infected Saimiri sciureus monkeys.[6]

This was followed up by further studies at AMI with Aotus monkeys infected with the chloroquine-resistant FVO strain of *P. falciparum*. Since many patients were not cured of their malaria infections because they failed to complete 3-day courses of treatment, might just a single dose of artemisone, combined with subcurative single doses of mefloquine, be sufficient to cure infected Aotus monkeys? In a pilot study, three monkeys cleared parasites within one day and two monkeys receiving only 10 mg/kg artemisone and 5 mg/kg mefloquine were cured.[28] This was far below the curative mefloquine dose of 20 mg/kg for Aotus monkeys. The remaining monkey that received 2.5 mg/kg mefloquine had a recrudescence of parasitaemia 24 days after treatment. The findings suggested that this ACT might eventually prove useful in areas with low malaria transmission but, because of mefloquine's very long persistence in the body, the likelihood of developing resistance to mefloquine would be increased in areas with high levels of malaria transmission.

Additional investigations were carried out in collaboration with GMI in Panama, using a larger group (23 Aotus monkeys) than was available at AMI. 29 Artemisone was administered in combination with two other partner drugs – amodiaquine and clindamycin. Although amodiaquine is a 4-aminoquinoline drug, parasites were often less resistant to this inexpensive drug than to chloroquine.[30] Clindamycin, an antibiotic, was another drug which had been used in combination with artemisone for treating malaria patients. Whereas monkeys failed to be cured after one day of treatment with amodiaquine (20 mg/kg) and artemisone (30 mg/kg), they were cured after three days treatment with amodiaquine (20 mg/kg/day) and artemisone (10 mg/kg/day). A 3-day course of clindamycin (100 mg/kg/day) and artemisone (30 mg/kg/day) was also effective in curing falciparum infections.

In view of the encouraging results obtained in studies with non-human primates, Phase I human safety and tolerability studies with artemisone were initiated in healthy German volunteers.[31] With the support of MMV and BAY, AMI assisted by assessing the pharmacokinetic properties and *ex vivo* pharmacodynamic antimalarial activity of artemisone and its metabolites. Artemisone was well tolerated, with no serious adverse events and no clinically relevant changes in laboratory and vital parameters, during and following administration of single or multiple ascending doses (10-80 mg range) of artemisone to 56 healthy volunteers. The pharmacokinetics of artemisone demonstrated dose linearity, with a Cmax of 140 ng/mL, an elimination half-life of 2.8 hours, a high oral clearance of 284 L/h, and a large apparent volume of distribution of 14.5 L/kg following a single 80-mg dose. Plasma samples taken after multiple dosing showed marked *ex vivo* pharmacodynamic antimalarial activities against two multidrug-resistant *P. falciparum* lines and confirmed the presence of active metabolites. Compared to other artemisinin derivatives, such as artesunate and dihydroartemisinin, artemisone's longer elimination half-life (2.8 hours versus 1.0 hour for dihydroartemisinin) appeared to favour this artemisinin as a candidate ACT drug for treatment of falciparum malaria. As a result of these findings, further clinical studies with artemisone were planned, including Phase II efficacy studies in Thailand.

3. PROPHYLAXIS AND TREATMENT OF LIVER HYPNOZOITES OF VIVAX MALARIA

The outbreak of vivax malaria among several hundred soldiers after returning to Australia during 2000 re-emphasised the need for improved measures to prevent exposure to infected mosquitoes. But it also highlighted the urgent need for antimalarial drug regimens that would reduce the risk of this happening in the future. The fact that most of these soldiers experienced their first attack of malaria more than a month after leaving an endemic area indicated that inadequate drug suppression of blood stage parasites was not the problem. Rather, the outbreak of vivax malaria was due to the activation of dormant hypnozoites in the liver at different time intervals up to a year or more after leaving Timor Leste.

Since it was unclear what determined the number and timing of relapses, AMI attempted to investigate to what extent molecular diversity of parasites might influence the relapse patterns experienced by soldiers

after their return to Australia.[32] Although high molecular diversity was observed, primary infections and relapses were produced by the activation of a single hypnozoite clone in 99% of cases. Even in patients with more than two genetically different hypnozoites, 71% of them still experienced clonal relapses. The activation of a single hypnozoite genotype, when multiple genotypes were present in the liver, suggested that hypnozoites were activated according to a genetically determined biological clock and not triggerrd by non-specific environmental or host factors. The findings also suggested that multiple liver hypnozoite genotypes were associated with multiple replases. Therefore, any measures to reduce exposure to mosquitoes would reduce not only the number of malaria infections but also the number of relapses.

While providing assistance with the diagnosis and management of these infections in Timor Leste, it became obvious that, in attempting to deal with the situation, soldiers were receiving a variety of different treatment regimens.[33,34] Although regimens with higher primaquine doses were more effective in preventing *P. vivax* relapses,[6] the lengthy duration of medication did not encourage drug compliance. More user friendly drug regimens would undoubtedly be more effective in eradicating the dormant hypnozoites remaining in the liver after leaving an endemic area. With this in mind, clinical studies were initiated to evaluate the efficacy and safety of shorter courses of primaquine and tafenoquine taken either during or after deployment overseas.

Shorter primaquine prophylactic and treatment regimens

The very large number of vivax infections observed in soldiers after their return to Australia from Timor Leste[6] emphasised the urgent need for better post-exposure drug regimens to eradicate the residual dormant hypnozoites of *P. vivax* malaria. Earlier studies in ADF personnel returning from Timor Leste had indicated that primaquine 30 mg (15 mg twice a day) was more effective than 22.5 mg daily for 14 days in curing these infections.[6] As the lengthy 14-day regimens were contributing to poor compliance, a pilot volunteer study was initiated to assess the tolerability of higher dose, shorter courses of primaquine.[35] Australian soldiers tolerated primaquine 22.5 mg twice a day for 10 days and 30 mg twice a day for seven days just as well as 15 mg twice a day for 14 days. The findings indicated that additional studies were desirable to further define the tolerability, safety and effectiveness of shorter, high dose courses of primaquine.

Poor compliance was also a problem in patients who were being treated with 14-day courses of chloroquine/primaquine after developing malaria. This drug regimen had the additional handicap that chloroquine-resistant *P. vivax*, first identified at AMI,[4] was being reported from many areas of Asia, Oceania and South America. By contrast, *P. vivax* malaria continued to be susceptible to the artemisinins. Might a shorter treatment course of artesunate (200 mg twice a day for two days) followed by primaquine (22.5 mg base twice a day for seven days) be the answer?

Under the auspices of VADMP, this drug regimen was administered to 28 adult patients infected with *P. vivax* in Vietnam.[36] All patients responded quickly to treatment with mean parasite and fever clearance times of 14.2 hours and 18.6 hours, respectively. The high daily dose of primaquine was generally well tolerated, and only one patient (3.6%) had a recurrence of parasitaemia during the 28 day follow-up period. As most patients infected with Southeast Asian strains of *P. vivax* have their first relapse within 28 days after treatment with a rapidly eliminated blood schizonticide, such as quinine or artesunate, the failure to do so by 96% of the patients suggested that this drug regimen was active against both blood and liver stages of vivax malaria. These findings indicated the need for further studies to confirm that rapidly acting and short artesunate-primaquine regimens are able to provide better patient compliance and treatment outcomes than standard chloroquine-primaquine regimens.

Figure 4: Key contributors to the Vietnam Australia Defence Malaria Project attending the 14th Asia Pacific Military Medicine Conference, Brisbane, May 2004. Front row (L to R): Senior Colonel Nguyen Xuan Thanh, Lieutenant General Cuong Tien Chu, Professor Karl Rieckmann, Professor Bui Dai, Lieutenant Colonel Michael Edstein, Senior Colonel Vu Quoc Binh.

Influence of gender and food on primaquine pharmacokinetics

Although primaquine had been used for 50 years for the radical cure of *P. vivax* dormant (hypnozoite) stages, little information was available on the effect of gender and food on the disposition of primaquine. Earlier studies appeared to indicate that female ADF personnel had a higher prevalence of gastro-intestinal (GI) disturbances than their male counterparts during post-exposure prophylaxis with primaquine.[37] This could have been due to higher blood primaquine concentrations in females than in males. Under the auspices of VADMP, a randomised, two-phase cross-over study was conducted in which 10 healthy male and 10 healthy female Vietnamese soldiers were administered a single oral dose of 30 mg primaquine in the fasting and fed states.[38] The pharmacokinetics of primaquine was comparable in both groups, with geometric mean ratios of Cmax = 0.89 and AUC = 0.80, although males had a slightly higher plasma clearance than females. When primaquine was taken in conjunction with a fatty meal, the geometric mean Cmax of primaquine increased by 26% and the AUC by 14%. When the same dose of primaquine was given to nine healthy male and nine female ADF personnel, no significant differences in the pharmacokinetics of primaquine between the genders were observed.[39] These findings suggested that, based on single dose assessment of primaquine, there was no need to modify primaquine doses for women. However, the greater bioavailability of primaquine when consumed with a fatty meal might lead to improved antimalarial effectiveness irrespective of gender.

Tafenoquine for the prevention and cure of vivax malaria

Ground breaking investigations at AMI had shown that tafenoquine might be more effective than primaquine in the prevention and cure of vivax malaria.[5,6] This new, long-acting synthetic analogue of primaquine might not only improve patient compliance with post-exposure prophylaxis and treatment regimens, but might provide protection against vivax and falciparum malaria if taken on a weekly basis. Because of the potential importance of this 8-aminoquinoline drug in reducing the malaria burden in ADF personnel, considerable time and effort was devoted to carrying out further clinical studies with this drug in Australian soldiers contributing to peacekeeping duties. In addition to pharmacokinetic studies involving male and female ADF personnel, several hundred soldiers deployed to Timor Leste participated in the first Phase III trial to determine the safety, tolerability and effectiveness of tafenoquine for malaria prophylaxis.

Tafenoquine post-exposure prophylaxis at end of deployment to malarious area

A previous short report had already described preliminary findings from a study in which 173 Australian soldiers had received a 3-day course of tafenoquine as post-exposure prophylaxis at the end of their peacekeeping duties in Bougainville, PNG.[6,37] Since GI disturbances are a well known feature associated with the use of 8-aminoquinolines, 87 volunteers (76 males; 11 females) received a single tafenoquine dose (400 mg once a day) and 86 voluneers (73 males; 13 females) received a split tafenoquine dose (200 mg twice a day) to determine whether the split dose would lower the incidence of side-effects. Although GI disturbances were generally mild, self-limiting and not significantly different between the two groups, the frequency of nausea and abdominal distress in both groups was more than two-fold higher in females than in males. Furthermore, plasma tafenoquine concentrations were significantly higher in females than in males (mean values: 737 ± 118 ng/mL vs. 581 ± 113 ng/mL) with similar body weight.[40] Whilst little difference was observed in the way both sexes tolerated single and split doses, the findings did suggest that there might be an association between tafenoquine concentrations and GI disturbances and that adjustments might have to be made in the dose of tafenoquine administered to women.

Tafenoquine treatment of *Plasmodium vivax* malaria

Relapses of vivax malaria were common among ADF personnel after their return to Australia, despite post-exposure prophylaxis and/or treatment with 14-day courses of primaquine. Following the successful treatment of two patients with 3-day courses of tafenoquine,[41] a further 27 patients were treated with tafenoquine after their vivax infections had failed to be cured by chloroquine and primaquine.[42] After a standard course of chloroquine (1,500 mg base over three days), they received a loading dose of tafenoquine (200 mg/day for three days) followed by 200 mg a week for eight weeks. Only one of the patients experienced a relapse during the next six months. Although further optimum dose-finding studies are indicated, these findings suggested that intermittent weekly dosing with tafenoquine over several weeks might prove more effective than daily dosing over a shorter period of time. The advantages of such a tafenoquine regimen might be similar to those observed following weekly doses of primaquine administered over a period of eight weeks.[43]

Tafenoquine prophylaxis during deployment to malarious areas

By 2000, doxycycline, Malarone® and mefloquine were being used to protect ADF personnel against malaria during their deployments overseas, but they all had shortcomings, including their inability to prevent relapses and to radically cure *P. vivax* infections. Although post-exposure prophylaxis with tafenoquine might prove to be more effective than using primaquine, could such prophylaxis be dispensed with altogether by taking tafenoquine throughout the time spent overseas? During a previous collaborative field study in Thailand, the administration of tafenoquine (400 mg) at monthly intervals for five months had been shown to be highly effective in preventing vivax and falciparum infections.[6] Based on various considerations, including tafenoquine analysis of Thai blood samples at AMI, it was decided to conduct the first Phase III trial on the safety, tolerability and effectiveness of tafenoquine in Australian soldiers, with reduced doses of the drug being administered at shorter time intervals. So in October 2000, a randomised double-blinded study was started which involved the participation of 654 soldiers during the entire period of their peacekeeping deployment to Timor Leste. [44,45]

During the six month period, 492 soldiers received a loading dose of 200 mg tafenoquine daily for three days followed by a weekly dose of 200 mg tafenoquine. A comparator group of 162 soldiers received a weekly dose of 250 mg mefloquine. As the soldiers had acquired no prior immunity to malaria, ethical considerations obviously precluded incorporation of a concurrent no-drug placebo group. After their return to Australia, the mefloquine recipients were administered primaquine (15 mg twice a day) for 14 days whereas the tafenoquine recipients were given a placebo. While they were in Timor Leste, none of the 654 volunteers developed malaria, but four tafenoquine recipients (0.9%) and one mefloquine recipient (0.7%) had acute attacks of *P. vivax malaria* within 16 to 20 weeks after returning home. This was in marked contrast to the 168 malaria cases observed in the 1,351 soldiers of two battalions that were deployed to the same area during the previous wet season between October 1999 and February 2000.[6] Although the exposure of soldiers to malaria could not be estimated directly without a placebo control, malaria transmission continued to occur in several villages in close proximity to where the soldiers were located.[16]

Drug-related adverse events were generally mild or moderate in severity and comparable in the two groups. The most common drug related events were GI disturbances, with eight (<2%) of the tafenoquine recipients reporting that the drug did not allow them to complete their daily duties. Only three soldiers in the tafenoquine group discontinued prophylaxis because of possible drug related adverse events (none in the mefloquine group). Mild vortex keratopathy, detected in 93% of a subset of 74 volunteers, was not associated with any visual disturbances and had fully resolved within one year after stopping medication.[45]

The population pharmacokinetics of tafenoquine was determined in 476 male and 14 female participants in this study by analysing plasma tafenoquine concentrations in blood samples collected after the last loading dose and then at weeks 4, 8, and 16.[46] Analysis of specimens revealed that tafenoquine had a relatively low plasma clearance (CL/F) of 4.5 L/h, a high apparent volume of distribution (V/F) of 1,896 L, suggesting that the drug was widely distributed to body tissues and organs. As expected, the elimination half-life of tafenoquine was long at 12.7 days. Pharmacokinetic data from the four soldiers who developed vivax malaria after returning to Australia were similar to those who remained free of malaria. Neither could any links be established between pharmacokinetic parameters and the prevalence or severity of GI disturbances or other adverse events, suggesting that plasma tafenoquine concentrations were not the primary predictor of tafenoquine tolerability. These findings indicated that (1) the derived population one-compartment pharmacokinetic model for tafenoquine satisfactorily described the disposition and variability of tafenoquine in ADF personnel, and (2) the pharmacokinetic properties of the drug were well suited for long-term weekly malaria prophylaxis during military deployments.

This study involving ADF personnel was the first and only Phase III study to show that weekly tafenoquine taken for six months was an effective prophylactic drug against both *P. falciparum* and *P. vivax malaria* in non-immune individuals.

4. MALARIA DIAGNOSIS

Rapid diagnostic tests (RDTs)

Early diagnosis and treatment are critical to prevent severe complications and death from malaria, particularly in individuals with little or no prior exposure to malaria. Although definitive diagnosis of malaria can only be established by microscopic examination of blood films, the availability of a non-microscopic test would be a distinct advantage during the deployment of ADF personnel to remote malarious areas where reliable malaria microscopy might not be available.

In the mid-1990s, AMI had participated in the field evaluation of the ICT Malaria Pf test card which was the first immunochromatographic test card to detect a specific antigen (PfHRP2) produced in patients infected with falciparum malaria.[5] By 2004, about 25 branded malaria rapid diagnostic tests (RDTs) were commercially available; some of them detected *P. falciparum* only, while others detected *P. falciparum* plus one or more other plasmodial species. However, the performance of these products (sensitivity, specificity, heat durability, ease of use, etc) were reported to vary greatly between different products and between the same products used in different settings.

In view of the variability observed in the performance of these tests, WHO/WPRO organised an informal consultation on laboratory methods for the quality assurance of malaria RDTs. Following this meeting, to which Dr Qin Cheng had been invited, DRD became a key laboratory in the WHO malaria RDT Quality Assurance network, making significant contributions (described below) to the development of positive controls and the testing of various products and lots. As a WHO Collaborating Centre for Malaria, AMI also collaborated with QIMR in examining several important parasite and host factors that could affect the performance of RDTs.

Since many RDTs were based on the detection of *P. falciparum* histidine rich protein 2 (PfHRP2), might variability in RDT results be related to genetic diversity of PfHRP2 antigen? After amplifying and sequencing the pfhrp2 gene from 75 *P. falciparum* lines and isolates originating from 19 countries, extensive diversity in this antigen was observed both within and between countries. When a subset of parasite isolates was tested in two popular brands of RDTs, a correlation was observed between detection sensitivity and antigen structure. The results demonstrated for the first time that the variability of PfHRP2 could affect the detection sensitivity at parasite densities ≤250/μL blood.[47] Significant differences were also observed between the reactivity of four PfHRP2 specific mononclonal antibodies to parasite PfHRP2 from a single isolate and also when one of the antibodies was tested against different isolates. When the target epitopes of these antibodies were determined they were found to vary in frequency in different isolates.[48] These findings appeared to indicate that variability in PfHRP2 antigen might have an effect on the sensitivity of PfHRP2-detecting RDTs. However, further investigations including isolates from Africa and South America suggested that RDTs were not greatly affected by the diversity of PfHRP2 at parasite densities exceeding 200 parasites/μL blood.[49]

Some of the RDTs were based on the detection of aldolase, a key enzyme in the glycolysis pathway of malaria parasites. Since RDTs targeting aldolase were showing highly variable sensitivities, the genetic diversity of parasite isolates originating from geographically different areas were determined by sequencing the coding genes.[50] The results showed that aldolases were highly conserved, indicating that antigenic diversity was not a cause of variable RDT sensitivity. However, in general, aldolase-detecting RDTs were less sensitive than their HRP2 counterparts.

In their excellent article in ADF Health, Baker et al.[51] reviewed the results of investigations carried out with RDTs at AMI and elsewhere, and pointed out their advantages and limitations. Although RDTs offered distinct advantages for early diagnosis and treatment, especially when expert malaria microscopy was not available, ADF medical personnel needed to be aware that a patient might still have malaria despite a negative RDT result. This would be more likely during the early stages of a malaria infection when parasite densities were still at a low level. For this reason, competent malaria microcopy remained the preferred method of arriving at a definitive species diagnosis of malaria. Patients with persisting symptoms of malaria should have repeated RDTs within 24 hours of the initial test, and microscopy should be performed if at all possible.

Figure 5: Lieutenant Joanne Baker assessing efficacy of malaria rapid diagnostic tests (RDTs).

Polymerase chain reaction (PCR) test

Earlier efforts to employ sensitive and specific PCR-based methods for malaria detection[6] were followed up by the establishment of nested PCR and a multiplex PCR to detect or verify Plasmodial species in ADF personnel suspected of having malaria but in whom negative or discrepant results were obtained

by microscopy or RDT. This could now be performed using whole blood samples, plasma samples, dried blood on filter papers and blood smears. In combination with results obtained with microscopy or RDT, it ensured that accurate malaria information was entered into the ADF Central Malaria Register.

5. ASSESSMENT OF DRUG RESISTANCE

Malaria control activities in the Asia-Pacific region continued to be frustrated by the changing susceptibility of parasites to standard antimalarial drugs. This also affected ADF operational and peacekeeping activities. Many countries were using chloroquine (CQ) and sulfadoxine-pyrimethamine (SP) for first- and second-line treatments of uncomplicated malaria. CQ continued to be used because it was readily available and relieved symptoms in patients who were infected with vivax malaria or had become partially immune to falciparum malaria. When too many falciparum infections failed to be cured, SP was usually introduced for malaria treatment. Whereas both components of SP act synergistically against *P. falciparum*, this is not the case for *P. vivax* because of its innate resistance to the sulfadoxine component. In the presence of low to moderate degrees of pyrimethamine resistance, this meant that, unlike its activity against *P. falciparum*, SP was often ineffective against *P. vivax* malaria.[52] Since *P. falciparum* could not be distinguished from *P. vivax* in many malarious areas due to unavailable or unreliable malaria microscopy, CQ was often co-administered with SP to increase the patient's likelihood of responding adequately to treatment irrespective of the infecting Plasmodial species. The response to treatment was of course far less satisfactory in areas with CQ-resistant vivax malaria.

Susceptibility of *Plasmodium falciparum* to sulfadoxine/ pyrimethamine (SP) in Timor Leste

When ADF personnel were deployed on peacekeeping duties to Timor Leste in 1999 the efficacy of CQ and SP for the treatment of uncomplicated *P. falciparum* malaria was unknown. AMI was approached by the non-government organisation, MERLIN, to assist in determining the efficacy of the antimalarial drugs by genotyping for drug resistance and measuring blood drug concentrations. Earlier investigations at AMI had already shown the value of molecular markers for monitoring the resistance of *P. falciparum* to CQ and atovaquone.[6] Collaborative investigations with WEHI and PNGIMR had also indicated that the 76T allele of the *pfcrt* gene was strongly associated with chloroquine resistance.[53] After documenting a high level of CQ resistance in 48 patients,[6] a further 40 individuals infected with falciparum malaria were treated with SP following the collection of their blood to determine whether genetic mutations could be detected in the dihydrofolate reductase (DHFR) of their parasites. Although 90% of these partially-immune patients were cured, 80% of them were infected with parasites which carried double genetic mutations (S108N/C59R) in SP's target molecule *(Pfdhfr)*.[54] This suggested that the useful life of SP might be limited and that alternative drugs were required to treat patients with lower levels of acquired immunity to malaria.

Susceptibility of *Plasmodium falciparum* and *Plasmodium vivax* to chloroquine (CQ) and sulfadoxine-pyrimethamine (SP) in Indonesia

Malaria epidemics in Central Java had increased concern about the re-emergence of endemic malaria which could threaten the island's 120 million residents. AMI was approached by NAMRU-2 to collaborate in a 28 day *in vivo* test of the efficacy of CQ and SP among 167 villagers from Central Java with 33% of 1,389 residents being infected prior to enrollment.[55] Drug analysis was done at AMI to ensure that the patients had adequate blood concentrations of CQ and SP after starting treatment. The study revealed CQ and SP to be ineffective therapy for *P. falciparum*, with therapeutic failure rates of 47% and 22%, respectively, and 18% and 67% in the treatment of *P. vivax*. These findings suggested that the presence of CQ- and SP-resistant *P. falciparum* and *P. vivax* would compromise efforts to control resurgent malaria in Java and that ACTs should be introduced as soon as possible to improve efficacy.

In addition to Central Java there had been a steady rise in the number of reported cases of emerging drug resistance in southern Papua, Indonesia. In collaboration with MSHR, AMI carried out the drug measurements in the assessment of the therapeutic efficacy of CQ monotherapy for *P. vivax* infections as well as CQ plus SP for *P. falciparum* infections.[56] Of the 143 patients enrolled in the study (40 treated with CQ and 103 treated with CQ+SP), early treatment failures occurred in 15% of patients with *P. vivax* and 4% of patients with *P. falciparum* The failure rates by days 28 and 42 were 65% for *P. vivax* and 48% for *P. falciparum*, respectively. These findings further confirmed the existence of a high prevalence of drug resistance of *P. vivax* and *P. falciparum* to both the first- and second-line treatments in Indonesia.

Prevalence and extent of pyrimethamine resistance in *Plasmodium vivax*

The above mentioned study in Timor Leste exemplified the fact that genetic mutations in the dihydrofolate reductase (DHFR) of *P. falciparum* could also be used

to assess drug resistance to pyrimethamine and SP. Furthermore, one to four genetic mutations in DHFR of *P. vivax* had been shown to confer various degrees of resistance to pyrimethamine and other antifolate drugs. How prevalent might genetic mutations in Pvdhfr be in different areas of the Asia-Pacific region? In collaboration with QIMR, NAMRU 2 and WRAIR, 70 *P. vivax* isolates from six countries were examined for mutant genes.[57] Overall, 74% of *P. vivax* isolates carried a mutant Pvdhfr, with the prevalence of mutants being lower in isolates from China, Philippines, Timor Leste and Vietnam than in those from PNG and Vanuatu. Furthermore, they only carried single or double mutations whereas isolates from PNG and Vanuatu carried up to quadruple mutations. The data suggested that both the prevalence and degree of resistance of *P. vivax* to antifolate drugs was higher in the Southwest Pacific countries of PNG and Vanuatu than in their counterparts in Southeast Asia. Because sulfadoxine could not be expected to potentiate the activity of pyrimethamine, these findings indicated the limited value of SP for the treatment of vivax infections.

Efficacy of sulfadoxine-pyrimethamine (SP) combined with artesunate or chloroquine (CQ) against *Plasmodium vivax* malaria in Papua, Indonesia

Widespread CQ resistance of *P. falciparum* and *P. vivax* in Papua, Indonesia, during the late 1990s led to the use of CQ/SP combinations and the evaluation of artesunate/SP. Since artesunate/SP proved highly (96%) effective in curing falciparum infections, NIHRD and MSHR conducted a study to compare the efficacy of this combination with that of CQ/SP in two groups of patients with vivax malaria.[58] Not unexpectedly, the treatment failure rate was higher in the CQ/SP group (33%) than in the artesunate/SP group (10%), and would have been higher in patient groups who were not partially immune to malaria. In fact, molecular analysis of parasite samples at AMI revealed that 80% of these patients were infected with parasites carrying one to four genetic mutations in the *P. vivax* dihydrofolate reductase (pvdhfr) gene and that patients infected with parasites carrying quadruple mutations had a higher risk of treatment failure. Although artesunate/SP was more effective than CQ/SP, it was obvious that an alternative drug, such as piperaquine, might prove to be more useful than SP as a partner for artemisinin-based combination therapy (ACT).

In vitro drug susceptibility of malaria parasites in Vanuatu

In collaboration with VBDCU and NAMRU-2, a preliminary survey was conducted in Malo Island to assess the *in vitro* susceptibility of malaria parasites to various drugs.[59] Using the WHO microtest, six *P. falciparum* isolates showed a low level of resistance to CQ and pyrimethamine, but were sensitive to mefloquine, cycloguanil, dihydroartemisinin and amodiaquine. The parasites were also 50 to 400 times more active against WR99210, a remarkably active experimental antifolate drug,[5,6] than against pyrimethamine. Although patients with falciparum malaria on this island might have a recrudescence of parasitaemia following CQ treatment, the results indicated that they should be cured after SP treatment. No conclusions were possible regarding the drug susceptibility of *P.vivax* because only two isolates were cultured.

Figure 6: Captain Alyson Auliff examining malaria blood films.

6. NEW INSIGHTS AND TESTS FOR DRUG RESISTANCE

Drug susceptibility test for *Plasmodium vivax*

In vitro assessment of drug activity against malaria parasites had been an integral part of AMI activities for many years. The WHO *in vitro* field test (schizont maturation test) had proven to be a simple and reliable means for determining the sensitivity of *P. falciparum* to antimalarial drugs. However, early attempts to use this test for *P. vivax* had proven unsuccessful because, unlike *P. falciparum*, parasite stages other than rings were usually present in the peripheral blood at the start of culture. With recent advances in *in vitro* culture techniques, further efforts were made at AMI and in Thailand (in collaboration

with MAH and AFRIMS), to develop an effective *in vitro* field test to determine the sensitivity of *P. vivax* to various drugs.[60] Although the processing of freshly-collected parasitised blood samples was more complex than for *P. falciparum*, it was still considered possible to use this method in a field setting. Chloroquine, sulfadoxine and tafenoquine halted maturation of *P. vivax* at the late amoeboid or trophozoite stage, whereas dihydroartemisinin did so at the ring stage. As with the *P. falciparum* test, this field method avoided the use of expensive or dangerous reagents (monoclonal antibodies or radioisotopes) and expensive equipment (beta counters or robotic plate washers and dispensers). The whole 25-37 hour procedure also did not require a biological safety hood. With increasing concern about the emergence of drug-resistant vivax malaria, it was felt that this field *in vitro* assay could be used for assessing the true drug susceptibility of *P. vivax* in various areas, without being obscured by various degrees of immunity acquired by malaria patients. Furthermore, in view of the inability to maintain *P. vivax* in long-term cultures, the test might also play a role in screening new antimalarial drugs for their efficacy against this species.

Polymorphism of *pmvdr1* possibly associated with *Plasmodium vivax* resistance to chloroquine

Unlike *P. falciparum*, no genetic markers for CQ resistance had yet been identified for *P. vivax*. A collaborative effort attempted to shed further light on this by examining the chloroquine susceptibilities (using a modification of the above mentioned *in vitro* test) and molecular polymorphisms of *P. vivax* isolates collected in Papua, Indonesia, where high levels of clinical CQ resistance prevailed, and from Thailand where CQ treatment was still generally effective.[61] Isolates from Papua were considerably less susceptible to chloroquine than those from Thailand, although *in vitro* results raised the possibility of a low level of CQ resistance along the western border of Thailand.

Significantly, molecular analysis of the pvmdr1 gene revealed that 96% of Indonesian isolates had the Y976F allele compared to 25% in Thai isolates. It is noteworthy that the 976 mutation was not always associated with high IC50 CQ values, suggesting that other major molecular determinants were likely to be involved. Nevertheless, the predominant presence of the Y976F allele in Papua, known for its widespread clinical resistance to CQ treatment, indicated that pvmdr1 played an important role in modulating the susceptibility of *P. vivax* to CQ. Since gene amplification of the *pfmdr1* gene had already been shown to be a major determinant of multidrug resistance in *P. falciparum*, this might indicate similar molecular mechanisms for *P. vivax* resistance to CQ. This study not only emphasised the need to further refine the *in vitro* test as a means of identifying the presence of chloroquine resistance, but also raised the possibility that the *pvmdr1* polymorphism at Y976F might provide a useful tool to monitor the emergence of CQ resistance.

Identification of molecular markers for sulfadoxine resistance in *Plasmodium vivax*

Although widely used for treating falciparum infections, SP was less effective against *P. vivax* because its sulfadoxine component was less able to potentiate the activity of pyrimethamine against the parasite.[52] To understand the mechanism of this innate resistance to sulfadoxine, studies were undertaken to identify and sequence the *P. vivax* dihydropteroate synthetase (DHPS) gene, construct a 3D homology model of the DHPS enzyme, and investigate the interactions between sulfadoxine and DHPS.[62] As a result, an amino acid residue (V585) unique to the *P. vivax* DHPS was identified causing a reduction in binding to sulfadoxine. This explained why *P. vivax* was innately less susceptible to sulfadoxine than *P. falciparum*. After examining *pvdhps* in a number of *P. vivax* isolates collected from different areas, mutations were identified in some isolates which were likely to be responsible for acquired resistance to sulfadoxine. These mutations were subsequently validated as molecular markers for SP resistance in Thailand[63] and other areas,[57] and have been used worldwide for monitoring SP resistance.

Plasmodium falciparum cultures used to assess the activity of dihydrofolate reductase (DHFR) inhibitors on *Plasmodium vivax*

As described above, treatment of most malaria patients in endemic areas was based on a clinical diagnosis rather than a parasitological one. In areas where *P. falciparum* and *P. vivax* co-existed, this implied that the drug(s) used for treatment of multidrug-resistant falciparum malaria also needed to be effective against vivax malaria. With the increased prevalence of CQ-resistant and SP-resistant *P. vivax* and the inability to culture *P. vivax* continuously, *P. falciparum* from continuous culture was transfected with functional *P. falciparum* and *P. vivax* dhfr-ts alleles.[64] The development of this *P. falciparum* expression system allowed for the first direct assessment of the effect of DHFR inhibitors on *P. vivax* DHFR.

Previous investigations at AMI with one of these DHFR inhibitors, WR99210, had shown this

new antifolate drug to be far more effective than conventional antifolates against drug-resistant *P. falciparum*.[5,6] How effective would it be against drug-resistant *P. vivax*? The results showed that the PvDHFR quadruple mutant conferred greater resistance to WR99210 than the PfDHFR quadruple mutant. This was also the case for cycloguanil and clociguanil, but not for pyrimethamine. Further work, including modeling of both *P. vivax* and *P. falciparum* DHFR quadruple mutants suggested that mutations unique to *P. vivax* DHFR were responsible for differences observed in parasite susceptibility to antifolate drugs. Looking ahead, the development of the *P. falciparum* expression system appeared to be an important step forward in identifying potential *P. vivax* drug-resistance markers and in investigating the potency of existing and novel antimalarial drugs against known or putative *P. vivax* gene targets.

Molecular changes are associated with the development of *Plasmodium falciparum* resistance to artemisinin derivatives during *in vitro* cultures

During the previous decade AMI had carried out numerous studies relating to the *in vitro* and *in vivo* efficacy, and the pharmacokinetics of existing and novel artemisinin derivatives. In view of the increasing reliance of artemisinin-based combination therapy (ACT) for treating drug-resistant falciparum malaria (see above), there was mounting concern about the possible emergence of parasite resistance to the artemisinins. This prompted WRAIR and AMI to collaborate on investigating the development of artemisinin resistance *in vitro*.[65] Applying discontinuous drug selection pressure, resistance to artemisinin derivatives was established in several clones and lines of *P. falciparum*. Furthermore, apart from parasites being also cross-resistant to mefloquine and other artemisinin derivatives, they were able to tolerate artemisinin concentrations equivalent to those usually found in plasma samples after treatment of malaria patients.

The development of artemisinin-resistant parasites *in vitro* provided the opportunity to study various aspects of artemisinin resistance, including the identification of putative molecular markers of resistance to these drugs. Preliminary data suggested that parasites could tolerate increasing concentrations of artemisinin drugs by amplifying the *pfmdr1* gene, but they also suggested that this was not the central determinant of artemisinin resistance. Nevertheless, since amplification of *pfmdr1* was also associated with mefloquine resistance, attention was drawn to the possibility that this might have practical implications for the use of artesunate-mefloquine as an ACT in areas with high levels of mefloquine resistance. Finally, it was pointed out that the artemisinin-resistant mutants produced during these investigations constituted an important resource in the further search for molecular markers of artemisinin resistance.

7. EVOLUTION OF DRUG RESISTANCE

The aim of these NIH-supported studies was to obtain a better understanding of how malaria parasites developed drug resistance and what host, parasite and environmental factors might enhance or hinder the development and spread of drug resistance.

Origin and dissemination of chloroquine-resistant (CQR) *Plasmodium falciparum* in the Philippines

Following identification of the *pfcrt* gene as CQR marker,[6] mutation patterns were suggesting that CQR parasites had arisen independently in four different parts of the world: (1) Southeast Asia, then spreading to Africa; (2) Peru in South America; (3) Colombia, South America; and (4) Papua New Guinea. However, it was not clear how CQR parasites had developed and spread in Asia/Pacific countries other than PNG. During the CQ efficacy study conducted in Timor Leste,[6] the *pfcrt* mutation patterns in *P. falciparum* parasites indicated that CQR parasites shared a common origin with CQR parasites in PNG, suggesting that CQR in Timor Leste had most likely spread from PNG. Further investigations, carried out in collaboration with RITM, revealed that 90% of parasites sampled in Luzon Province, Philippines, carried two novel mutations in their *pfcrt* gene which had not been reported elsewhere in the world.[66]

To better understand the development and dissemination of CQR *P. falciparum* in the Philippines, a collaborative study was undertaken with QIMR to analyse mutation patterns in *pfcrt* and microsatellite patterns flanking *pfcrt* in 82 *P. falciparum* isolates collected throughout the Philippines between 1989 and 2002.[67] While mutation patterns demonstrate CQR status, microsatellite patterns point to the origin of CQR parasites. The results showed that the majority of CQR parasites in Luzon Province (in the North) developed *in situ* while most CQR parasites in Mindanao and Palawan Provinces (in the South) had originated in PNG. These findings demonstrated that CQ selection pressure could induce parasites with different genetic backgrounds to become resistant to CQ by mutating different positions in the *pfcrt* gene. Such new information should be helpful in gaining a better insight into the evolutionary process of CQR and in preventing a similar process from occurring following the introduction of newer drugs.

Figure 7: Dr. Nanhua Chen determining mutation patterns of malaria parasites.

Role of antigenic variation in the evolution of drug resistance

Antigenic variation in malaria parasites is a well known phenomenon hampering not only the development of effective vaccines but also of effective drugs. This is facilitated by a family of antigens, *P. falciparum* erythrocyte membrane protein 1 (PfEMP1), expressed by *P. falciparum* on the surface of infected red cells which enables them to adhere to the wall of blood vessels and prevents them from being destroyed by the host spleen. Since each parasite expresses only one of its many member antigens at a time, and regularly switches them around, it is able to evade host immunity. The number and diversity of PfEMP1 antigens in each parasite and in a parasite population are important for the survival of drug resistant parasites and determine the speed at which humans develop immunity against parasites. After examining the repertoires and genetic diversity of genes encoding PfEMP1 in isolates collected from the Solomon Islands, Philippines, PNG and Africa, AMI demonstrated that generally each parasite had genes encoding 40 – 50 members of PfEMP1.[68] However, each parasite had quite a distinct set of genes, with only 0-6 genes being shared between any two parasite isolates. These findings suggested that the global repertoire for PfEMP1 was immense and could be potentially selected by the host's immune response against PfEMP1.

Despite the high diversity of genes encoding PfEMP1 between parasites, five genes were identified that were shared at relatively high frequency among 63 genetically diverse *P. falciparum* isolates collected from five islands in the Western Pacific region. Upon further examination, three of the five genes were located on chromosome 4 near a mutant pfdhfr while two remaining genes were located on chromosome 7 near a mutant *pfcrt*. Therefore, the conservation of these genes was a result of their physical linkage to SP and CQ resistance markers and a probable outcome of the widespread use of SP and CQ in the region.[69] This provided strong evidence that drug resistance can influence the shape of parasite populations.

To understand how and how quickly parasites switch the expression of PfEMP1, the transcription of genes encoding PfEMP1 was studied in a number of human volunteers, infected with the 3D7 line of *P. falciparum*, who had participated in a vaccine trial conducted at QIMR in the early 1990s.[70] The results demonstrated that the expression of PfEMP1 was reinitiated each time after mosquito inoculation of parasites. Parasites then switched away rapidly from the first expressed PfEMP1 likely to facilitate establishment of infection at a rate of about 18% per generation. Subsequent switching at later phases of infection occurred at much lower rates.[71] It appeared likely that a parasite requires a group of 15-20 fast switching genes to establish an infection and a group of at least 20 slow switching genes to maintain the infection for transmission to mosquitoes.[72] The results indicated that anything that might be able to interrupt the switching of PfEMP1 would probably interfere with the normal life cycle of the malaria parasite.

Loss of fitness in drug resistant parasites

Following the emergence of drug-resistant parasites, would such parasites suffer a loss of fitness compared to their drug-sensitive siblings? The answer to this question could influence strategies used to delay or even reverse the spread of drug resistance. This was examined by comparing the relative fitness of atovaquone resistant *P. falciparum* parasites to their atovaquone sensitive parent parasites.[73] An equal number of resistant and sensitive parasites were combined with each other and, after 100 days of *in vitro* culture, the ratio of resistant to sensitive parasites was measured. Without any drug pressure, atovaquone resistant parasites that carried two mutations (M133I and G280D) in their cytochrome b suffered a 5 to 9% loss of fitness compared to their sensitive parents. Further molecular modelling revealed that the loss of fitness was due to the mutation (G280D) weakening the binding of cytochrome b to ubiquinones. These findings supported the concept that drug resistance could be reversed if the old drug was withdrawn and a new drug introduced long before the prevalence of resistance prevalence reached fixation. They also highlighted the importance of continuously monitoring the prevalence of drug resistance so that drug policy can be changed in a timely fashion.

Establishing a *P. falciparum* in-host dynamics model

In addition to epidemiological and laboratory studies, mathematical models were established to study the evolution of drug resistance. Mathematical modelling is a powerful tool for studying interactions of different factors in complex processes and for predicting the dynamics of changes resulting from interventions that are difficult to study using laboratory or epidemiological tools. The first model was an in-host dynamic model which mimicked the dynamics of *P. falciparum* infections in naïve hosts.[74] The model was constructed using data collected during human malaria studies between the 1930s and 1970s and produced output mimicking the infection dynamics of these infections. To ensure that the model prediction was biologically relevant, several parameters were determined experimentally, including PfEMP1 switching rates (see above), pyrogenic threshold, development of clinical immunity, parasite susceptibility to antimalarial drugs, pharmacodynamics/pharmacokinetics of drugs, and interactions between drugs.

Pyrogenic threshold information was obtained by a retrospective statistical analysis of two existing human infection data sets to determine the relationship of *P. falciparum* parasite density to the onset of fever in naïve human hosts. The pyrogenic threshold (parasite density triggering a fever) varied significantly between different strains and host ethnicities and became progressively higher as immunity developed following one and more attacks of malaria.[75] It was well known that individuals living in malaria endemic areas developed an acquired immunity to malaria, following repeated attacks of malaria, which enabled them to remain asymptomatic while still carrying parasites. In developing the *P. falciparum* in-host dynamics model, the acquisition of clinical immunity was investigated under different conditions of malaria transmission conditions, levels of parasite diversity, and exposure to treatment.[76] The time required to develop clinical immunity increased in areas where parasite diversity was high and decreased in areas where transmission intensity was high. Treatment of symptomatic infections did not prevent the development of immunity, only doubled the time required to develop immunity compared to circumstances where no treatment was available.

The *P. falciparum* in-host dynamics model was used to investigate the evolutionary steps that were involved in the development of de novo SP resistance. The results indicated that the development of SP resistance evolved in three steps: (a) SP selection of existing mutant parasites, which is driven by the long pharmacological half-life of SP; (b) SP selection of parasites with higher resistance, to which the time of treatment plays a role; and (c) treatment failures due to presence of highly resistant parasites. The model output reaffirmed the importance of correct treatment of confirmed malaria cases in slowing the development of SP resistance.[77]

8. PERSONAL PROTECTION AGAINST MOSQUITOES

Insect Repellents

Mosquito repellents are an important first line of defence against vector-borne diseases, such as malaria and dengue,[78-80] but the ADF repellent provided to ADF personnel was not being widely used by them. Although previous assessment of the repellent (35% Deet in a gel preparation) by AMI had shown it to be effective in providing a broad spectrum of activity against mosquitoes, soldiers complained that it felt uncomfortable on the skin and melted plastic and some other synthetic materials. During the 2000-2001 deployments to Timor Leste, AMI conducted further field observations on the use of insect repellents by ADF personnel and asked them to complete a questionnaire. In their response, 84% of 955 soldiers indicated that they used repellents, but they were mainly commercial repellents purchased by them.[78,81] To ensure that ADF personnel were receiving suitable protection, laboratory and field studies were conducted to assess the effectiveness of commercial formulations available in Australia.[82]

Picaridin was a new repellent which was starting to be used in commercial preparations. In 2001, a collaborative study between AMI, WRAIR and VADMP was carried out at Cowley Beach Training Area (CBTA) in northern Queensland to compare the effectiveness of picaridin and Deet preparations with one another. In night-time tests, both 20% Picaridin and ADF 35% Deet in a gel provided >95% protection

Figure 8: Collaborative investigation with mosquito repellents at Cowley Beach Training Area, Queensland, April 2001. (L to R) Major S. P. Frances (AMI), Dr N. Beebe (UTS) Major M. Debboun (WRAIR, USA), Senior Colonel N.V. Dung (VADMP, Vietnam) preparing to test repellent effectiveness on themselves.

against mosquito bites for 7-9 hours. Similar protection was observed in day-time tests with 20% picaridin and 33% Deet in a polymer cream. However, 10% picaridin provided >95% protection for only 2 hours.[83]

A further field study was conducted at Mt. Bundey Training area (MBTA) in the Northern Territory in March 2003 which compared the effectiveness of 20% picaridin with 20% Deet and ADF 35% Deet in a gel against *Anopheles* spp. and *Cx. annulirostris*. The protection provided against *Anopheles* spp. was relatively poor, with 20% picaridin and ADF Deet providing >95% protection for only 1 hour. By contrast, the repellents provided good protection against *Cx. annulirostris*, with 20% picaridin providing 5 hours protection, and both Deet formulations providing >95% protection for over 7 hours.[84] A comparison of commercial formulations against primarily *Cx. annulirostris* was also undertaken in the same area during 2003. Autan Repel (containing 10% picaridin) provided 2 hours protection, RID (10% Deet) 7 hours protection, and Bushman (80% Deet) 8 hours protection. Commercial repellents containing higher concentrations of Deet provided better protection than picaridin.[85]

Synthetic pyrethroids as barrier treatment for military fabrics

Previous studies at AMI had established the best methods for using permethrin insecticide in DPCU, bednets and tentage.[6] In 2000, after a new active ingredient, bifenthrin, became available in Australia, studies were undertaken to determine the potential use of this insecticide within the ADF. Laboratory studies showed that uniforms treated with bifenthrin and permethrin provided similar protection against *Anopheles farauti* and *Aedes aegypti* mosquitoes.[86] Chemical assays of ADF shirt fabrics showed that active ingredient was lost after cold water washing, with 78.5 to 85% of the active ingredient lost after three cold water washes. Since bifenthrin did not provide any additional protection, it was decided to continue using permethrin, with bifenthrin potentially available as an alternative insecticide.

In early 2003, a field trial was conducted in MBTA to determine the effectiveness of spraying ADF tents with 0.1% bifenthrin as a means of protecting people inside the tents from being bitten by mosquitoes.[87] The treated tents provided an 81% increase in protection from mosquitoes entering the tents, and 90.4% increase in protection from biting *Culex annulirostris*, an important arbovirus vector. In a subsequent study carried out in the Wide Bay Training Area in Queensland (WBTA) during 2005, the effectiveness of bifenthrin and permethrin in preventing mosquitoes from entering tents were compared with one another.[88] The results showed that barrier tent treatment provided increased protection against mosquitoes entering tents for at least four weeks, and that both insecticides provided similar levels of protection.[88] During further investigations, low concentrations of bifenthrin and permethrin, applied to tent fabric, were discovered to inhibit egg hatching and larval survival of *Aedes aegypti* in water accumulating in tent folds and, in addition, inhibit bloodfeeding by host seeking adults.[89] In view of the previous long use of permethrin by the ADF and the findings that it was just as effective as bifenthrin, it was decided to continue using permethrin and to reserve bifenthrin for future use. The additional barrier protection against mosquitoes could have important military and civilian applications, such as might occur when the sheltering of refugees requires the quick erection of tents.

9. VECTOR SURVEILLANCE

Timor Leste

In 1999-2000, ADF forces deployed to Timor Leste on peacekeeping duties suffered from high infection rates of malaria and dengue. The disease outbreak and management team deployed to Timor Leste in 2000 (see above) was involved not only in controlling the malaria situation but also contributed to monitoring the dengue outbreak[6] and instituting effective control measures. To guard against further outbreaks during subsequent deployments, surveys were carried out around ADF installations along the Timor Leste western border with Indonesia. The vectors of dengue virus, *Aedes aegypti* and *Aedes albopictus*, were found both in the towns that were co-located with defence installations and within the defence installations themselves. The larvae of these container breeding mosquitoes were commonly found in portable water containers used by local residents. Multiple breeding sites were also created following the establishment of defence installations, the most common being water trapped in folds of plastic wraps and tarpaulins, and car and truck tyres. The findings of these surveys were communicated to the deployed preventive medicine personnel who carried out source reduction (physical removal of breeding sites) and larviciding.

Anopheline mosquitoes were surveyed to determine the soldiers' risk of exposure to malaria. The surveys were carried out in the ADF installations by conducting human landing catches. Using this simple technique the degree of exposure the soldiers had to biting anopheles could be determined, the specimens collected were identified using molecular based techniques and further tested for malaria parasite antigen.

Several species of anophelines were found biting humans: *An. barbirostris, An. aconitus, An. annularis, An. maculatus, An. peditaeniatus, An. sundaicus, An. flavirostris* and a newly discovered species *An. vagus* genotype B. The most common species biting humans were *An. barbirostris* and *An. vagus* genotype B and specimens of both species were incriminated as vectors at the time of these surveys.[90] Larval surveys were also conducted around the ADF installations, primarily to identify anopheline breeding sites for larviciding by preventive medicine personnel. Detection of malaria parasites in mosquitoes is a laboratory based procedure requiring specialised equipment; so the surveys in Timor Leste provided an opportunity to evaluate a novel diagnostic test that could be applied in the field.[91]

During the deployment to Timor Leste, anti-filarial antibody levels were measured in 907 soldiers to determine whether they had been exposed to mosquitoes infected with filarial parasites, the causative agent of lymphatic filariasis.[92] Initial testing using *Dirofilaria immitis* antigen demonstrated that 49 of them (5.4%) developed antifilarial IgG1 antibodies after deployment, and one out of 944 (0.1%) seroconverted to IgG4 antibodies. When a subsample of 88 *D. immitis* reactive sera was subjected to a test using Brugia malayi antigen at NIH, 46 had elevated IgG antibodies and five had elevated IgG4 antibodies. A total of 24 soldiers seroconverted to *B. malayi* IgG, and a single soldier seroconverted to IgG4. The study showed that a relatively low number of Australian soldiers seroconverted to *B. malayi*, indicating a low but measurable risk of exposure to human filarial parasites. This re-emphasised the importance of soldiers adhering to personal protective measures against mosquito bites during their deployment to tropical areas.

Australia

Ross River virus and Barmah Forest virus

In Australia, ADF personnel were at risk of acquiring mosquito-borne infections not transmitted by anopheline mosquitoes. They were at greater risk of becoming infected by arboviruses, such as Ross River (RR) and Barmah Forest (BF), than civilians because they deployed regularly to areas where the natural animal hosts and vector mosquitoes of these viruses were in abundance. Concentration of soldiers within training areas provided alternative human hosts, thereby facilitating the transmission and spread of these viral infections. During the evaluation of tent barrier treatments with bifenthrin and permethrin in WBTA, 3,497 mosquitoes (primarily *Aedes vigilax*) were collected between January and March 2005 and processed for the presence of arboviruses. None of the 130 pools of mosquitoes showed any evidence of arboviral infection.[88] A subsequent longitudinal surveillance study commenced in 2005 revealed that, out of 348 pools of 9,380 mosquitoes (primarily *Ae. vigilax, Ae. multiplex, Ae. kochi* and *Culex annulirostris*), five were positive (two Edge Hill virus, one Stratford Virus, and two unidentified).[93]

Incursion of dengue virus vectors into Australia

In Australia the primary dengue virus vector *Aedes aegypti* is only found in far northeastern Queensland, but another less efficient vector - *Ae. albopictus* - has recently been discovered moving south through Papua New Guinea and into the Torres Strait islands.[94] Because both species are container breeders and can lay desiccant resistant eggs they are easily transported from one country to another. Consequently, a continual threat existed that these dengue vectors could be introduced into air and sea ports around Australia. A major problem in monitoring for possible incursions was that larvae of both species, the most common stage encountered by preventive medicine and quarantine services, were very difficult to use for species identification. To meet this problem, AMI, in collaboration with UQ and QSH, developed molecular diagnostic tools for identifying these species and for tracking their movement into and within Australia.[95-97]

Studies on *Culex annulirostris* - a potential vector of Japanese encephalitis in Australia

The Japanese encephalitis virus had been moving down Southeast Asia through the Malay Archipelago and into Papua New Guinea and, in 1995, there had been an outbreak in the Torres Strait islands resulting in two deaths. Using sentinnel animals, surveillance activities had indicated that the arbovirus was circulating on Cape York Peninsula in wild pig and bird populations though, as yet, there had only been one human case. Although the Asian vector species for this virus is not present in Australia, vector competency studies had shown that *Culex annulirostris* could readily transmit the virus. However, this species was sometimes difficult to distinguish from *Cx. sitiens* and *Cx. palpalis* using traditional morphological markers. To overcome this handicap, AMI collaborated with UQ and QSH in examining the ribosomal DNA Internal Transcribed Spacer Region I to develop a molecular marker to separate the three species reliably from one another.[98] The consistency of the procedure was documented following the examination of specimens collected in Australia, PNG and the Solomon Islands. Further collections of field material in Cape York Peninsula and the Northern Territory were analysed using the CO1 gene of the mitochondrial DNA.[99] Analysis of the

specimens revealed that there are five independently evolving haplotypes of *Cx, annulirostris* and three independently evolving haplotypes of *Cx. palpalis*, and that these populations might differ in their ability to transmit Japanese encephalitis on Cape York Peninsula.[100]

Vietnam

Malaria vectors and malaria transmission in rural villages in Vietnam (2000-2005)

Under the auspices of VADMP, malaria transmission was studied in rural communities in Vietnam. The aim was to determine what anopheline species were present, which were responsible for malaria transmission, and to learn something of their biology and ecology which might aid in their control and the protection of military forces in the field. A field site was selected at Truong Xuan Commune in Quang Binh Province, 500 km south of Hanoi, where malaria transmission was perennial but where less than 15% of the villagers carried malaria parasites. This was primarily due to the fact that the anophelines in the area were not particularly efficient malaria vectors, preferring to feed on cattle and buffalo.[101]

There was a perception in Vietnam that most malaria was transmitted in the forest by *An. dirus*, a notoriously efficient malaria vector, and that people contracted the disease in the forest while hunting, timber cutting, and food gathering. At a second field site in Phuoc Chien Commune there was an opportunity to study this concept of forest malaria. Although villagers in the commune lived in the valley floor where they were not exposed to any malaria vectors, they spent several months of the year cultivating their crops on the surrounding hillsides. Vector surveys conducted around these hillside communities showed that *An. dirus* was present and that a sufficient number of people spent enough time cultivating these crops to sustain malaria transmission.[102] These findings had implications for community malaria control activities because indoor insecticide spraying and treated bed nets were only supplied to village houses situated in the valley floor, whereas little or no emphasis was placed on preventing the acquisition of malaria at hillside garden dwellings.

China

Malaria vectors associated with *P. vivax* epidemics in China

In 2003, AMI received a WHO grant, in collaboration with Dr Nigel Beebe, UTS and Professor Gao Qi (JIPD), to investigate the possible discovery of a new malaria vector in China. During the late mid-1990s there was a resurgence of vivax malaria in China involving millions of cases. The vector thought responsible for these epidemics was *An. sinensis*, but this species is primarily zoophilic, feeding mainly on cattle, and therefore not a very efficient vector. Field studies in Chinese provinces where the malaria outbreaks occurred revealed the presence of another anopheline which appeared morphologically similar to *An. sinensis* but which readily fed on humans. This mosquito was believed to be a new species and was named An. anthropophagus. The aim of the collaboration was to determine, using molecular tools, if *An. anthropophagus* was indeed a new species and not *An. sinensis*. Analysis and sequencing of the ribosomal DNA Internal Transcribed Spacer Region II showed that *An. anthropophagus* and *An. sinensis* were in fact different species.[103] Following the epidemics in China, the Korean Peninsula experienced severe epidemics of vivax malaria in the early 2000s. As in China, *An. sinensis* was at first thought to be responsible, but the vector was later found to be a closely related species - *An. lesteri*. Further studies revealed that *An. anthropophagus* and *An. lesteri* were in fact the same species, thus incriminating *An. lesteri* as the major malaria vector responsible for the malaria epidemics in both China and the Korean Peninsula.

10. VACCINE DEVELOPMENT

Dengue

The dengue outbreak among ADF personnel in Timor Leste provided the impetus for AMI to conduct the first tetravalent dengue vaccine study in Australia involving 10 healthy volunteers admitted to the military hospital at Gallipoli Barracks, Brisbane. The Phase 1b study was designed to evaluate the immunogenicity and safety of two live attenuated vaccine formulations.[104] After one injection, all subjects reported systemic reactions consistent with a mild dengue-like syndrome. Seven volunteers developed dengue 3 viraemia after vaccination and all of the volunteers developed a neutralizing antibody response against serotype 3, with a partial response against other serotypes. The study was terminated early due to formulation issues relating to the dengue 3 vaccine component. Managing viral interference and balancing attenuation to produce acceptable tetravalent immunogenicity with minimal reactogenicity may be a recurring problem for future multivalent live vaccines. This initial study with dengue vaccines led to a long-standing collaboration between AMI, AP and ACR to evaluate chimeric arboviral vaccines using their envelope antigens combined with a core yellow fever vaccine.

Japanese encephalitis

With the spread of Japanese encephalitis (JE) throughout the region and even into mainland Australia, almost half of the ADF budget for vaccination was being spent on protecting its military personnel against this mosquito-borne disease.[105] In efforts to extend the lifespan of the Australian stockpile of the discontinued Biken JE vaccine, previous studies at AMI had shown that comparable serological levels of immunity could be attained by administering considerably lower doses of the vaccine intradermally rather than by subcutaneous inoculation.[6] Furthermore, cellular immunity continued to provide protection following the decline of antibody levels.[106,107] Although this inactivated, mouse brain-derived vaccine induced a good immune response, there was uncertainty about the duration of protection and concern about some infrequent adverse events following immunisation, and production of the Biken JE vaccine was completely discontinued in 2005.

In 2003, a randomised double-blind study involving 202 healthy ADF personnel was initiated to evaluate the safety, immunogenicity and persistence of antibodies after administration of a live, attenuated JE chimeric virus vaccine (JE-CV) - Chimerivax™-JE.[108] To assess adverse events related to vaccination, volunteers were randomised to receive the vaccine and placebo subcutaneously 28 days apart in a cross-over design. A subgroup of 98 participants were inoculated with a JE-CV booster six months later to determine whether this would prolong the protective efficacy of the vaccine. Vaccination was well tolerated and the incidence of reactions was comparable to that observed after placebo inoculation. Almost all volunteers (99%) achieved seroprotective antibodies within 28 days of receiving the single dose of JE-CV vaccine and 90% were still seroprotected two years later. The seroprotection rate at this time was even higher (99%) for those JE-CV recipients who received a booster dose at six months. These findings indicated that JE-CV vaccination was safe and that just a single dose provided prolonged immunity against JE infection. Plans were put in place to continue monitoring seroprotection for another three years into the 2005-2010 quinquennium.

In 2004, a further randomised double-blind study involving 108 volunteers was carried out to evaluate the safety and efficacy of concomitant or sequential administration of JE-CV vaccine and yellow fever 17D vaccine (YF-17D).[109] The rationale for this study was based on the fact that JE-CV was produced by removing the pre-membrane and envelope coding sequences from the yellow fever virus and replacing them with the corresponding sequences from an attenuated strain of the JE virus. Consequently, both vaccines shared antigenic determinants and non-structural coding sequences which might boost or suppress immune responses if these vaccines were administered at the same time or in either order one after the other. After administering two inoculations, 30 days apart, using various JE-CV, YF-17D and placebo cross-overs, there were no serious adverse events and seroconversion rates were above 90% in all the groups. Neutralising antibodies against the JE and YF vaccines continued to be detected in 82-100% of volunteers up to the last follow-up blood sample collected six months after immunisation. The results suggested that both vaccines could be given together, either concurrently or 30 days apart, without reducing their protective efficacy.

In order to exclude the possibility that vaccinees might transmit JEV to susceptible mosquitoes, *Culex annulirostris*, Culex gelidus, and Aedes vigilax were fed on Chimerivax™-JE.[110] None of the mosquitoes fed on the vaccine became infected, in contrast to mosqitoes fed on JEV-Nakayama or the yellow fever vaccine virus 17D. The findings indicated that it was unlikely that transmission of JEV could be established in Australia following vaccination with Chimerivax™-JE.

11. TECHNICAL ADVICE AND TRAINING

AMI continued to provide the Office of the Surgeon General with periodic updates regarding malaria and other VBDs, including a review of Policy Directive 215 and subsequent issue of a new version in 2005. In addition to responding to frequent enquiries by medical staff regarding prevention and treatment of VBDs of ADF personnel, AMI was actively involved in providing assistance and training to preventive medicine personnel during field deployments. In 2004 a new annual training course was initiated in "Vector Borne Diseases Surveillance and Control". This one-week course for preventive medicine technicians was administered by Army Logistic and Training Centre, and conducted by AMI staff.

Following inauguration of the Vietnam Australia Defence Malaria Project, AMI hosted medical officers and scientists from Vietnam and trained them in all aspects of work undertaken at the Institute. Concurrently, AMI staff benefited greatly from experience gained during joint clinical and field studies conducted in Vietnam. Apart from contributing to WHO-sponsored training projects in various locations (see above), AMI staff continued to remain involved in other less structured efforts to promote training and information on VBDs.

Conclusions

The second half of the fourth decade (2000-2005) was characterised by the most wide-ranging and significant activities yet undertaken by AMI. Many of them could not have been carried out without the continued collaboration with other institutions in Australia and overseas. Significant events and achievements included:

1) Successful control of malaria and dengue outbreak among Australian peacekeepers in Timor Leste following various epidemiological, chemoprophylactic and mosquito control measures instituted by AMI field teams.

2) Demonstration that currently-used regimens of antimalarial drugs, including mefloquine and primaquine, can be modified to provide more effective protection against malaria under field conditions.

3) Prospect that tafenoquine, a new, long-acting synthetic analogue of primaquine, might not only improve compliance with post-exposure prophylaxis and treatment regimens, but might provide protection against vivax and falciparum malaria while in malarious areas.

4) Assessment of the influence of food, gender and pregnancy on the effectiveness, tolerability and/or pharmacokinetics of various antimalarial drugs.

5) Demonstration that artemisone, a new artemisinin derivative, is more active *in vivo* than other artemisinins in curing falciparum malaria.

6) Detailed evaluation of malaria rapid diagnostic tests (RDTs) and development of *in vitro* drug susceptibility test for *P.vivax*.

7) Identification of molecular markers for *P. vivax* resistance to chloroquine and sulfadoxine.

8) Documentation of worsening resistance of first- and second-line drugs used for malaria treatment in various parts of the Asia/Pacific region.

9) *In vitro* assessment of drug activity against *P. vivax* parasites enabled by successful transfection of *P. vivax* genes to *P. falciparum*.

10) Artemisinin resistance of *P. falciparum in vitro*, produced by applying discontinuous drug selection pressure, is associated with amplification of the *pfmdr1* gene.

11) Investigation of factors influencing the evolution and spread of drug resistance in malaria parasites.

12) Evaluation of insecticides applied to skin, clothing and tents to maintain optimum protection against mosquito bites.

13) Entomological investigations in northern Australia with vectors of Ross River, Barmah Forest, Dengue and Japanese encephalitis viruses.

14 Epidemiological investigations with malaria vectors in Vietnam and China.

15) Inititation of dengue vaccine studies.

16) Prolonged protection against Japanese encephalitis obtained after administration of a single dose of a live, attenuated JE chimeric virus vaccine (JE-CV).

17) Consolidation of close collaboration with US and Vietnamese Army investigators following the establishment of a Walter Reed Army Institute of Research laboratory at AMI and inauguration of Vietnam Australia Defence Malaria Project (VADMP) laboratories in Hanoi.

18) Redesignation of AMI as a WHO Collaborating Centre for 4 years, with AMI hosting, participating in, or conducting several WHO-sponsored courses, conferences or workshops.

Highlights

2000/2001

- Vietnam Australia Defence Malaria Project (VADMP) established (2000-2005).
- Walter Reed Army Institute of Research laboratory established at AMI following arrival of Lieutenant Colonel Dennis Kyle.
- Investigations on "Evolution of drug resistance in *P. falciparum*" commence under three-year NIH RO1 grant (2000-2003).
- AMI field teams control malaria and dengue outbreak in ADF personnel deployed to Timor Leste.
- Shorter and higher dose primaquine regimens evaluated to determine tolerability and effectiveness for post-exposure prophylaxis and radical cure of *P. vivax malaria*.
- Weekly tafenoquine prophylaxis during six-month deployments on peace keeping duties in Timor Leste prevents falciparum and vivax malaria both during and following deployments.
- Population pharmacokinetics of tafenoquine supports the use of a loading dose of 200 mg daily for 3 days followed by 200 mg weekly for six months for effective malaria protection.

- Mosquito repellents evaluated at Cowley Beach Training Area, Queensland.
- WHO *in vitro* test modified to assessof *P. vivax* susceptibility to antimalarial drugs.
- Entomological investigations in Timor Leste identify potential malaria vectors and incriminate a new vector species.

2002

- AMI hosts WHO-sponsored 13th Southwest Pacific Malaria meeting.
- Official opening of VADMP laboratories in Hanoi.
- Large-scale study with mefloquine, including pharmacokinetic evaluation, indicates that 250 mg every other day during the first week followed by the same dose once a week is well tolerated and effective in providing malaria protection for six months.
- Artemisone is more effective than other artemisinin drugs in curing falciparum infections in Aotus monkeys.
- Increased plasma clearance (50%) of atovaquone, proguanil and cycloguanil in pregnant malaria patients suggests that the dose of atovaquone-proguanil might need to be increased for the treatment of malaria during pregnancy.
- *P. falciparum* parasites process a highly diverse family of PfEMP1 on the surface of red cells and switch rapidly between these antigens to establish an infection.
- Sulfadoxine/pyrimethamine treatment is less effective in patients infected with *P. vivax* carrying a quadruple mutant dihydrofolate reductase (DHFR) gene.
- Atovaquone-resistant parasites are less fit than sensitive parasites, suggesting reversal of drug resistance following use of alternative drugs.
- Molecular diagnostic tools are developed to identify larvae of dengue virus vectors and to prevent their importation into Australia.

2003

- Lieutenant Colonel Robert Cooper replaces Lieutenant Colonel Michael Edstein as Commanding Officer.
- Amplification of *pfmdr1* gene plays an important role in the development of *P. falciparum* resitance to artemisinin drugs.
- Chloroquine resistance in the Philippines is due to mutations of both indigenous and imported parasites from Papua New Guinea.
- Field evaluation of picaridin as a mosquito repellent and of bifenthrin as barrier treatment in military shirts and tents at Mount Bundey Training area, Northern Territory.
- Food containing 30 g fat may enhance primaquine effectiveness by augmenting plasma drug concentrations.
- New molecular diagnostic tools are developed to identify potential Japanese encephalitis vectors in Australia.
- Immunisation with live, attenuated Japanese encephalitis chimeric virus vaccine (JE- CV) is safe and induces seroprotection for at least two years.

2004

- High dose, shorter courses of primaquine are tolerated just as well as longer primaquine courses by glucose-6-phosphate dehydrogenase normal Australian soldiers.
- Seven-day courses of primaquine (22.5 mg twice a day), preceded by two days of artesunate (200 mg twice a day) are well tolerated and effective in Vietnamese patients infected with vivax malaria.
- Pharmacokinetic studies with artemisone during Phase I human safety and toxicity studies support the potential value of this drug for artemisinin combination therapy.
- *P. vivax* is both innately resistant and can develop resistance to sulfadoxine due to variation and mutation, respectively, of the parasite's dihydropteroate synthetase (DHPS) enzyme.
- Investigations on "Antigenic variation and drug resistance in *P. falciparum*" commence under second three-year NIH RO1 grant (2004-2007).
- *P. falciparum* in-host dynamics model assists in understanding diverse factors influencing the development of host immunity and the evolution of drug resistance.
- Field evaluation of commercial repellents in Queensland.
- Entomological studies identify the malaria vectors in rural communities in north central Vietnam and investigate their biology and behaviour.
- Long-term persistence of neutralising antibodies after sequential administration of JE- CV and yellow fever 17D vaccines suggest that both vaccines can be given together without reducing their protective efficacy.

2005

- Food containing 17 g fat increases plasma piperaquine concentrations in healthy Vietnamese soldiers, which may benefit malaria patients receiving ACT using this drug and dihydroartemisinin.
- Relapses of *P. vivax* infections in ADF personnel deployed to Timor Leste result from activation of a single strain of hypnozoite in the liver.
- Highly diverse target antigen HRP2 may cause variable sensitivity of malaria RDT's, whereas highly conserved aldolase produces more reproducible test results but is less sensitive than HRP2.
- Pvmdr1 is a molecular marker for drug resistant *P. vivax*, with mutant pvmdr1 predicting chloroquine resistance while multicopy pvmdr1 predicts mefloquine resistance.
- *P. falciparum* expression system established to assess *P. vivax* response to dihydrofolate reductase (DHFR) inhibitors.
- Drug resistance exerts a strong force in shaping a parasite population.
- Barrier treatment of tents with bifenthrin is just as effective as permethrin in reducing exposure to mosquitoes in the Wide Bay Training area, Queensland.
- Entomological aspects of forest malaria studied in central Vietnam.

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Veterans with co-morbid posttraumatic stress disorder and mild traumatic brain injury: the nurse practitioners role in facilitating treatment

Lori Wheeler & Kathryn Puskar

Abstract

Background: Many military veterans experience events during deployment that cause mild traumatic brain injury (mTBI) and symptoms of Posttraumatic Stress Disorder (PTSD). Due to the inconsistencies in treatment plans for patients with these co-morbid conditions, it is important that nurse practitioners and other mental health care providers are aware of the options available and facilitate appropriate treatment in order to improve outcomes for this patient population.

Purpose: To discuss standard evidence- based practice protocols to treat co-morbid PTSD and mTBI in veterans, evidenced by the review of a case study, and to highlight the importance of the role of the nurse practitioner in facilitating appropriate treatment.

Methods: A case study and article review of published literature related to treatment options for patients with co-morbid mTBI and PTSD will be discussed.

Conclusion: This paper will illustrate the findings and discuss implications for the nurse practitioner's role in facilitating appropriate treatment plans in order to improve outcomes for patients with co-morbid mTBI and PTSD.

Keywords: Veterans, Posttraumatic Stress Disorder, Mild Traumatic Brain Injury, Nurse Practitioners, Treatment

Introduction

PTSD can occur after someone experiences or witnesses a traumatic event in which their physical or emotional well-being is threatened. Many veterans experience traumatic events while deployed that cause symptoms of PTSD, ranging from combat related incidents, to training accidents or traffic collisions. Bogdanova and Verfaellie noted that among combat deployed troops, there is a relatively consistent prevalence of PTSD in the range of 10-17%.[1] Richardson et al. noted that recent studies have suggested combat related PTSD rates are between 4-17%. Among different nations, the rates vary, with the highest prevalence noted in the United States at approximately 17%, compared to a 12% prevalence in Australian and United Kingdom veterans, and 7.2% of Canadian veterans.[2] The highest rates of PTSD are reported among veterans who also have a history of mTBI at a prevalence of 33-39%,[1] although it is debatable as to whether the development of PTSD is related to the fact that the patient sustained a mTBI or if the condition would have also occurred in the absence of a mTBI.

Otis et al.[3] describe the symptom profile of PTSD, which includes: 1) experiencing a traumatic event, 2) re-experiencing the event via recurrent thoughts, nightmares, or flashbacks, 3) avoidance of stimuli, thoughts or places associated with the traumatic event, and 4) emotional detachment and symptoms of hyper-arousal which cause increased startle reflex, problems with sleep, attention and concentration problems, hypervigilance, and the presence of irritability and anger.

Sripada et al.[4] define a mTBI as a traumatically induced physiological disruption of brain function, as manifested by at least one of the following: 1) any period of loss of consciousness not exceeding 30 minutes, 2) any loss of memory for events immediately before or after the accident, 3) any alteration in mental state at the time of the accident such as feeling dazed, disoriented, or confused, and 4) focal neurological deficits that may or may not be transient such as weakness, loss of balance, and vision changes. The symptoms of mTBI can last days or weeks, but usually resolve before three months. When the symptoms last longer than three months,

the patient is considered to have post concussive syndrome (PCS).

Otis et al.[3] cite The Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, 2000 and describe PCS as a clinical syndrome where at least three symptoms of concussion persist after the initial three months following a head injury. Symptoms of concussion include fatigue, difficulty sleeping, dizziness, persistent headaches, irritability, increased anxiety, depression, mood changes, and apathy.[3,5]

Many of the symptoms of PTSD and mTBI overlap, namely problems with executive functioning, learning and memory, and attention. For this reason, it is often difficult to distinguish whether or not a patient's symptoms stem from PTSD, mTBI, or both. It is important that the patient is initially examined and a thorough work up is performed to rule out a more serious medical condition caused by the head injury during the traumatic event. Another factor to consider is that the patient may not seek the care of a mental health care provider within the first three months of their event. Identification of PTSD specific symptoms, such as hyper-arousal and avoidance, which are typically not seen in civilian mTBI, can be helpful for the differential diagnosis.[1] It is also important to consider the timeframe of the mTBI when implementing treatment plans. Residual symptoms of PCS may subside by one year after the injury, while symptoms of PTSD may persist, and the majority of cases are unlikely to resolve without proper treatment.

Treatment options for PTSD with mTBI

Traditionally, there have been specialised clinical teams who treat each of these disorders separately. Challenges have been identified by providers in regards to scheduling and engaging patients with co-occurring mTBI and PTSD in treatment, determining the aetiology of patients' presenting problems, coordinating services, and knowing whether or how to alter standard treatments.[6] With the evolving role of the nurse practitioner, and the increased autonomy in practice, nurse practitioners are faced with treating some of these difficult cases. Although little has been established in terms of evidence-based practice guidelines for the treatment of these co-morbid conditions, nurse practitioners must use current research to guide their practice. Findings point to the need for further research on best practices to assess and treat mTBI/PTSD.[6]

The two primary non-pharmacologic treatments for PTSD are cognitive processing therapy (CPT) and prolonged exposure therapy (PE), both of which are trauma focussed cognitive behavioural therapy-based treatments.[7] CPT and PE are proven equally effective for treatment and have been established as the recommended protocols to reduce and eliminate symptoms of PTSD.[7] In CPT, clinicians rely on cognitive processing techniques by working with patients to address inconsistencies between trauma generated thoughts and pre-existing belief systems. On the other end of the spectrum, PE relies on emotional processing through systematic exposure to memories or physical reminders of the trauma to reduce symptoms.[7]

Peterson et al.[8] define CPT, which usually consists of approximately twelve 60 minute sessions, and includes psycho-education about PTSD, cognitive restructuring, and exposure. In the exposure component of CPT, the patient writes an account of the event to read aloud in therapy and at home. The cognitive therapy component begins with an impact statement in which the patient describes the impact of the event on his or her perspective of self, others, and the world, such as "it's all my fault". Throughout therapy, problematic cognitions are identified and challenged through Socratic questioning until more accurate beliefs replace any distorted thoughts. The last few sessions focus on cognitions that are troublesome in PTSD such as safety, trust, power, esteem, and intimacy.[8]

Peterson et al. also define PE, which usually consists of ten to twelve 90 minute sessions, and includes psycho-education, breathing retraining, imaginal exposure, and in vivo exposure. Patients are educated about the evolution and treatment of PTSD, are taught breathing techniques to promote relaxation, and practice imaginal and in vivo exposure to promote adaption to the feared trauma memory. PTSD patients usually avoid thoughts and situations that are reminders of the trauma, but PE requires the patient to confront the memories by repeatedly retelling the trauma story (imaginal exposure) and confront feared situations associated with the trauma (in vivo exposure).[8] The major difference between the two therapies is that CPT teaches the patient cognitive restructuring techniques to allow them to realise their distorted thoughts and develop coping mechanisms, and PE forces the patient to directly confront their situation over and over in order to desensitise the patient to their fear.

Few studies have tested the effectiveness of these treatments for co-morbidity in mTBI and PTSD, although the little evidence found suggests that these cognitive behavioural based therapies are almost equally effective for PTSD with mTBI and PTSD alone. Davis et al.[9] found that treatment adherence was greater than 61% in both groups. The

average attended sessions for the PTSD alone group was 9.6 and for the mTBI/PTSD group was 7.9. Although the study did not evaluate the end outcome of effectiveness, it was noted that the treatment was tolerable for both groups.

Sripada et al.[4] investigated the utility of PE for individuals with and without a history of mTBI in a sample from a military hospital PTSD clinic. As hypothesised, PE was highly efficacious for individuals with PTSD, and there was no evidence to suggest that the presence of mTBI impacted the efficacy of PE. They compared their results to a study they found by Wolf and colleagues in 2012[10] that demonstrated a 45% post-PE reduction in PTSD symptoms in 10 veterans with PTSD plus mTBI. As stated previously, some providers have voiced concerns that individuals with a history of mTBI are more likely to experience cognitive impairment and thus will not benefit from trauma-focussed treatment. This study challenges these concerns, stating that PE utilises processes that depend heavily on limbic and medial prefrontal circuits that are conserved across species, and there is little reason to believe that minor impacts on the brain would preclude them.[4,10]

Aside from the cognitive behavioural approach, there are also medications that are prescribed to treat PTSD. Pharmacologic interventions that are frequently prescribed include antidepressants, antipsychotics, and sedative hypnotics. Some of the prescribing trends are not supported by guidelines developed for the treatment of PTSD. In fact, there is suggestion that benzodiazepines may interfere with psychotherapy treatments that are first-line PTSD recommendations. The release of the updated Clinical Practice Guideline(CPG) highlight the need to investigate prescribing trends among veterans with PTSD to document changes in patterns, identify gaps between recommendations and practice, and determine areas for clinical intervention.[11,12] The CPG recommends a combination of cognitive behavioural therapy, and a selective serotonin re-uptake inhibitor(SSRI), specifically sertraline or paroxetine, as first line interventions for combat related PTSD treated in specialty clinical settings.[8,11]

Case Study

Mr. A is a 23 year old single Caucasian male, previously in the U.S. Marine Corp, who was deployed to Afghanistan during his enlistment. He received a general discharge after experiencing a primary blast injury which caused a mTBI. He was experiencing symptoms of PTSD which included 1) involvement in a traumatic event that caused physical harm, namely, being thrown from a tank when the rear was hit with an explosive missile, 2) the event was re-experienced via nightmares and memories when he witnessed or heard about violent acts, such as news stories, violent television, or heard loud noises, 3) he avoided turning on the television or radio, 4) he became less social and was detached from friends that he was close with prior to deployment, 5) he had trouble sleeping, difficulty concentrating, and reported irritability, 6) he had been experiencing these symptoms for approximately 4 months after he returned home from deployment. He also experienced residual effects from his mTBI which included anxiety, dizziness, and frequent headaches almost every day. His symptoms of troubled sleep, irritability, and difficulty concentrating are overlapping symptoms that could have been caused by either diagnosis mentioned above.

Mr. A presented to the outpatient clinic stating "I can't take it anymore, I just want to be normal again". He stated that ever since the incident he had been unable to maintain a normal lifestyle. As stated above, all of his symptoms were preventing him from getting a job, seeing friends and family, and doing things that he used to do on a daily basis. He was living at home with his parents and younger sister, who were also very concerned for his well-being. He then decided to seek treatment and presented to an outpatient mental health clinic for treatment. His parents accompanied him for emotional support.

Prior to his traumatic event, Mr. A was a healthy young male with no medical problems. He had never been on any medications. He had no history of childhood illnesses, seizures, head trauma, or surgeries. He denied use of nicotine, caffeine, or herbal medications. He was taking ibuprofen to relieve his headaches. He denied use of any illicit substances in the past or present. He was a social drinker, having 3-4 beers on Saturday nights when he was out with his military buddies. He stated that he was never a big drinker, but that he would find himself having 5-6 beers a night since he returned home because he felt it numbed him and helped him sleep better. He stated he had a great childhood, with loving family and many friends in high school and in the military. He was always interested in school and was an above average student. Since his return home after discharge, he found himself wanting to be alone, and had difficulty concentrating. He denied any suicidal ideation or suicide attempts. His psychiatric review of systems was negative for hallucinations, delusions, mania, or depressed mood. His family history was negative for any serious medical problems, substance abuse, or psychiatric history. After his initial injury, he was evaluated by military medical specialists, before

he was discharged. His blood work was normal, which included complete blood counts, chemistries, thyroid studies, urinalysis, and drug screen. He had a computed tomography (CT) scan and magnetic resonance imaging (MRI) that showed normal brain images with no evidence of injury, which is typical for mTBI.

Upon initial presentation to the psychiatric outpatient clinic, he was evaluated by a psychiatric mental health nurse practitioner. The patient was started on sertraline 25mg at bedtime for his PTSD symptoms. The dose was titrated up to 100mg by the third week. He was also prescribed prazosin 1mg at bedtime for insomnia and nightmares, which was titrated up to 5mg by the third week. He attended 12 weekly sessions of prolonged exposure therapy in which he was initially educated about the development and treatment of PTSD. He was then taught breathing retraining, which he was instructed to use any time he felt anxious or when he was confronted with a situation that reminded him of his traumatic experience. Imaginal exposure was initiated, where he had to re-tell the event at each session, and utilise his breathing exercises to reduce his anxiety. He was also confronted with in vivo exposure, in which he engaged in watching devastating news stories, scenes from movies that had violent war scenes, and was exposed to startling loud noises.

He was tolerating his medications with minimal side effects, and was progressing at a steady pace each week during his therapy sessions. By the end of the twelve weeks, he was able to talk about his traumatic experience with very little anxiety. He had also begun to watch television at home without worrying about seeing something that would cause panic. He started to see his friends again and enjoy activities that he used to enjoy with them like fishing and golfing. He had also stopped using alcohol as an escape at night to decrease his anxiety, although he admitted to social drinking on the weekends with his friends. He very rarely experienced irritability and his concentration improved. He also noticed that his headaches decreased from nearly every day to once or twice a week. He was no longer experiencing nightmares related to his traumatic event.

This case of Mr. A shows a patient who had severe symptoms of PTSD after a mTBI from a traumatic event he experienced during military deployment. As shown in the research, CBT along with proper medication management improved and helped to alleviate his symptoms of PTSD. At the end of his therapy sessions, Mr. A was approximately eight months post injury. His residual effects from his mTBI such as irritability, decreased concentration, and headaches were also subsiding. Since these are also symptoms of PTSD, it is difficult to assess whether the medications and therapy improved these symptoms, or if adequate time to recover from the mTBI had an effect. Overall, this case shows a similar outcome when compared to results from studies that used CBT for treatment of PTSD along with co-morbid mTBI.

When a patient presents with history of mTBI sustained during a traumatic event, the nurse practitioner should follow specific protocols to ensure that the patient is receiving adequate treatment. A treatment algorithm can be followed, which consists of a thorough medical workup including lab work, CT scan, and MRI. A comprehensive history and physical examination, including psychiatric background, should be performed in an initial interview with the patient. The nurse practitioner or psychiatrist should initiate approved medications. The FDA has approved the SSRI's paroxetine and sertraline for the treatment of PTSD. Sleep related complaints in PTSD have been poorly investigated, but prazosin has been approved for the treatment of PTSD related nightmares, and has shown promising results.(13) For treatment resistant patients, antipsychotic medications such as risperidone can be used off label for treating PTSD. As stated previously, avoid medications such as benzodiazepines and other sedative hypnotics because they may interfere with the efficacy of therapy and other medications.[11] The nurse practitioner should refer the patient to a therapist who specialises in CBT programs that are trauma focussed and include CPT or PE. Assessment and management of medications should be performed by the nurse practitioner every two weeks in the beginning stages of treatment, and should then follow the patient monthly after the first six weeks until the patient is stable. At the point where the patient is finishing therapy and has stabilised, three month follow ups are adequate. When the patient has completed the recommended course of therapy, and has been stable on their medications for one year, a plan to titrate down medications can be discussed between the patient and the nurse practitioner.

Implications for the Nurse Practitioner and other Mental Health Care Providers

Psychiatric mental health nursing is a specialty area that is dedicated to promoting the mental health of patients. The American Psychiatric Nurses Association has developed standards of practice that relate to assessment and treatment for all areas of nursing practice. The standards of practice for nurses are followed when treating patients with PTSD and mTBI, taking into account that the prevalence rates of these co-morbid conditions is high. There are six

standards of practice, which include assessment, diagnosis, outcomes identification, planning, implementation, and evaluation.[14] All of equal importance, it is of particular interest to consider the implementation phase when treating a patient with co-morbid PTSD and mTBI. Although there is very little evidence to support treatment of these co-existing diagnoses as one, the few studies that have been completed show that PTSD symptoms can be equally reduced with or without the presence of mTBI. The Beck Institute for Cognitive Behavior Therapy in Philadelphia, Pennsylvania recognises the high incidence of PTSD in returning veterans, and offers a three day workshop for advanced practice nurses where the participants learn in depth cognitive behaviour techniques related to CPT and PE.[15] Using techniques from this workshop and other educational programs, protocols must be established based on positive results that include standard treatment plans for PTSD with mTBI. Proper documentation and reporting of results can be used to support the evidence- based practice data that currently exist. Nurse practitioners currently provide medication management for PTSD. They must encourage other practitioners to implement the use of approved CBT programs to reduce and eliminate PTSD symptoms, regardless of whether they have sustained a mTBI or not. By recognising the efficacy and facilitating the use of these approved treatments, patients who have experienced a mTBI and suffer from PTSD have a significantly higher chance of recovering and living more functional lives.

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Rabies post-exposure prophylaxis in Australian Defence Force personnel in Afghanistan

Leonard B. Brennan

Abstract

Background: Australian Defence Force (ADF) personnel have been deployed to Afghanistan since 2002. The 2011 death of a US Army soldier from rabies raised the awareness of rabies in ADF personnel deployed in Afghanistan.

Purpose: The study aims to review rabies exposure in ADF personnel supported by the Australian Role 1 health facility in Tarin Kowt, Afghanistan during a 6 month period.

Materials and Methods: The Australian Role 1 rabies vaccination register and associated animal bite reports were reviewed to identify rabies exposures and subsequent management.

Results: 21 ADF members reported a potential rabies exposure during the period.

Eighty five percent were due to a cat bite or scratch with an average delay of 51 days between exposure and reporting, when 32% and 57% respectively were classified as a category II or III exposure. All exposures were managed in accordance with National Health and Medical Research Council (NHMRC) post-exposure prophylaxis (PEP) recommendations.

Conclusion: Rabies remains a disease of military significance for ADF personnel operating in Australia's area of military interest. ADF health staff need to encourage military personnel to minimise contact with local animals and report animal bites or scratches promptly in order to ensure that PEP is administered early.

Keywords: rabies, post-exposure prophylaxis, Afghanistan, Australian Defence Force

Introduction

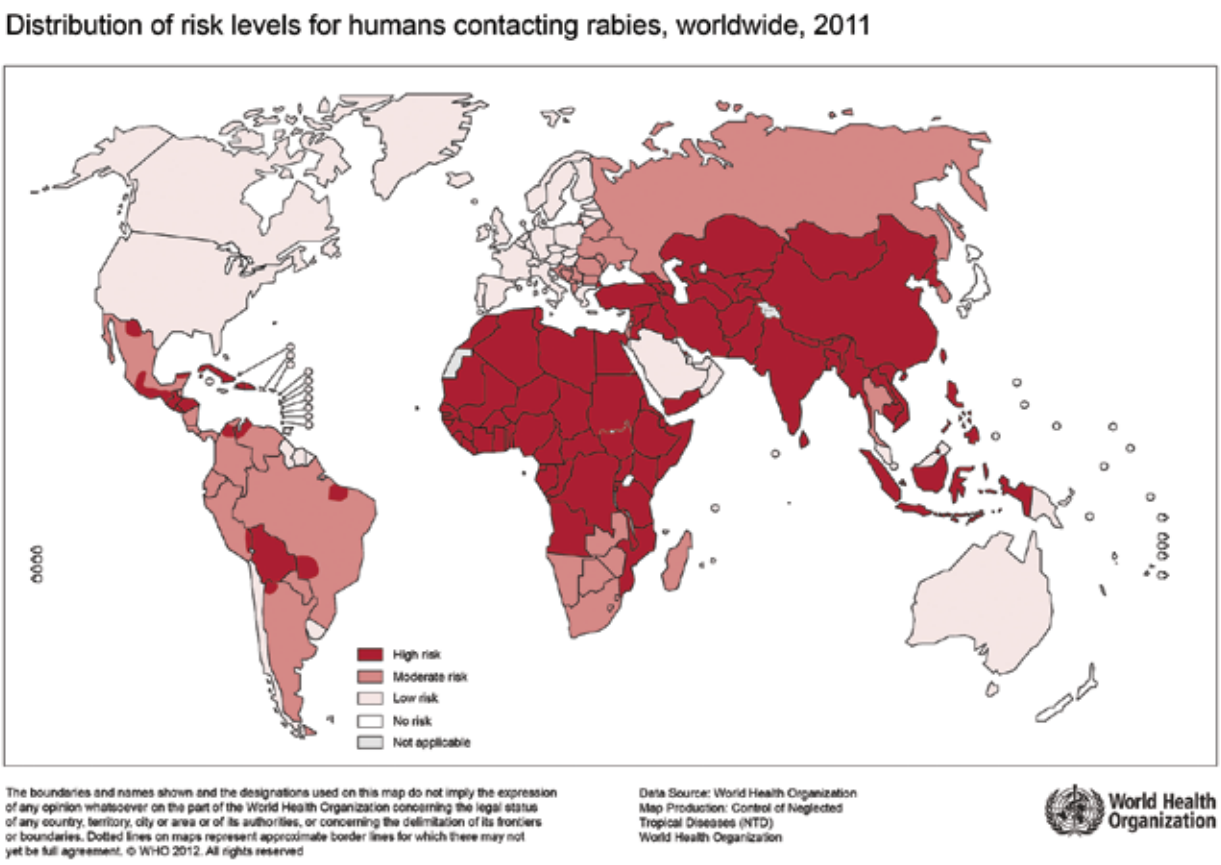
The rabies virus is a single-stranded RNA virus from the family Rhabdoviridae, genus Lyssavirus which also includes the Australian bat lyssavirus (ABLV).[1] Humans exposed to saliva or any nerve tissue of an animal infected with rabies may become infected, with the incubation period usually being 3-8 weeks, although the range quoted in separate reports is as short as 1 week and as long as several years after exposure. Rabies is almost invariably fatal, with non-specific symptoms preceding the classical rabies symptoms of a progressive encephalopathy and hypersalivation. Death from cardiac or respiratory arrest usually occurs within 3 weeks of developing symptoms.[1]

Human exposure can occur via a scratch or bite that has broken the skin, or via direct contact with the mucosal surface of an infected animal. Most human cases of rabies occur after an animal bite(s). Cases following animal scratches, the licking by animals of open wounds or contact with animal saliva when the mucous membranes are intact is very rare.[1] Post-exposure prophylaxis (PEP) involves treatment of the acute wound, administration of immunoglobulin and a course of rabies vaccination and approaches 100% effectiveness when conducted with complete compliance.[2]

Rabies within the Indo-Pacific region

The Australian Defence Force (ADF) is required to contribute to contingency and security operations in the Indo-Pacific region, with a priority for o Southeast Asia.[3] Rabies remains endemic in most of Asia and human deaths from rabies are estimated to be greater than 30,000 annually.[2] Within Asia the only countries considered to be rabies-free are Hong Kong, Japan, Singapore, Taiwan, the Maldives, the Malaysian state of Sabah and a number of India's southern islands. In contrast, most countries in the Pacific Oceania region are considered to be rabies-free and include Australia, New Zealand, Papua New Guinea and the US state of Hawaii.[4] The status can change however, as demonstrated in 2008 when

Figure 1. WHO map – Distribution of Risk levels for humans contacting rabies, worldwide, 2011



the previously 'rabies-free' Indonesian island of Bali reported rabies in local dogs and subsequently in humans.[5] Figure 1 illustrates the World Health Organisation (WHO) 2011 world map detailing the risk levels for human contact with rabies, and highlights the large areas within the region that are at medium and high risk of rabies[6].

Whilst the potential rabies reservoir within the region includes a wide range of mammals, dog, monkey and cat bites or scratches were responsible for over 90% of potential rabies exposure in Australian travellers, with approximately 30% resulting from an unprovoked contact.[7,8]

During contingency or security operations, measures must be taken to monitor and control rabies in endemic areas or to prevent its importation. Lack of such control is likely to compromise the safety of deployed personnel.

The Australian Afghan Experience

The ADF health support plans for deployment to Afghanistan recognised the threat of rabies and pre-deployment health briefs included advice to minimise contact with local animals, but did not emphasise the requirement to report and seek

Box 1. Case report of Death of US soldier from Rabies

Death of US Soldier from Rabies

"On August 19, 2011, a male U.S. Army soldier with progressive right arm pain, nausea, vomiting, ataxia, anxiety, and dysphagia was admitted to an emergency department (ED) in New York for suspected rabies. Rabies virus antigens were detected in a nuchal skin biopsy, rabies viral antibodies in serum and cerebrospinal fluid (CSF), and rabies viral RNA in saliva and CSF specimens by state and CDC rabies laboratories. An Afghanistan canine rabies virus variant was identified. The patient underwent an experimental treatment protocol but died on August 31. The patient described a dog bite while in Afghanistan. However, he had not received effective rabies postexposure prophylaxis (PEP)."

Extract from MMWR Morb Mortal Wkly Rep 2012 May 4; 61(17):302-5

Figure 2. ISAF Medical Alert on Prevention of rabies

immediate treatment for animal bites or scratches. Currently, preventive medicine personnel, military dog handlers and personnel trained in feral animal capture and euthanasia are required to have rabies vaccination prior to deployment, although prior to 2011 there were no predeployment rabies vaccination requirements. All Australian military working dogs are routinely vaccinated against rabies and have their immunity confirmed by a Rabies Neutralising Antibody Titre Test (RNATT) prior to deployment.[9]

The death of a US Army soldier in 2011[10] (see box 1) from rabies, following a dog bite whilst deployed in Afghanistan, resulted in the International Security Assistance Force (ISAF) in Afghanistan initiating a formal program of rabies awareness training, tracking, treatment and reporting requirements in September 2011. The ISAF Medical Alert notice, see Figure 2, was issued as part of the program highlighting the need to avoid animal contact and to report any bite or scratch immediately. The Australian post-deployment health screen includes a specific question on whether the member had suffered an animal bite or scratch during the deployment. A number of exposures were identified from positive responses to this question.

Materials and Methods

The Australian Role 1 Tarin Kowt Master Rabies Vaccination register as at 22 January 2012 was used to identify ADF members who had reported a potential rabies exposure in the previous 6 months. The register was an excel spreadsheet compiled in December 2011 and based on monthly animal bite reports between August and November 2011. The 'NATO-ISAF Report of Animal Attack – Potential Rabies Exposure' is required to be completed for rabies exposures in non-US personnel deployed to Afghanistan as part of ISAF. These reports were reviewed to establish the date of exposure, the animal species involved, the category of exposure and the date and type of treatment administered. PMKeyS, Defence's human resource management system, was utilised to access demographic and employment data.

Results

There were 23 reported exposures documented, involving 21 Australian Army members. The remaining 2 exposures were civilian contractors and were excluded from further analysis as ongoing treatment was transferred to another health facility. One exposure was reported after the offending animal had been observed for 10 days and PEP was no longer indicated. In all other cases the full PEP was completed as the offending animal was not observed for the minimum 10 days or tested for the presence of the rabies virus.

A cat bite or scratch was responsible for 18 (85%) exposures, a dog bite for 2 (1%) and not specified in 1 case.12 (57%) exposures were classified as grade III, 8 (32%) graded as II and not specified in 1 case. The reports do not differentiate between provoked and unprovoked exposures. All but 2 cases occurred in a forward operating base within the Uruzgan Province with the remaining 2 cases occurring on the main operating base in Tarin Kowt. Table 1 summarises the nature and treatment of the identified ADF exposures.

There was a significant delay between exposure and the seeking of medical advice, with an average of 51 days and a median of 31 days; Only four cases were treated within 1 week of exposure, all being managed within 24 hours. PEP was administered in accordance with NHMRC guidelines, although three of the four cases received the shorter four dose vaccination course as recommended by the US Center for Disease Control (CDC).

Table 1. Nature and treatment of ADF possible rabies exposure August 2011 - January 2012

		Rank			
		Other ranks	Non-commissioned officers	Officers	Total
Sex	Male	11	7	1	19
	Female	0	2	0	2
Category of bite or scratch	I	0	0	0	0
	II	5	2	1	8
	III	6	6	0	12
	Not specified	0	1	0	1
Time between exposure and presentation (days)	<7 days	1	3	0	4
	7-28 days	0	4	0	4
	28+ days	6	6	1	13
Source of bite or scratch	Cat	9	8	1	18
	Dog	1	1	0	2
	Not specified	1	0	0	1
Employment	Combat	7	4	1	12
	Combat Support	1	0	0	1
	Combat Service Support	3	5	0	8

Discussion

Despite the pre-deployment and health briefs given at the destination, Australian soldiers of all ranks continued to suffer bites and scratches from local animals. As the vast majority were related to a cat bite or scratch occurring inside a patrol base, most of these exposures could have been avoided had the advice in the health briefs been heeded. More importantly, the delay between exposure and presentation may have had fatal consequences had the injuries resulted in viral transmission. There were medical technicians on all the patrol bases where exposures occurred and there were no cases in which treatment was delayed because of lack of access to medical assistance or PEP.

There were two cases, both preventive medicine technicians (now recognised as a high risk occupation), whose PEP would have been significantly simplified by pre-exposure vaccination. A change in ADF policy to include rabies pre-exposure vaccination for preventive medicine personnel, military dog handlers and personnel trained in feral animal capture and euthanasia who are on short notice to deploy, would be relatively inexpensive and consistent with NHMRC recommendations for personnel working with terrestrial animals in rabies-enzootic areas.[1]

The knowledge and understanding of rabies by health staff was generally rudimentary prior to being required to manage a clinical exposure. The deployed medical officers readily identified the requirement to consider PEP and they provided the appropriate PEP despite utilising protocols from a variety of different sources.

Working in a multinational environment can result in variations of the treatment protocols utilised. There were subtle differences between ADF, NHMRC, WHO and CDC policies and guidance at the time. Whilst the ADF policy refers to the NHMRC guidelines, it does not draw the distinction between category II and III exposures, recommending administration of human rabies immunoglobulin (HRIG) for all exposures in non-immune individuals. The ADF, NHMRC and WHO guidelines current at the time recommended a five dose vaccination course PEP, whereas the CDC had adopted a four dose schedule (which was subsequently adopted by the other agencies). The US military directed their staff to resume the five dose schedule on the basis that antimalarials may compromise the immune system.[11] All the major authorities recommended a fifth dose for immunocompromised individuals. The US military directed their staff to resume the five

dose schedule on the basis that antimalarials may compromise the immune system.[11] Antimalarials are not normally associated immunocompromise at chemoprophylactic dosages. There is evidence that chloroquine specifically interacts with rabies vaccine to decrease its immunogenicity. This has been extended by some sources apply also to mefloquine, despite the available evidence failing to demonstrate any such interraction.[12] In any case, the recommendation emphasised that the intramuscular route should be used rather than the intradermal route.[4] Antimalarial use should not impact on PEP.

Conclusion

It is likely that rabies exposure will be a feature of future ADF deployments and whilst pre-deployment health briefs should highlight the risk, ADF health staff needto be familiar with PEP and to promote early reporting of animal bites or scratches. ADF policy should be revised to be consistent with NHMRC guidance, pre-exposure vaccination of high risk personnel on short notice to deploy should become standard practice and efforts to specifically address interactions (or lack there of) with antimalarial medications should be made.

Disclaimer

The views expressed in this paper are those of the author and do not necessarily reflect the official policy of the Australian Defence Force.

Ethics Statement

The information presented in this paper was collected and analysed as part of routine deployed public health surveillance and, in accordance with the Australian Defence Health Manual Volume 23, does not constitute human research and therefore does not require approval by the Australian Defence Human Research Ethics Committee (ADHREC).

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DVA Symposiums

Resilience symposium - development of self-management and resilience training resources for ADF members and veterans

Kym Connolly & Nicole Sadler

Many younger serving and ex-serving Australian Defence Force (ADF) personnel are more likely to use online resources to seek information on mental health support than through traditional print media. For this reason, the Department of Veterans' Affairs (DVA) and Defence are working in partnership to develop a range of client and provider-driven initiatives aimed at improving awareness and understanding of mental health and the available support services. This includes the development of websites and smart phone applications (apps).

This presentation will outline the development of a suite of online products based on the ADF Self-Management and Resilience Training (SMART) program.

The 2013-14 Veterans' Affairs Budget package Veteran Mental Health Services – Expansion included the development of a resilience website that builds on the SMART skills learned in the ADF. The SMART website, currently under development, will feature tools and information that build resilience, improve mental health literacy and reduce stigma related to seeking help for mental health conditions. The website will target those with wellbeing concerns or seeking to renew the SMART skills learnt in the ADF. The website will be complemented by a self-help mobile app using interactive Cognitive Behavioural Therapy (CBT) tools which are currently used in the ADF SMART program.

DVA and Defence have worked closely to develop the online SMART resources to ensure they are consistent with the SMART objectives, as well as being relevant to serving and ex-serving personnel and their families. Clinical practitioners have been involved in the development of the online products to make sure they are evidence-informed and can be used in conjunction with a treatment regime.

The Transition and Wellbeing Programme – AMMA Symposium

Symposium Introduction:

The Transition and Wellbeing Research Program, comprising a suite of three studies, will examine the impact of military service on the mental, physical and social health of serving and ex-serving personnel and their families in order to ensure policy and service delivery is responsive to future needs. The three studies included in this program are: The Health and Wellbeing Study, The Impact of Combat Study, and the Family and Wellbeing Study. Together, the results from this program of research will provide the Department of Veteran's Affairs (DVA) and the Department of Defence (Defence) with robust information about the re-adjustment process faced by contemporary veterans and their families who are in the process of transitioning from the Australian Defence Force (ADF), or have already left. The following symposium will describe the key aims and objectives and proposed methodology of each of these three studies.

Presentation 1:

The Health and Wellbeing Study: Investigating the mental, physical, and social health of serving and ex-serving Australian Defence Force (ADF) personnel

Miranda Van Hooff[1], Alexander McFarlane[1], Stephanie Hodson[2], Nicole Sadler[3], Helen Benassi[3], David Forbes[4], Richard Bryant[5], Malcolm Sim[6], Helen Kelsall[6], Jeffrey Rosenfeld[6], Jane Burns[7].

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The Health and Wellbeing Study will target over 30,000 serving and ex-serving ADF personnel to determine their mental, physical and social health. It will provide a comprehensive picture of the mental health and wellbeing status of contemporary veterans as well as particular subgroups within the ADF (i.e. ab initio reservists, a representative sample of 2014 regular ADF personnel). This study is the first of its kind to use a two-phase design in order to provide prevalence estimates of lifetime, 12 month and 30 day ICD-10 mental disorder in ADF personnel who have recently transitioned from fulltime regular ADF service. Additionally it will examine the trajectory of disorder and pathways to care for individuals previously diagnosed with a mental health disorder as well as investigate veteran use of technology and its utility for health and mental health programmes, including implications for future health service delivery.

Presentation 2:

The Impact of Combat Study: Investigating the longitudinal trajectory of mental, physical, biological and neurocognitive profile in ADF personnel deployed to a combat zone

Alexander McFarlane[1], Miranda Van Hooff[1], Ellie Lawrence-wood[1], Stephanie Hodson[2], Nicole Sadler[3], Helen Benassi[3], David Forbes[4], Richard Bryant[5], Malcolm Sim[6], Helen Kelsall[6], Jeffrey Rosenfeld[6], Jane Burns[7].

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The Impact of Combat Study will follow up all individuals who participated in the Middle East Area of Operations (MEAO) Prospective Health Study (including current and ex-serving ADF members), with the aim of examining the longitudinal trajectory and risk and protective factors for mental, physical, and social health and wellbeing. In addition to assessing mental health, pathways to care, psychosocial factors and physical health status, this study will also examine the neurocognitive and biological profiles of a subgroup identified as being engaged in high-risk roles and who were likely to have been exposed to deployment-related trauma or blast injury. This longitudinal study is the third follow-up of 1871 personnel who were deployed to the MEAO between 2010 and 2012 and who were previously assessed pre and post deployment. This presentation will describe the aims and methodology of the study as well as review the current status of the neurobiological literature in relation to military service.

Presentation 3:

The Transition and Wellbeing Family Study: Investigating the social, physical, and emotional health of family members of men and women who have recently transitioned out of the Australian Defence Forces (ADF)

Benjamin Edwards[1], Walter Forrest[1], Jacqui Harvey[1]

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Although there has been a great deal of research investigating the welfare of veterans in Australia, much less is known about the social, physical, and emotional health of their families. There is growing evidence, however, that military service can have both long-term effects on the partners and children of service personnel after leaving the military. In turn, the social and emotional health of family members can have important implications for the health and welfare of veterans. The Transition and Wellbeing Family Study (TWFS) is a new research project that aims to address this gap by investigating the wellbeing of family members of men and women who have recently transitioned out of the Australian Defence Forces (ADF). Part of the Transition and Wellbeing Research Program (TWFP), the project is being funded by the Department of Veterans' Affairs and is being managed by the Australian Institute of Family Studies. It is based on an online survey of approximately 30,000 family members of ex-ADF personnel who will be surveyed as part of the Transition and Wellbeing Program. In this presentation, we describe the aims and objectives of the TWFP, briefly review the results of Australian and international research on the social, physical, and emotional health of military and veteran families, and discuss key aspects of the survey methodology, including its online administration, key concepts and measures, potential sources of data linkage, and possible ways of limiting the effects of sample selectivity.

Governance

How do we define 'deployable'? Establishing a standard guide for clinicians to assess when a soldier is fit for upgrade.

Isaac Seidl

The ADF moved to a tri-service system for Medical Employment Classification in the early 2000s. At that time, the single standard for assessing fitness was based on 'deployability'. Yet, there has continued to be discussion about how to define this.

Army has moved over recent years to establish physical employment standards, in consultation with the Defence Scientific and Technology Organisation, which are based on tests that soldiers are expected to undertake in their deployed roles, known as the Physical Employment Standards Assessment (PESA). These are used to determine readiness for deployment for many Army roles. However, it is hypothesised that they are not appropriate to be used at the point of upgrade, that is, as a measure of effectiveness for rehabilitation.

Likewise, the Basic Fitness Assessment (BFA), holds little basis in scientific evidence for predictability of deployability.

This presentation will outline an ongoing discussion, brought out in 2014, in which establishment of clinical guidelines for practitioners and confirming authorities, has become necessary, and propose appropriate tests that could be used, where appropriate. This would necessitate setting out, preferably in advance at the point of downgrade, the test that would be undertaken at the conclusion of rehabilitation, and offer a single Army Rehabilitation Fitness Assessment (ARFA) as one option.

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Components of an effective deployed clinical governance system for the ADF

LTCOL Michael C. Reade[1,2] LTCOL Nicholas Duff [3]
COL Bradley McCall [3]

Clinical governance is "the measurement and benchmarking of clinical performance through implementation of predefined standards and established mechanisms that identify, address and continuously review problems or problematic trends that arise".[1] Clinical governance comprises mechanisms to ensure and improve healthcare quality (for example, that the best treatments are prescribed) and safety (for example, that treatments prescribed are given as directed), along with oversight of individuals, teams, systems and equipment; research; education; open disclosure; legislative compliance; congruence with strategic intent; and audit of results. Such features can be categorised as inputs, processes, and outcomes. The Australian Government Commission on Safety and Quality in Healthcare requires a system of clinical governance as the first of ten National Standards.[2] Applying these standards to deployable ADF hospitals is problematic – not least because infrequent deployments mean meeting many standards in theory not practice. Further problems are imposed by austerity (invalidating most civilian benchmarks), frequent postings, and a peacetime exercise caseload that bears little resemblance to the high complexity trauma that ADF Role 2E hospitals are designed to treat.

While accepting many standards are not applicable, deployed ADF hospitals are nonetheless obliged to implement the best possible clinical governance framework. Under a CO's directive, the 2nd General Health Battalion (2GHB), Army's only Role 2E hospital, has embraced this challenge. With respect to inputs, all ADF clinicians are familiar with annual documentary credentialing, but fewer may know of Army Health Instruction 5 (Clinical Readiness Standards) which mandates military and clinical skills currency. However, even this does not guarantee competency to work in the deployed environment as well as, for example, the US Center for Sustainment of Trauma and Readiness Skills (C-STARS) programme. ADF clinical courses such as the combined DSTC/MILAN, major exercises, and civilian strategic alliances are increasingly filling this need. Clinicians are assessed by the 2GHB credentialing committee to fill specific roles. Features common in civilian healthcare, such as infection control, training, and patient safety officers, have been appointed. Deployed hospital processes are guided by doctrine and clinical practice guidelines, the expansion and revision of which are now high priorities recently resulting in, for example, HEALTHMAN 07 (Military Anaesthesia) and HEALTHMAN 16 (Transfusion). Hospital processes (albeit in simulation) have been audited against an ADF modification of the UK military trauma Key Performance Indicators. The role of a Clinical Director has been confirmed in doctrine, with responsibility for audit and continuous improvement as well as individual patient care. A morbidity and mortality committee operates in the field, ensuring contemporaneous peer review. Quantitative assessment of outcomes remains impossible without a sufficient number of patients, making conventional indices (such as standardised mortality ratio) inapplicable. Nonetheless, the systems to collect such data are under consideration – for example a deployed trauma registry patterned on UK and US models. The best quantitative measure of a deployed governance framework might be the number of changes to inputs and processes that have been achieved. By this metric, the 2nd General Health Battalion compares very favourably to the best civilian trauma centres.

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History

Captain B.g.pockley Aamc – A Hero Before Gallipoli

Michael Dowsett

Last month at Rabaul a service was held to commemorate the centenary of the Battle of Bita Paka at the graveside of Able Seaman Billy Williams and Captain Brian Pockley, the first Australians to die in World War I.

Captain Pockley enlisted as a medical officer in the AAMC as part of the Australian Naval and Military Expeditionary Force. His actions during the battle that led to his death were described as those of "conspicuous gallantry in action and as a matter of fact he forfeited his life for those under his command."

Most Australians are unaware of this important campaign in Australia's history as the events of that period have been overshadowed by Gallipoli, the Western Front and Palestine. The New Guinea campaign of 1914 saw a number of significant "firsts" for Australia including the first overseas military expedition planned and coordinated by the new nation, the first land operation of the war, the first joint operation by the Navy and the Army, the loss of the RAN submarine AE1 and the first act of bravery by Australians in that war.

Leadership

Effective Leadership on Operations: Perspectives from Commanding Officers of NZDF deployments

Lieutenant Christopher Liddell (Trainee Psychologist, New Zealand Defence Force)

Over the last fifteen years the New Zealand Defence Force (NZDF) has deployed personnel in a number of different operational settings including significant contribution to the Middle East, Solomon Islands and Timor Leste. As research across Allied Nations militaries suggest, the leadership behaviours of command teams on operations can significantly impact deployment satisfaction and mental health outcomes for soldiers that deploy under their command. Leveraging off this research body, NZDF investigated leadership behaviours from the perspectives and experiences of its Commanding Officers who had deployed over the past 15 years. The roles of the Commanding Officer (CO) and Senior National Officer (SNO) contain unique challenges and can be socially and professionally isolated. And whilst NZDF has a reasonable amount of organisational knowledge and lessons learnt captured from our senior officers on operations, recent information regarding effective and ineffective operational command is not always readily available to new senior leaders on operations.

This presentation highlights research conducted which sought to gather learnings from NZDFs recent operational involvement by interviewing senior leaders of operations in CO or SNO positions. Twenty senior leaders were interviewed and provided information about the unique challenges senior operational leaders face, as well as their perceptions of what created effective and ineffective senior command behaviours. The findings of this study will be presented, which identified key themes of subordinate well-being, effective interpersonal style, performance management, motivations of leaders and command isolation. There will also be discussion on the utility of the research within NZDF and its use for development of a COs aid memoir for senior leadership on operations.

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The Secrets of Very High Performance Medical Teams

WGCDR David Cooksley[1] (Emergency and Retrieval Physician)

Medical teams that care for seriously ill or injured patients should, almost by definition, be high performance in nature. However there are some, such as the London Helicopter Emergency Medical Service (HEMS) and its military equivalent, the RAF Medical Emergency Response Team (MERT), that stand apart and are widely regarded as very high performance teams. They are selected and trained to function expertly and consistently in hostile, unpredictable and high consequence environments where there is little margin for error. This presentation will examine some of their 'secrets' with regard to selection, training, clinical application and clinical governance that enable these teams to perform so well.

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Innovating change by encouraging rebels in the Defence health workforce

Isaac Seidl

What sets a rebel apart from a troublemaker is the ability to be creative, mission-focussed, passionate, optimistic, energy-generating, see possibilities, attract followers and work together.[1] These are individuals who not only influence change, but drive it, for the better, by 'rocking the boat but staying in it'.[2] At a time when the Defence healthcare budget is stretched, under pressure from increasing governance and crippling clinical workload arising from 15 years of continuous operations, we need 'rebels' at all levels to constantly ask, 'how can we do better?'

This presentation will examine how even John Kotter has changed his view on change management. It will challenge attendees to move from the comfortable centre, to the edge.[2] It will define the difference between rebels and troublemakers, in order to empower those who can, and often do, speak out, to do so in ways that lead innovation, rather than compromise the organisation by throwing stones from the sidelines. We need to embrace change, examining processes that we hold dear and critically evaluating whether they add value, or if, on the other hand, they stifle excellence in health care.

At the end of the presentation, attendees should be able to reflect on their practice, as clinicians, managers, or indeed as consumers of Defence health care, in order to understand better, ways that their engagement will improve outcomes.

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The Good Workplace: how management and culture contribute to health and productivity

GPCAPT James Ross

Much has been written about the need to promote the value of early return to work after injury or illness. There are very important individual, family, enterprise and societal benefits from focussing on vocational rehabilitation. The value of being part of the workforce also relates to people with permanent disabilities, who may have been out of the workforce for extended periods. However, there it is vital that people are not placed into an environment which is detrimental to their physical and mental health. The work must be 'good'. Just what is it the distinguishes 'good work' and allows work participation to realise its benefits? Much of it lies around workplace culture, management systems and the competence of supervisors and managers. There is a fear that individuals could be required to work in circumstances that are detrimental and such an outcome needs to be avoided.

The Australasian Faculty of Occupational and Environmental Medicine has, for the last 4 years, been at the forefront of advocacy for the need for ways to ensure the potential of work to be a positive is realised. AFOEM has released a series of position statements, initially 'The Health benefits of Work' which states that 'Good Work is generally good for you', and in 2013 two sister documents – 'Health and Productivity' and 'What is good Work'. These documents speak to what is needed for a job to be 'good', and also how workplaces can readily improve productivity through insightful, sensible approaches which engage workers and negates potentially negative outcomes.

This presentation will discuss some of the approaches taken by AFOEM in engaging with Government, Regulators, Insurers, Industry, Unions and patient advocate groups, where the campaign is up to and what still needs to be done to truly see a return on this program. It will also consider how such concepts are translatable into the Military environment.

References:

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Valuing religious beliefs through the health care experience.

FLTLT Jenny Sutton

The religious beliefs of patients has the ability to greatly affect the delivery, success and ethical acceptability of health care interventions. Australia has seen increasing multiculturalism in recent decades leading to a greater diversity in the religious backgrounds within the Australian population, reflected within the military population, and diverse spiritual beliefs amongst patients receiving humanitarian aid, both within Australia and overseas. As health care professionals, the provision of holistic, effective and appropriate interventions, includes the use of religiously sensitive knowledge,

provided through a greater understanding of the role of religion in our patient's experiences, the benefits of spirituality and an overview of how religious beliefs impact what and how health care is provided.

The discussion will aim to explore some of the factors and beliefs within various religions that may lead to contradictions in the prevailing medical model compared to the spiritual needs of the patient, whilst exploring some of the barriers preventing religiously sensitive care. The importance of religious values and beliefs for the patient is examined to explore the holistic nature of spiritual care within the health care setting, particularly in times of trauma, humanitarian crisis or disaster.

Some of the various religions are reviewed to demonstrate the contradictions to care, which affect the expectations, wishes and experiences of our patients, within the great variety of customs associated with differing religions and even various traditions within the same belief. Consideration of how spiritual beliefs can contrast with prevailing medical models can provide cues to the ethical and moral considerations within the provision of health care. Factors affecting the way spiritually sensitive holistic care is conducted, may be discussed to provide a greater understanding of how patient care can be improved leading towards better patient outcomes and reduced morbidity.

Religious devotion can be at the core of our patients understanding of both their own health status, the ways they wish health care to be provided as they embark as an equal partner within the health setting and also the positive outcomes achieved through the empathetic and cognisant, spiritually sensitive care of our patients. In order to provide patient centred, holistic care, the health care professional is aware of the role of spiritual care and how their part in providing religiously sensitive health care enables the best patient outcomes and better experiences for our patients within the health care setting.

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Lessons

Are the Current Priorities for the Control of Plague Misplaced?

Louise Gertner

Plague is a highly virulent infection caused by the bacillus Yersinia pestis, from the family Enterobacteriacea. Plague has been responsible for the deaths of millions throughout history, and its very name is synonymous with pestilence and suffering.

After being largely absent for much of the 20th century, plague has re-emerged, and is now considered endemic in a number of countries throughout Asia, Africa and the Americas. Along side the reoccurrence of wild plague, another threat also emerged in the early 21st century, that of bioterrorism.

Plague is primarily a zoonotic disease of rodents, with human infection only occurring incidentally, however when human cases do occur, the outcomes are often extremely poor for those infected. Plague is one of the most virulent diseases known to man, with a complex pathogenicity derived from a combination of toxins, proteins, and plasmid-based antigens. Without treatment, the mortality rate for bubonic plague is approximately 50%. Untreated septicaemic and pneumonic plague cases are almost always fatal, and even with early treatment mortality is between 10-20%.

Because of its extreme pathogenicity, coupled with the fact that it is readily available in nature, simple to culture, and can be aerosolised, Y. pestis is considered a potential agent for bioterrorism. This fear of a man-made plague outbreak has had a significant impact on research and control of plague in the modern age, however not all of it has been positive.

This presentation will provide an overview of the geographic distribution, clinical features, mode of transmission, and treatment of human plague, along with an examination of the environmental, socio-economic and cultural factors underlying its spread.

The presentation then considers whether plague's reputation as a destroyer of cities is warranted in the modern age, and explores how strategies for the control of plague and research into the disease has been shaped by the construct of plague as a terrorist threat, at the expense of other equally valid drivers of research, such as climate change, to the detriment of those most at risk.

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Management

ADF Clinical Handover Improvement Project (CHIP)

Dr Darrell Duncan & Ms Madeline Makeham

In 2012 it was identified through the Garrison Health Clinical Governance Working Group, (GHCGWG) the need to adopt and implement an organisational system for structured clinical handover relevant to the ADF Healthcare setting. This was identified in response to a recognised trend of adverse healthcare incidents related to issues with effective clinical handover.

The primary aim of the project was to ensure there is timely, relevant and structured clinical handover that supports safe patient care in Defence healthcare environments.

The scope of this project applies to all health care services provided to Defence members in any Defence healthcare environment.

A dedicated sub working group of the (GHCGWG) was formed. The inaugural ADF CHIP WG meeting was held in November 2012. Membership of the WG includes representation from Joint Health Command, Joint Operations Command, single Services and Regional Health Services to facilitate an integrated approach to quality and safety in clinical handover care across the ADF.

The ADF CHIP WG is accountable to the Vice Chief of the Defence Force via the Surgeon General of the Australian Defence Force. Terms of Reference and a project plan has been developed and was endorsed by SGADF in July 2013.

The primary standard referenced to develop the systems and strategies for effective Clinical Handover in ADF healthcare environments was Standard 6-Clinical Handover of the Australian Commission on Safety and Quality in Health Care.

Outcomes of the project include:

- Identification of the key points of clinical handover in the Defence health environment occurred. The ISOBAR framework was assessed for applicability against the tool.
- Agreement by all members of the Working Group to use the ISOBAR framework as the standard when undertaking Clinical Handover in Defence. This tool is already used in the single Service environments when using the Primary Care Clinical Manual (PCCM) and is taught to Medics as part of their basic training.
- A baseline audit of current clinical handover practices was completed in garrison health facilities
- A JHC Health Instruction and ISOBAR intra facility and inter facility templates developed for use in clinical handover. These tools were trialled and used by pilot sites in the garrison health environment.
- Outcomes from the JHC facilities who participated in the pilot phase of the project will be presented.

Next Steps to finalise the project will be:

- Evaluation of the pilot phase of the project.
- Implementation of the ISOBAR handover tools for use in all JHC health facilities.
- Development of broader ADF guidance to ensure consistency in the single Service and Operational environments using ISOBAR as the accepted clinical handover framework in Defence healthcare environments.

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Standard 6 Clinical Handover, NSQHS Standards; Primary Clinical Care Manual, QLD Health

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ADF Post-discharge GP health assessment

Department of Veterans' Affairs /Discipline of General Practice, Flinders University Adelaide

This presentation will focus on a new Australian Defence Force post-discharge health assessment, to be conducted by GPs and funded under Medicare. A new assessment tool has been developed by Flinders University to help support this assessment, and the presentation will work through this new tool.

Tackling mental health challenges facing veterans and their families is a pillar of the Government's plan for veterans' affairs. The 2013-14 Veterans' Affairs Budget package Veteran Mental Health Services – Expansion included the introduction of the GP health assessment for former serving members of the ADF.

In an effort to promote the importance of identifying health issues early, this health assessment has been specially designed to help for former serving members and GPs identify and act on any physical and/or mental health issues before they become major problems. The assessment is available to all former ADF members, including former serving members of permanent and reserve forces, and supports them in using primary health care after leaving Defence.

DVA has worked with Flinders University, Discipline of General Practice to design the ADF Post-discharge GP Health Assessment Tool. The tool assists GPs to assess their patient's current physical and psychological health, and includes specific screening tools for alcohol and substance use disorder, posttraumatic stress disorder and psychological distress.

This presentation will outline the development and implementation of the assessment and the specially designed assessment tool, including the consultation undertaken with medical practitioners and the Department of Defence.

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Operational Health

Will an injury prevention program delivered during pre-week of Australian Defence Force (ADF) Infantry training lead to a decrease in preventable injuries amongst trainees: a randomized controlled trial.

Carney Garland, Rebecca Sellwood, Dr Darrell Duncan

This presentation outlines some research undertaken at the School Of Infantry in 2012/13. We were interested to know if an injury prevention program delivered during the pre-week of Infantry Initial Employment Training led to a decrease in preventable injuries through the 13 week program. We conducted a randomised controlled trial of 13 platoons with 403 male Infantry Trainees randomly assigned to one of two groups: the clinical education intervention group (n=251, 8 platoons), or the control group with no education (n=152, 3 platoons). There were no significant differences between the groups in terms

of baseline characteristics. The intervention consisted of an injury screening questionnaire, a theory and practical injury prevention education session as well as selected individual assessments. The education covered contributing factors to injuries, knowing the difference between an injury and a minor sprain or strain, biomechanics, basic stretching, core stability and its role in maintaining fitness and postural awareness. Based on the responses to the self reporting questionnaire within the intervention group we were able to identify trainees who may benefit from a one off individual assessment with the Physiotherapist to assist them with self management strategies for any musculoskeletal issues they may be experiencing. The primary outcome measure was the number of preventable injuries. Secondary measures included the number of trainees sustaining preventable injuries that were subsequently removed from training for rehabilitation, and the eventual disposition of injured trainees (completed infantry training, Corps transfer or discharge). All trainees were offered the normal routine of medical and physiotherapy assistance through the course of their training regardless of the platoon they had been assigned to.

Although the intervention showed no significant decrease in preventable injuries we did identify two strongly predictive risk factors for injury during training. These were: reported pain with pack marching and having an injury at Kapooka, (rather than history of an earlier injury). Basic Fitness Assessment failure was close to a statistically significant predictor (p=0.08). Those trainees with these risk factors had a significantly higher chance of being sent to the trainee rehabilitation wing in Sydney for extended rehabilitation. The Injury Prevention Program did not statistically make any change to the number of preventable injuries presented during the infantry training, but the predictive risk factors were able to provide the staff with early identification of those trainees who may be at a higher risk of sustaining an injury during training.

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Forward Combat Critical Care – Time for a New Paradigm?

WGCDR David Cooksley[1] (Emergency and Retrieval Physician)

The recent military conflicts in Iraq and Afghanistan have led to many changes in the care of the battle casualty. Some of those, like haemostatic resuscitation, have even been adopted into civilian practice. One unique development by the British Military is their Medical Emergency Response Team (MERT) created to provide very rapid, advanced and aggressive resuscitation and critical care far forward in the battlespace. The MERT comprises an experienced critical care doctor, emergency nurse and two intensive care paramedics. The team undertakes considerable addition training and operates within a strong clinical governance framework. They bring to the patient lifesaving capabilities normally only found within a hospital. This paper will discuss the MERT rationale, training, operational approach to dealing with critically unwell combat casualty and patient outcomes compared to conventional forward military care and evacuation. The author will give an example of how the MERT concept could be integrated into the ADF to enhance our current forward and tactical critical care capability.

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Nurse Practitioners in Air Force Health

Danny O'Neill and Matt Luther

Work is underway within the Royal Australian Air Force to add capability to the current health care model. In Australia Nurse Practitioners have been providing a specific capability to the civilian workforce, bridging many gaps in service provision with great success. With this in mind, the global responsibility to support those in need, whether arising from; political unrest and instability, environmental disaster or industrial incidents, will continue to provide the Royal Australian Air Force with ample opportunity to provide health care in austere and complex environments. Taking on-board these issues, Air Force Health is beginning to embrace the challenges ahead with a well-trained and well equipped health care workforce.

Nurse Practitioners currently only exist in the reserve element of the Royal Australian Air Force. Whilst their advanced credentials are acknowledged they are not formally appointed in current health doctrine

as Nurse Practitioners. Work is underway to review ways of applying this capability in to Air Force health practice.

The professional attributes of a Nurse Practitioner that align it to a Defence application are those that highlighted the role appropriate to fulfil the need for health care provision in rural and remote Australia, late in 1990s. Advanced practice within an autonomous, yet collaborative model, allows the Nurse Practitioner to immerse themselves in varied health care environments, complementing the existing structure, whilst bridging the historical gap between nursing and medicine. Nurse Practitioners are already a force multiplier, with significant impact, in many international military models and offer an attractive adjunct for Air Force Health. The robust nature of Nurse Practitioner accreditation ensures that the Medical Officers (MOs) collaboratively working with a Nurse Practitioner, can rely on a competent, qualified and professional health care provider.

During a recent review of the Nurse Practitioner service, correlating the skill set of a civilian Nurse Practitioner to those required by Air Force in a military health facility, a best fit relationship can be found in the civilian Emergency Nurse Practitioner (ENP) role. An ENP brings specific skills and experience in the acute care setting, mapping across to the identified health professional requirements of a Role One or Two facility including; triage, acute injury and trauma management, acute illness assessment, health promotion, resuscitation and primary health care. This professional profile provides maximum capability for operational service within a single health care provider.

The subsequent assumption of Nurse Practitioners being recognised as a significant health resource within Air Force health would lead to their effective and efficient use during peacetime and combat/war like operations. Reviewing and implementing other Nurse Practitioner skill sets such as primary health care, mental health and flight nursing will all benefit the future further capability in meeting service requires.

Utilising Nurse Practitioners in the nursing career structure could improve morale, retention and have benefits for Air Force and the greater Defence health community.

This presentation will discuss the benefits, what has been done so far by RAAFSR Nurse Practitioners and the future of Nurse Practitioners in the Air force.

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Noise-Induced Hearing Loss in the Military Environment – a review of upcoming preventative pharmacological agents

FLTLT Patrick O'Neill

Personnel serving in the ADF will be exposed to high intensity noise from any number of sources including small arms fire, artillery, explosions, aircraft or engine noise. Without suitable hearing protection some of these personnel will go on to develop noise induced hearing loss (NIHL).

Good hearing is essential for safety in the military environment. Damage to hearing can lead directly to personnel becoming unsuitable for current employment resulting in personal and financial consequences. The impact upon the ADF includes the loss of skilled and experienced personnel, the financial costs associated with the retraining and replacement of personnel as well as any associated compensation. To illustrate the magnitude of this problem, for veterans of recent conflicts (East Timor, Solomon Islands, Afghanistan and Iraq) the third largest disease claim made to Veterans Affairs is directly associated with noise induced hearing damage with sensorineural hearing loss representing 1,368 compensated cases. Furthermore amongst Vietnam veterans sensorineural hearing loss represents the largest claimed disability with 21,105 cases.[1]

Until the mid-1990s it was believed that NIHL occurred primarily as a consequence of mechanical trauma. Based on this paradigm the only existing strategies for reducing NIHL were use of mechanical devices.[2] However there are limitations inherent in the sole use of mechanical interventions which restricts their effectiveness in many circumstances. Additionally it is now thought that NIHL occurs largely as a result of metabolic not mechanical damage.[3] This metabolic damage acts through various biochemical pathways, the foremost being

oxidative stress but with contributions from excess glutamate concentrations and cochlea hypo-perfusion. By targeting these pathways with suitable pharmacological agents there is potential to protect the ear against NIHL.[4] Animal testing has identified a number of likely agents including MET, NAC, ebselen, glutamate antagonists, magnesium and salicylic acid. Human clinical trials are already underway on some of these agents. The results of these studies "have the potential to drive changes in evidence-based clinical practice."[5] It is probable that within the next decade[6] NIHL will be mitigated not only with mechanical means but also treated with a host of pharmacological agents. In order to maximize the safety of ADF personnel it is imperative that the ADF be aware of these upcoming agents, their suitability to the military environment and the need to develop policy governing their use.

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Alphabet Soup: WHS, AME, SRCA, MRCA and the 10-1-2-Metric – Providing a safe workplace for those left behind after withdrawal of operations (A Case Study in Timor-Leste)

Miss Rachelle Warner

Following the withdrawal of Australian Forces from Timor-Leste, a number of concerns regarding the safety of Defence personnel working in Timor-Leste have been raised. With the departure of the International Stabilisation Force and the closure of the Aspen medical facility in 2013, there is now an increased risk for staff travelling outside of Dili to undertake Defence directed work, particularly in regards to medical support and evacuation.

The WHS legislation has extraterritorial application for international workers, as well as specific requirements for remote and isolated workers, which are all applicable to workers in Timor-Leste. There is both an expectation and a legislative requirement to look after our people, wherever they are in the world.

This Case Study follows the comprehensive risk assessment, development and implementation of an action plan to provide Defence personnel in Timor-Leste with an equivalent service of medical support and access to medical evacuation to that they would expect in Australia.

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Psychology I

NZ Peacekeepers in South Sudan: A Case Study of Trauma Exposure and Impact on Mental Health

Major Alana MacDonald (Senior Psychologist Joint, New Zealand Defence Force)

New Zealand has deployed approximately 50 personnel to South Sudan since New Zealand's contribution began in 2005. New Zealand provides a small number of personnel on six-monthly rotations to cover observation and liaison officer posts which contribute to the wider United Nations (UN) peacekeeping campaign in South Sudan. New Zealand Defence Force (NZDF) personnel deployed to South Sudan experience a range of additional stressors over and above typical deployment stressors many encounter on other NZDF deployments, which include isolation, extreme environmental hardship, deprivation of food, exposure to severe illness, constant and real threat, heightened involvement in and exposure to psychological trauma, as well as severe restrictions around the ability to intervene and use force. Since NZs involvement began, a

number of personnel returning from this deployment have experienced reintegration difficulties on their return and been referred for clinical psychologist treatment. In 2013, volatility within South Sudan significantly rose, and as a response the type of psychological support provided to our personnel deployed in this area was reviewed. It was at this time that NZDF deemed our deployment to South Sudan as a 'Psychologically High Threat' mission and a more intensive psychological support programme was implemented. This presentation serves to address some of the unique psychological stressors NZDF personnel and other Nations peacekeepers face working in South Sudan and the impact this appears to have placed on our previously deployed personnel. The presentation will review the criteria used in determining this mission as a high psychological threat, as well as the provisions then provided based on this assessment, for a comprehensive psychological support programme. A brief case study will provide a review of MH screening data throughout a six month deployment to South Sudan over periods of heightened country volatility, and into their reintegration period back home in New Zealand.

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The Changing Landscape of Operational Mental Health

LTCOL Andrew Cohn; MAJ Michelle McInnes

With the reduced operational tempo, both current and forecasted, the roles and tasking of the operational mental health workforce is evolving and developing to better meet Army's requirements. In response to the reduced operational tempo, 1st Psychology Unit has developed a strategy to provide support to Army units across the spectrum of operational mental health. This support addresses the needs of units across all stages of the Force Generation Cycle, from Readying to Ready and Reset. Areas in which 1st Psychology Unit is working closely with Joint Health Command to achieve this goal includes development and expansion of the psychological resilience training (BattleSMART), unit climate measures (Profile of Unit Leadership, Satisfaction and Effectiveness – PULSE), and coordination of large scale Post Operational Psychology Screening (POPS) campaigns. This presentation addresses the ways that 1st Psychology Unit is evolving to adapt to operational changes, including support to remote personnel via telephone and Internet, and meeting the needs of individual and units in the post deployment environment. Specific challenges such as support to reservists and resource constraints will be discussed.

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The Provision of Psychological Support to HMNZS TE MANA Personnel on an 8 month Anti-Piracy Operation

New Zealand Defence Force Navy Psychological Service

The RNZN routinely deploy on operations within New Zealand's seas, which see personnel on ship and away from their families for extended periods of time. Whilst psychological support is available to ships at anytime, a structured psychological support programme is provided for deployments over four months duration. In August 2013, HMNZS TE MANA embarked on an eight month anti-piracy deployment in the Gulf of Aden and Arabian Sea, in support of the Combined Maritime Forces (CMF) multi-national naval partnership of 30 nations and NATO's anti-piracy mission Operation Ocean Shield. Due to both the length and nature of this operation, personnel of HMNZS TE MANA were provided with a tailored Psychological Support to Deployment Programme (PSDP) which is routinely provided to land and other Joint Forces missions. This presentation will outline the components of the PSDP provided over the full deployment cycle to the 176 personnel and families of HMNZS TE MANA on their anti-piracy mission. This presentation will also provide a brief summary of the psychological screening data, as well as highlighting the strains experienced by personnel and need for psychological support for our peacekeeping focused operations.

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Participation in The Technical Cooperation Program (TTCP) HUM Technical Panel 13: Psychological Health and Operational Effectiveness: Perspectives and Learnings from Australia and New Zealand

Colonel Nicole Sadler (Director Strategic and Operational Mental Health / Head of Corps Australian Army Psychology Corps) and Major Alana MacDonald (Senior Psychologist Joint, New Zealand Defence Force)

Psychological health is important in all military operations (combat, peace support, humanitarian) and is an essential contributor to safety, productivity, and efficiency both in garrison and in operating

environments. A great deal of research has been undertaken on ways to enhance psychological health within military forces in order to best prepare, maintain and return from operations. The Technical Cooperation Program (TTCP) is a collaborative military research and information exchange program amongst five member nations – the United States, United Kingdom, Australia, Canada and New Zealand - to foster cooperation amongst member nations, so as to facilitate effective research and policy development at reduced cost. TTCP Technical Panel 13: Psychological Health and Operational Effectiveness, conducts collaborative research and exchanges information and resources, that leads to the development of new strategies in the prediction, prevention, treatment, optimisation, and management of psychological health factors that impact (positively and negatively) on military activities. Involvement in TP13 has been one of the major forms of international engagement on psychological health research for both Australia and New Zealand. This presentation serves to highlight some of the significant contributions developed through the workings of TP13 and how they have influenced our respective strategies, policies and practices, including in the areas of psychological health training, psychological resilience, management of cultural stigma and barriers to care and optimisation of mental health care.

References:

- The Technical Cooperation Program (TTCP) HUM Technical Panel 13: Psychological Health and Operational Effectiveness Business Case May 2013

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Psychology II

The Long Way Home Theatre Production – The Military Nursing Perspective on Rehabilitating our Wounded Injured and Ill through the Arts

LT Dianne Hutchinson and CAPT Emma Palmer RAANC

The Australian Defence Force (ADF) joined with the Sydney Theatre Company (STC) to embark on an historic event of national significance representing servicemen and women's stories and experiences through live theatre. The Long Way Home (TLWH) an initiative of the Chief of Defence Force (CDF) saw service personnel perform live on stage alongside professional actors. This play represented their experiences on operations in Iraq, Afghanistan and East Timor and the impact that these operations have had on our members and their families. The majority of the ADF cast members were wounded, injured or ill (WII) and carried physical or psychological wounds and sometimes both.

The title was chosen long before the play was written, none the less it appropriately represents the journey our members often encounter of returning home, healing and recovery. TLWH provided an opportunity for our members to tell their personal stories of the challenges they faced and the sacrifices their families made to the author, who then wrote deeply moving interpretations of their experiences on operations. Our defence members performed their very human story to the general public many times and the raw emotion was evident on their faces at the conclusion of each show.

Having the opportunity and privilege to be involved in the ADF Theatre Project (ADF-TP) as a nurse was at times challenging but humbling and rewarding. Providing care is the effortless component of our profession however, this project came with its unique challenges because it was and continues to be, novel. The greatest clinical opportunity of this project was being involved in the development workshops allowing us time to spend many hours with our group at the theatre. This provided the opportunity to hear the soldier's stories, get to know them more on a personal basis, build trust as well as gain a greater understanding of their health care requirements. The importance of getting to know them intimately assisted us in recognising their triggers both physical and psychological and therefore supporting them appropriately.

Although there is no clinical evidence to support our observations we have witnessed many positive aspects from this project. Soldiers speaking 'through theatre' from the stage to their wives, parents and families for the first time. Soldier's who came to the project with no sense of purpose and have left with clear ideas about the future, hugely increased self confidence and determination. Soldiers with the self-assurance to confidently socialise outside of their defence circle of friends and some who have reconnected with defence. While anecdotal, these changes were so obvious that comments came from the members themselves, their colleagues and their families.

Where to from here? The anecdotal and observational evidence from this project is immeasurable and therefore it is incumbent upon us to design the next step ensuring that our methods in dealing with WII soldiers are based on sound evidence in order to provide a variety of modalities for healing from the performing arts to sports and everything in between.

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Longitudinal predictors of 'better than expected' post-deployment mental health among Australian Defence Force (ADF) personnel.

Searle A.[1], Lawrence-Wood E.[1], Van Hooff M.[1] & McFarlane A.[1]

Experiencing deployment-related trauma like direct combat and witnessing atrocities (rather than simply having deployed) is associated with subsequent mental disorder in military personnel. Furthermore, cumulative trauma is more strongly associated with disorder than any one trauma type. However, there is great variation in military personnel's response to trauma; while personnel experience high levels of trauma during deployments to the Middle East Area of Operations (MEAO), only a minority develop clinical-level mental disorder. Despite this, most research on deployed personnel focuses on predictors of disorder, and relatively few studies examine factors that are associated with 'better than expected' functioning, or 'resilience'.

We analysed data from the MEAO Prospective Study of Australian Defence Force members in order to examine the longitudinal predictors of resilience following deployment. Participating personnel reported their PTSD symptoms using the PCL at pre-deployment and post-deployment, and also completed a detailed checklist of traumatic deployment experiences. Overall, PTSD symptoms increased between pre- and post-deployment, with traumatic deployment experiences significantly associated with this increase. However, a number of personnel showed lower than predicted PTSD symptoms (thus demonstrating resilience). In accordance with ecological frameworks of resilience, we examine potential predictors from multiple spheres, including biological, social, psychological, organisational and deployment-related factors. Our findings may be used to inform pre-deployment prevention programs for deployed personnel, equipping them with the strengths and supports needed to cope with trauma, and disrupt pathways leading to disorder.

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Review of Mental Health Screening Data Following Operational Deployment within the New Zealand Defence Force

Captain Samuel Williams (Southern Regional Psychologist – New Zealand Defence Force)

Psychological mental health screening is common practice within Allied Nations militaries to identify personnel with possible adverse mental health outcomes following deployment that might not otherwise be detected or treated. In 2008 New Zealand Defence Force (NZDF) implemented a new Return to New Zealand (RTNZ) Psychological Screen which Service personnel completed upon their initial RTNZ and at 4-6 months following return from deployment. This presentation highlights the screening measures utilised at both administration points, as well as an overview of the screening data collected between 2008-2013 from deployed NZDF personnel. Key findings from this review of the NZDF deployment screening data have since been utilised to further inform the review and development of revised mental health screening tools administered following deployment, as well as informing best practice for the delivery of the NZDFs Psychological Support to Deployment Programme. Key findings from this screening review will be highlighted, as well as how the findings were utilised in further development and refinement of practices within NZDF.

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Psychology III

The Utilization of Computerized Balance Assessment to Examine the Physiologic Effects and Provide Differentiation Between Subjects with Combat-Associated mTBI and PTSD

Dr David Cifu, Dr Joanna Wares, Dr William Carne, Dr Kathy Hoke, Dr Steven West

Mild traumatic brain injury (mTBI) is common among military combatants, particularly among those Coalition Forces serving in Operations Enduring and Iraqi Freedom. Common complaints post mTBI are deficits in balance and orientation attributed to both mTBI and other medical concerns including post-traumatic stress disorder (PTSD). The objective of this study was to examine the relationship of mTBI with balance deficits and to assess variations in balance between four groups of combat exposed populations: (1) subjects with no history of either mTBI or PTSD, (2) subjects with a history of mTBI, (3) subjects with a PTSD diagnosis, and (4) subjects with both an mTBI and a PTSD diagnosis. Analyses were performed on equilibrium scores, which compare the most drastic anterior-posterior movements of the subject over each trial to a theoretical limit, from 6 computerized posturography tasks. Statistical measures included 5 ratios of equilibrium scores and a composite weighted average of the 6 equilibrium scores.

Descriptive Data: A total of 166 subjects were studied. 55 subjects had neither mTBI nor PTSD (Group 0). 65 subjects were diagnosed only with mTBI (Group 1). 25 were diagnosed with only PTSD (Group 2). 21 subjects were diagnosed with both mTBI and PTSD (Group 3).

Results: Using a non-parametric approach, we addressed the question, do people with mTBI or PTSD exhibit balance deficits. First, we compared all subjects not diagnosed with mTBI to those diagnosed with mTBI and found them significantly different on only 1 of the equilibrium ratios. Next, comparing all subjects with PTSD to those without PTSD, we found significant differences for the composite score and all equilibrium ratios.

We then examined differences between the four mutually exclusive sets, Groups 0, 1, 2, and 3, and found significant differences for five of the measures (exception ratio 5). Post-hoc analyses demonstrated significant pairwise differences between Groups 0 and 3, the subjects without either disorder versus the subjects with both disorders. This suggests that the combined deficits from mTBI and PTSD cause large enough deficits for differences to be significant, when compared with subjects that have neither disorder.

Next, we compared measures of those diagnosed with PTSD and those without PTSD in first, the subgroup of subjects not diagnosed with mTBI and next, in those diagnosed with mTBI. For subjects not diagnosed with mTBI, significant differences between PTSD groups (Group 0 and 2) were seen for 3 equilibrium ratios and the composite measure. Amongst patients diagnosed with mTBI, differences were found for PTSD, Groups 1 and 3, for only 1 equilibrium ratio, suggesting that mTBI lowers scores enough to mask the PTSD effect. Reversing the roles of PTSD and mTBI, we found significant differences in mTBI groups (Groups 0 and 1) in 2 measures. No differences differentiate mTBI for patients who are diagnosed with PTSD (Groups 2 and 3) suggesting that PTSD also lowers scores to a level which masks any mTBI effect.

Summary: Computerized balance assessment offers an objective technique to examine the physiologic effects and provide differentiation between subjects with combat-associated mTBI and PTSD.

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Psychology IV

Stigma and Accessing Mental Health Support in Military Organisations

Lieutenant Christopher Liddell (Trainee Psychologist, New Zealand Defence Force)

In recent years, many military organisations have had an increased focus on supporting the mental wellbeing of their employees. However, despite this increased awareness around mental health issues, considerable stigma still exists for service personnel in relation to accessing mental health facilities. This presentation highlights research conducted by NZDF into factors that contribute to mental health stigma, as well as ways in which mental health facilities can be made more accessible for service personnel. For this study, NZDF personnel who have made use of mental health support services provided through the NZDF were interviewed about their experiences. This

was done to provide real world accounts of accessing mental health support through the NZDF, and by function of this, reveal some of the factors that can make individuals reluctant to engage in help seeking behaviours. Broadly speaking, two main barriers existed for those who have made use of NZDF mental health support services. Firstly, the potential effects that admitting mental health issues can have on one's career progression and/or deployment appeared as a barrier. Secondly, the perception that accessing mental health support makes an individual weak or inferior to others had a strong potential impact. This study indicates that accessing mental health services is often a positive and beneficial experience, but that making the decision to seek help can be difficult. To make mental health support services more accessible, it is suggested that efforts be made to dispel myths around mental health. Additionally, further efforts need to be made to increase the visibility of mental health support services within the NZDF.

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Emotional Cycle of Deployment: A Validation using NZDF Personnel and their families

Sub Lieutenant Katherine Yardley (Trainee Psychologist, New Zealand Defence Force)

Military Service places high demands on its personnel, compounded through commitment to operations, which can place significant strain on both personnel who deploy and their families who remain at home. Currently, the NZDF provide a range of resources designed for both personnel and their families prior to deployment in which an important model, the Emotional Cycle of Deployment (ECOD) is utilised. The ECOD is used as a framework for both personnel and their families to describe and understand the normal range of behaviours and emotions generated through the experience of deployment. The ECOD first emerged in the late 1980s from studies focusing on emotions and behaviours of US Navy wives during deployment of their husbands. In the late 1990s, the NZDF adopted this model and gathered evidence from research for its use and implementation within NZDF. The ECOD has since been utilised in support resources for personnel since the 1990s and had not been reviewed since that time. This present research validated the use of the ECOD model within the NZDF by collecting both quantitative and qualitative data from a mixed sample of personnel and partners. The research investigated the models key components to ensure the ECOD was still a viable model to utilise for NZDF, along with a collection of common tips, experiences and advice for each stage of the ECOD from participants. The key findings from this research will be presented, as well as the further utility of this research for NZDF support to operations.

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The Relationships Between Blast-Induced Mild Traumatic Brain Injury, Post-Concussive Symptomology, Depression, Post-Traumatic Stress Disorder, and Alcohol Use in Active Duty Military Personnel

Dr Steven West, Dr David Cifu, Captain Brett Hart, Mr Justin Alicea

Nearly 250,000 U.S. military personnel have incurred deployment-related mild traumatic brain injury (mTBI) during the Global War on Terrorism. Many of these individuals have subsequent post-concussion syndrome (PCS). Occurrence of blast-induced mTBI is common in this population and has been hypothesized to alter the risk of PCS and presentation of individual symptoms particularly when repetitive. These individuals also present with a host of comorbid conditions including depression, PTSD, and increased risk of alcohol misuse. Recent research has been conflictive in terms of the influence of these concomitant conditions on one another particularly with regard to select characteristics of service members involved. Likewise, debate on treatment algorithms for these co-occurring conditions in patients with PCS concerns whether to focus on PCS as the primary point of treatment or vice versa. Currently, little empirical support has appeared to denote the impact of PCS on known corollaries of mTBI such as PTSD, depression, and alcohol misuse and it is unclear if PCS modifies the relationships between known symptomolgies post mTBI. The goal of this study was to: (1) detail the rates of such conditions in a military population recently returned from combat operations, and (2) to determine if PCS modifies the known relationships between depression, PTSD, and alcohol misuse. Data were obtained from 60 active duty service members within 90 days of return from theater. Analysis revealed no group differences with respect to age, pay grade, marital status, or race /ethnicity. All had a physician confirmed diagnosis of blast-related mTBI. Measurement data were PCS as indicated by Rivermead Postconcussive Symptom Questionnaire, depressive symptomology from Center for Epidemiologic Studies Depression Scale, PTSD by the PTSD Checklist, Military (PCL-M) and alcohol

misuse as indicated by Alcohol Use Disorders Identification Test (AUDIT). Data were analyzed to: (1) denote the rates of key variables, and (2) determine if PCS mediated or moderated the associations between depression, PTSD, and alcohol misuse. Rates of depression and PTSD were near roughly 90% of the sample, and most (80%) engaged in at-risk drinking. Results indicated that depression was the primary predictor of drinking, with those having greater depressive symptoms drinking more than those who were not depressed [t (58) = 2.362, p = 0.022, 95%CI 3.151, 0.260, d = 0.609]. PTSD did not predict drinking in this sample [t (58) = 1.464, p = 0.149, 95%CI -2.723, 0.423]. Regression-based path analyses tested potential moderating and mediating effects of PCS on the relationship between depression and alcohol use. No moderating [F (3, 56) = 2.3358, p = 0.0835] or mediating [F (1, 58) = 1.0619, p = 0.3071] effects were found. Although the overall model was significant [F (1, 58) = 26.6913, p = 0.00001], only direct effects for depression were found (p = 0.00001), with depression explaining 31.52% of the variance in alcohol use.

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Psychology V

The Post Deployment Transition Model: A Review of Experiences from NZDF Personnel

Sub Lieutenant Anna Hill (Trainee Psychologist, New Zealand Defence Force)

Returning from operations can often be a time of turbulence and change, as personnel transition back into their home environment. Common reintegration issues within the Allied Nations research focus on relationship difficulties, as well as heightened risk taking behaviours and a general sense of disruptiveness settling back into routine. Currently utilised in the NZDF return to New Zealand psychological support resources, is an important model to assist in normalising common behaviours and feelings during the transition process, called the Post Deployment Transition Model (PDTM). The PDTM was developed from the Kubler-Ross change curve, and was remodelled for use within a post deployment context within NZDF. Since its first implementation in the late 1990s, the PDTM had not been reviewed for currency or relevancy with todays Service members. This present research reviewed the relevancy of the PDTM within NZDF by collecting qualitative information regarding each stage of the PDTM. The key findings from this research will be presented, as well as the further utility of this research for NZDF support to operations.

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Translating the Mental Health Advice Book into an interactive electronic format

Kym Connolly, Olivia Mahn & Tim Adams (DVA)

The Department of Veterans' Affairs' (DVA) Veteran Mental Health Strategy 2013-2023 is guiding innovative policy and program delivery across the veteran mental health service system. Along with DVA's strategic plan, DVA Towards 2020, it is transforming early intervention and mental health treatment for a new generation of Australian veterans. Technology is integral in changing the way DVA engages with younger veteran clients as well as their mental health providers. DVA uses technology to support providers in improving their understanding of veterans and the use of evidence-based CBT treatments. In the past, DVA has sought to support providers through paper-based resources, face-to-face training and cooperative learning groups. Now, that same information is available through free online resources.

In 2007, DVA released the Mental Health Advice Book, a resource for professionals treating veterans with common mental health problems. This specialized publication is designed to ensure consistency and utilisation of best practice, evidence-based procedures in the assessment and treatment of common mental health problems for veterans. The book contains information on understanding veterans and their families, summary advice for General Practitioners and detailed information on assessment, formulation and treatment of common mental health problems amongst veterans.

Since its release, the Mental Health Advice Book has become one of DVA's most sought after provider resources. It was reviewed and updated in 2012/13.

Feedback from users showed that the information and advice contained within the Mental Health Advice Book, while being a valuable resource, is not always easy to access during a consultation. To aid providers in their screening and assessment of veterans with mental health concerns, an electronic companion to the book has been developed. The Veteran Mental Health Consultation Companion is an application for tablet devices and enables a

practitioner to quickly navigate to relevant assessment tools, outcome tools and patient handouts during a consultation. It is interactive and easy to navigate, making it more accessible to providers.

The Veteran Mental Health Consultation Companion is designed to complement the flow of a consultation and assist with assessment tool calculations. Practitioners who use the e-companion will have instant access to common assessment tools and will also receive information facilitating the interpretation of these results. All results can be printed or emailed, allowing them to be placed on a client's file. Patient handouts are also available, as are a range of online tools, such as psycho-educational videos.

By using Veteran Mental Health Consultation Companion during a consultation, practitioners can access the latest evidence-based tools for treating veteran mental health conditions in a more collaborative fashion. This encourages a recovery-focussed culture, as well as improving the efficiency of their practice management.

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An Overview of the Development and Practice of Psychological Support to Operations within the New Zealand Defence Force: Reflections on Past and Current Practice

Captain Samuel Williams (Southern Regional Psychologist – New Zealand Defence Force)

The New Zealand Defence Force (NZDF) has utilised uniformed psychologists in the provision of psychological support to operations since the early 1990s. Since that time, the components delivered at each phase of the deployment cycle have developed according to best practice and inclusion of Allied Nations research and methodology. 2008 saw a major review of NZDF psychological support to operations, largely drawing off the collaborative relationships within The Technical Cooperation Program (TTCP) Technical Panel 13 (TP13) Psychological Health and Operational Effectiveness. This review saw the implementation of post-deployment psychological screening more aligned with practices conducted within the Australian Defence Force (ADF). 2014 brings another review period of NZDFs practices of psychological support to operations and this presentation serves to highlight the history of psychological support to operations within the NZDF, as well as its newly revised Psychological Support to Deployment Programme (PSDP). Whilst covering the psychological support provided across the deployment cycle, the emphasis in this presentation will be to highlight the significant changes at post deployment and follow up, including an overview of the revised Initial Psychological Questionnaire (IPQ) and Follow-Up Questionnaire (FPQ) administered as part of psychological debriefing.

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Rehabilitation

ADF Recovery and Rehabilitation New Initiatives: Progress and Evaluation Findings

Julie Wilson

Mental health, rehabilitation and recovery are key focal areas for Defence. Defence currently has a successful occupational rehabilitation program but acknowledges that improvements can still be made.

The Simpson Assistance Program (SAP) aims to support and enhance the efforts of Defence to reduce the impact of serious injury or illness on Australian Defence Force (ADF) personnel. Through SAP we have identified and are developing strategic, enabling and service delivery initiatives to improve rehabilitation and recovery outcomes for serving Defence members.

Key initiatives of the Simpson Assistance Program include:

- Development of the ADF Rehabilitation Strategy and action plan
- Intensive Rehabilitation Teams;
- A Rehabilitation Research Investment Program, including the implementation of the 'The role of the family in the rehabilitation of SWII ADF

Members' research initiative;

- Assisting ADF personnel who cannot be gainfully employed during their rehabilitation programs with meaningful engagement options;
- Psychosocial support programs such as Mate to Mate Peer Visitation; and
- A "Member and Families guide" and a "Commanders Guide to Rehabilitation and Recovery".

This presentation will provide an update of program developments and evaluation findings which have occurred to date, key learnings and the future of Defence's rehabilitation reform initiatives.

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Training

Clinical Placements – How do we maintain our currency of practice?

CMDR Craig Spinks

All three Services have a long history of working hand in hand with public and private health systems in times of both conflict and peace with Service personnel working in civilian hospitals for as long as most of those currently serving can remember and these relationships continue today. However, with the increasing complexity of the professional clinical environment, Defence has sought to more appropriately formalise and standardise the basis under which these placements occur.

To do this, since around 2011, Defence has established a system of deeds between on the one hand, the Commonwealth, and on the other, the relevant State, regional or local health service provider. These deeds formalise clinical placement opportunities and set out the agreed terms under which Defence personnel may work in the civilian health environment. They establish agreement in a range of areas including professional liability, conduct and expectations and provide a system within which the parties may work to achieve their clinical placement objectives. There are currently some sixty deeds in place nationally, with a further twenty under negotiation.

Use of these deeds now enables the full spectrum of Defence health personnel, from Medical Specialists, through to Medics, Environmental Health personnel and beyond to undertake such placements and has proven to be a successful method of enabling Defence to maintain levels of clinical proficiency to ensure the availability of appropriately experienced personnel in support of Operations and Exercises as required.

Once the deed is in place, typically for a period of two to five years, then its schedules are completed that as well as identifying the individual undertaking a placement, identify the outcomes that are sought by Defence with acknowledgment by the health service provider that those outcomes are able to be achieved within their clinical environment. The Defence individual of course, needs to comply with any requirements of the health service provider in respect of for example, induction and credentialing.

To continue to obtain effective outcomes for all parties however there needs to be a level of communication associated with the use of these deeds that is perhaps greater than has been applied in the past. Both Defence and the health service provider are able to benefit from these relationships providing they are carefully and actively managed.

The purpose of this presentation is to expand on this program, inform the audience of its scope and purpose, and facilitate such communication.

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Experiences in the delivery of a flexible education program to military students

Dale Edwards, Anne-Marie Williams, Wayne Harris, David Lighton, Illya Selmes

Background: The delivery of higher education and professional development programs through a flexible online model has been increasing in popularity for education providers and students alike for some time [Chitkushev Et.Al 2014]. The delivery of these programs to military students comes with a unique set of challenges, especially in the field of health professions education. The University of Tasmania (UTAS) offers a wide range of courses through flexible delivery to military students, with the Bachelor of Paramedic Practice receiving increasing enrolments during the last 12 months. The current evidence base underpinning education delivery to military personnel is limited, with the majority of literature referring to the US military [Bunting 2013], which may have limited application in the Australian military context.

Aim: To investigate the issues affecting military personnel engaged in online education, with the aim of improving the delivery of services to this specific student population

Methodology: The university undertook a review of any cohort specific challenges faced by students enrolled in the Bachelor of Paramedic Practice (Conversion) in the first semester of 2014.

Results: Currently 20% of the students enrolled in the Bachelor of Paramedic Practice at UTAS come from the Australian Defence Forces. A review of communication with students over the first semester of 2014 has identified a range of challenges faced by both the student population and the university. These challenges can be summarised under five domains; communication; flexibility in content delivery; flexibility in assessment practices; access to technology; flexibility in enrolment policies and procedures.

Discussion: Whilst there are a number of issues that can be resolved internally within the faculty, there are a number of areas that require the development of new or updated policy relating to military students. A similar process occurs in the United States under the Military Friendly Colleges [Lederman 2008] program. This initial review reveals the need to further investigate the barriers and enablers for military students in undertaking further education, taking into consideration the unique nature of the military professional environment.

Conclusion: Universities face challenges in the provision of education to military personnel, due to their unique characteristics in comparison the wider student body. In order to better support the military student, it is important to fully investigate the issues facing this student cohort.

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Introducing HOSPEX to Australia

LTCOL G Mathews, LTCOL G Gill, LTCOL M Reade, MAJ P Butt MAJ A Chalmers MAJ G Brown, CAPT D Innes, CAPT B O'Malley

This full one hour presentation from 3 speakers introduces a wider ADF Health Service audience to the Australian Concept of HOSPEX.

HOSPEX (Hospital Exercise) is a United Kingdom simulation exercise developed to validate the competency of deploying hospital rotations to the fixed Role 3 field hospital at Camp Bastion in Afghanistan. It is conducted utilising a large team of assessors in a purpose built facility in York and assesses all hospital departments. The Australian Army has adapted the concept of HOSPEX to confirm that the personnel and clinical systems of its deployable Role 2 Extended medical facility, 2nd General Health Battalion (2 GHB), are sufficiently competent to provide services on deployments likely to be requested of it.

As part of its role 3rd Health Support Battalion (3 HSB) has assumed the responsibility for preparing personnel to conduct a HOSPEX type evaluation, to develop simulated scenarios across the surgical services of 2 GHB, and to conduct the HOSPEX evaluation.

The Australian HOSPEX attempts to test 2 GHB under a variety of conditions and is conducted in the field. Preceding each HOSPEX the operator/trainer (OT) team, currently seven personnel, meet to develop scenarios which will involve care across casualty reception, triage, initial resuscitation, first surgery, admission to ward or to intensive care unit, and preparation for rearward evacuation. Some scenarios will have involvement of primary care, psychological support, dental and environmental health team in providing care. Clinical findings, patient observations, diagnostic imaging and pathology results are prepared for each simulated casualty. Building on the British experience there is a strong emphasis on examining non-technical aspects of care, team situational awareness, clinical leadership, transmission of information during handover of care, and a general testing of 2 GHB administrative processes around casualty movement, casualty notification, overall situational awareness and special logistic requirements.

The scenarios are difficult and intended to extend the knowledge and coping mechanisms of the treating teams. Casualties suddenly deteriorate and require emergency treatment. At the scenario conclusion, the treating teams will debrief themselves and if required there will be some input from the OT team.

Before the HOSPEX activity the OT team is introduced to2 GHB clinical personnel. Where possible at the conclusion of the activity which generally lasts about 36 hours personnel attend a presentation from the OT team to ensure that the lessons identified are known to all, and an informal oral presentation is made by the OT team to the CO of 2 GHB and his staff. A formal Post Activity Report is produced by the team project officer and officially is returned to the CO 2 GHB by the CO of 3 HSB, ensuring that the training lessons learnt are known to the full-time and reserve elements who will form the deployable Role 2 E facility.

The speakers will describe the reasons why the Australian Army needed to adopt the HOSPEX concept, how it was adapted to suit local circumstances, and how the concept may evolve to meet the needs of the wider Australian Defence Force (ADF) and our allies.

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Trauma

ADF Military Medical 'Dogma' – Teaching Our People New Tricks

WGCDR David Cooksley[1] (Emergency and Retrieval Physician) and CAPT Kendall Crocker[2] (Veterinarian)

ADF health personnel on deployment or exercise may be called upon to provide urgent medical care to injured or ill military working dogs (MWDs) or other service dogs (such as police, customs, quarantine, USAR or AUSMAT) when there is no immediate veterinary support. Few ADF health personnel have had any formal training in the safe handling, assessment and management of these highly valuable service animal assets. This presentation will outline what may be required in terms of training, equipment and policy to allow human healthcare personnel to provide initial resuscitation and evacuation of injured or ill MWDs and to communicate effectively with ADF veterinary members providing remote support and/or subsequent ongoing care. It will also address some of the concerns raised about treating MWDs in human healthcare facilities.

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The CHORuS study – using a large animal model of acute traumatic coagulopathy to test the efficacy of cryopreserved red blood cells compared to aged and fresh refrigerated red blood cells.

Milford EM[1,2] van Zyl N[1] Diab S[1] Dunster K1,[3] Tung, JP1,[4] Reade MC5,[6] Fraser JF1,[7]

Haemorrhage is the primary reversible cause of death after trauma, estimated to cause 80% of preventable battlefield deaths[1], making the restoration of circulating blood volume and control of haemorrhage a clinical priority[2]. For the military, the threat of disruption to supply chains has driven the search for alternatives to refrigerated redblood cells (RBCs), which have a shelf life of only 42 days. Another, only recently recognised, problem with refrigerated RBCs is the development of a storage lesion over a period of time that is well within the current shelf life and is associated with poor clinical outcomes[3].

Cryopreservation of RBCs has emerged as the favoured alternative to address these problems[4]. Arresting metabolism by cryopreserving fresh blood should, in theory, deliver a storage lesion-free product that can be stored for up to 10 years. The logistic advantage of prolonged shelf-life has been utilised by the US and Dutch armed forces for over 15 years, and the ADF is acquiring this capability. From this limited use, we know that cryopreserved RBCs do not cause severe transfusion reactions, but there is no controlled, comparative evidence for their efficacy as a resuscitation fluid.

Coagulation, Haemorrhage and Oxygenation in Resuscitation of Severe trauma – Phase II (CHORuS-II) will use a large animal model of acute traumatic coagulopathy to study the effects of aged RBCs, fresh RBCs, cryopreserved RBCs, albumin and fresh frozen plasma transfusion at an organ and cellular level in the severe trauma setting. The study follows on from a successful pilot study (CHORuS-I) of twelve animals that demonstrated the development of acute traumatic coagulopathy from trauma and haemorrhage alone.

The study will test the hypothesis that cryopreserved RBCs are superior in efficacy to aged RBCs, and

equal in efficacy to fresh RBCs, using the following endpoints:

- Organ level oxygenation – measured by tissue oxygen probes in liver, heart, kidney and brain.
- Microcirculation blood flow – measured by tissue Doppler probes and sidestream darkfield camera images in the same organs.
- Inflammation – measured by inflammatory biomarkers.
- Cardiac function – measured by echocardiography and cardiac biomarkers.
- Acute traumatic coagulopathy – measured by ROTEM and MULTIPLATE as well as coagulation factor levels.
- Endothelial glycocalyx damage – measured by electron microscopy imaging.

The study will also contribute to understanding the pathophysiology of acute traumatic coagulopathy, and provide mechanistic data to support growing clinical evidence suggesting aged red cells are harmful, particularly for the trauma patient.

The results of this study will be of considerable interest to Defence given its acquisition of a cryopreserved RBC capability. In addition, the nascent collaboration between the Critical Care Research Group based at The Prince Charles Hospital in Brisbane and Defence will provide an enduring opportunity for Defence members to pursue research in pre-clinical and clinical areas of critical care.

The study is planned to start in late June 2014, finish in late 2014, with results published early 2015.

The study is supported by grants from the Defence Health Foundation, the Queensland Emergency Medicine Foundation and the Intensive Care Foundation.

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Do trauma operating theatres really need to be warmed to 42°C?

LTCOL Michael C. Reade

The Clinical Practice Guidelines of the United States military Joint Theater Trauma System recommend an operating room used for damage control resuscitation in military trauma should be heated to "ideally 108°F (42°C) or greater".[1] This recommendation is based on the repeatedly observed strong association between hypothermia in trauma and greater mortality, conventionally taught as one component of the "lethal triad" (along with acidosis and coagulopathy). However, there is only very weak evidence[2] that this association between core temperature and mortality is causative. It might be that greater severity of injury independently causes both hypothermia and greater mortality. Even if the association is causative, this does not imply that rewarming once hypothermia has developed would be beneficial. Only a single trial, involving 33 trauma patients, has ever shown benefit with active rewarming[3] – which in this study involved an extracorporeal circuit. Even if rewarming is beneficial in trauma, the efficiency of heat transfer from the ambient air or even forced air warming devices is poor,[4] and at least within the range of ambient temperatures 18-27°C there is no consistent effect on patient core temperature.[5] Very high ambient temperatures almost certainly degrade the performance of operating teams. Although this has never been demonstrated in a clinical context, the ability to monitor complex information is known to be increasingly degraded at ambient temperatures >25°C.[6] Therefore, the current enthusiasm for very high ambient temperatures in operating theatres may be unwarranted and even detrimental. Indeed, there is good animal evidence that induced hypothermia is beneficial in trauma,[7] a concept that will be familiar to military clinicians acquainted with anecdotes of unexpected survival after prolonged

severe hypothermia in battle casualties during the Falklands War.[8] In short, the current feverish zeal with which we increase the temperatures of our deployed ADF operating theatres may, or may not, be detrimental to our patients. In the context of substantial uncertainty, a clinical trial of ambient operating theatre temperature in trauma is warranted. Such a trial would be quite simple and inexpensive to conduct in Australian civilian trauma centres.

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The Chronic Effects of Neurotrauma Consortium: Studying the Future Effects of Combat-Related Brain Injury Today

Dr Steven West, Dr David Cifu

Nearly 20% of the more than 2.5 million U.S. Service Members (SMs) deployed since 2003 to Operation Enduring Freedom (OEF) and Operation Iraqi Freedom (OIF) have sustained at least one traumatic brain injury (TBI), predominantly mild TBI (mTBI),[1,2] and almost 8% of all OEF/OIF Veterans demonstrate persistent post-TBI symptoms more than six months post-injury.[3,4] Similar issues are present in all Coalition Forces personnel having served in these theaters of operation. Explosive munitions, predominantly improvised explosive device' (IEDs), have caused the overwhelming majority of these identified cases. The incidence is likely even significantly higher than reported, as many mTBIs may go unrecognized during and even after deployment because of more visible concomitant injuries capturing greater attention, clinicians' limited awareness of the often subtle initial findings, and patients' reduced subjective awareness related to cognitive deficits in the acute period.[5] Most symptoms associated with mTBI are transient; however, in a small percentage of individuals, these difficulties persist and even lead to lifelong disability. In these individuals, additional chronic effects, including neuroendocrinologic abnormalities, seizures and seizure-like disorders, fatigue, vision and hearing abnormalities, and numerous other somatic symptoms are more common over time. The long-term effects from these single or repeated TBIs on the persistence of these symptoms, on combat and trauma-related comorbidities, and on long-term brain functioning are unknown. Increasing evidence supports the linkage between both concussions and combat-related trauma with a degenerative neurologic disorder known as chronic traumatic encephalopathy (CTE), which results in progressive cognitive and behavioral decline in sub-populations that are 5 to 50 years out from repeated or cumulative exposures.[6,7,8] The possibility of a link between mTBI, persistent symptoms, and early dementia has widespread implications for SMs and Veterans; however, these chronic and late-life effects of mTBI are poorly understood. The Chronic Effects of Neurotrauma Consortium (CENC) is a research project sponsored by the U.S. Departments of Defense and Veterans Affairs devised to address the long-term effects of mild traumatic brain injury in military personnel and Veterans. The mission of the CENC is to fill the gaps in knowledge about the basic science of mild TBI (also termed concussion), to determine its effects on late-life outcomes and neurodegeneration, to identify service members most susceptible to these effects, and to identify the most effective treatment strategies. The CENC is a multi-center collaboration linking basic science, translational, and clinical neuroscience researchers from the DoD, VA, academic universities, and private research institutes to effectively address the

scientific, diagnostic, and therapeutic ramifications of mTBI and its long-term effects. This presentation will provide details of consortium's four research cores (1. Biorepository, 2. Biostatistics, Data Management and Study Management, 3. Neuroimaging, & 4. Neuropathology), and three principal studies (1. Longitudinal Cohort Study, 2. Tau Modification and Aggregation in Traumatic Brain Injury, and 3. Epidemiology of Chronic Comorbidities).

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JOURNAL OF MILITARY AND VETERANS' HEALTH

CALL TO AUTHORS

The Journal of Military and Veteran's Health is a peer reviewed quarterly publication published by the Australasian Military Medicine Association. The JMVH Editorial Board has indentified the following themes for future editions (please note these have been updated since previously communicated):

Edition	Theme	Publication Date	Manuscript Submission Deadline	Advertising Submission Deadline
Volume 23. No.2	Medical Aspects of WW1	April 2015	1 January 2015	1 March 2015
Volume 23. No.3	Trauma Management - Past & Present	July 2015	1 April 2015	1 June 2015
Volume 23. No.4	AMMA Conference abstracts - Mental Health	October 2015	As per AMMA conference submission process	1 September 2015

Categories for the above include:

Original Research/Original Articles, Short Communication, Review Articles, Reprinted Articles, Case Studies, Abstracts from the Literature, Biographies, History, Book Reviews, Commentary and View from the Front.

The Editor would be delighted to receive articles for consideration on these themes. However, please note that although these are the suggested themes, we encourage authors to continue to submit articles on a range of topics on military medicine and veterans' health including operational articles.

Please submit your articles via the JMVH website www.jmvh.org where the 'Instructions to Authors' can also be found.

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