CLINICAL EPIDEMIOLOGY OF SAGO INDUCED HAEMOLYTIC DISEASE IN RURAL LOWLAND COMMUNITIES IN PAPUA NEW GUINEA

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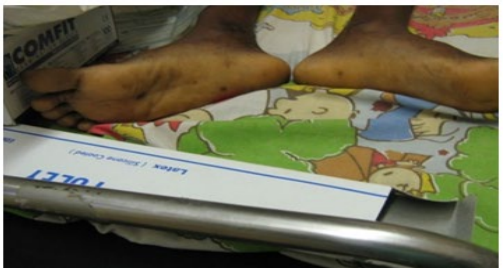

Figure i. Sago poisoning case in induced unconscious state with sallow yellow discoloration of soles of feet overshadows pallor following exponential intravascular haemolysis. Image Dr M Gena.

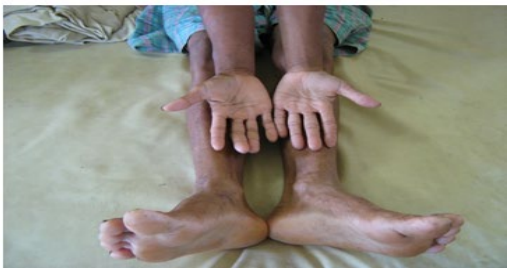

Figure ii. Sago poisoning case regained consciousnes and sitting up after one unit of blood transfusion. Return of colour of palms and soles of feet but still with pallor. Image Dr M Gena.

"Hypoxia not only stops the machine but wrecks the machinery"

attributed to British Physiologist J. S. Haldane, 1921 (1892-1964).

STATEMENT OF ACCESS

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STATEMENT OF SOURCES

I declare that this thesis is my work and has not been submitted in any form for a degree or diploma at any university or other institution of tertiary education. Information derived from published and unpublished work of others has been acknowledged in the texts and references given.

Miila Mary Gena October 2024

STATEMENT OF CONTRIBUTION OF OTHERS \

Nature of assistance	Contribution	Name and Title
Intellectual support	Supervision, admin, and editorial support	A/Prof Jeffrey M Warner
Intellectual support	supervision and editorial support that propelled progress towards the pre-completion seminar	Prof Bruce Gummow
Intellectual support	Brilliant JCU postgraduate program,	Extraordinary JCU Learning advisors
Intellectual support-open learning strategy	YouTube videos on how to videos assisted self-learning to complete the writing of the thesis and statistical analysis.	YouTube channel
Financial support AUD$760,000	Ok Tedi Mining Ltd provide a study grant to JCU for this study	CEO of Ok Tedi Mining Ltd, Mr. Keith Faulkner
Data collection	Hospital medical records review Health survey, field tests and laboratory tests and clinical samples from SHD cases.	Principal investigator, independent practitioners' Assisted by laboratory and hospital staff.
First and second field work logistic support to hospitals and rural communities	To create awareness of study to health workers and communities located by the Fly River. Use of the ship and fixed-wing flights	Ok Tedi Mining Ltd - CEO Mr. Keith Faulkner
Logistic support for third, main field work Community health surveys of remote villages in NFD and MFD and maintain outbreak surveillance	Accessing, living and conducting health clinics among remote villages NFD and MFD, Team transported by helicopter and fixed-wing flights with food supplies to live in the villages	Mr. Robin Moaina CBE Community relation Manager, Talisman Energy Niugini Ltd (TENL)
Nature of assistance	**Contribution**	**Name and titles**
JCU laboratory support	Setting up automated analysis of samples and fixing computer blitz	Ms. Sandra Pollard and her daughter

JCU laboratory support	Microbiology studies of implicated sample	Dr. Marshall Ferterl
Department of Health support	Access to government hospitals	Dr. Nicholas Mann
Kiunga Hospital management	Assist with access and support with sago poisoning cases and past medical records. Provided clinical duties support to hospitalized patient care by the principal investigator.	CEO/surgeon Sr. Joseph (Nun - Surgeon)
Kiunga District Health management support	Release of staff to immunize children during field visits	Mr. John Lari
Rumginae Hospital support	Access to patients, records of cases and Dr. Donovan's manuscript of cases	Dr. Daniel Priest Dr. Adeline Sitther
Balimo Hospital support	Access to known medical records of sago poisoning	Mr. Daniel Pelowa,
Targeted Field clinic	Conduct women's clinic	Dr. Fred Wurr
Targeted Field clinic	Conduct children clinic	Dr. Delma Natera
Targeted Field clinic	Conduct dental clinic	Ms. Galeva Sere
Targeted Field clinic	Support to the clinical team	Ms. Georgina Tendike
Targeted Field clinic support	Specialist nurses, midwives	Sr. Dilidi Yoto, Sr. Maureen Kuri, Sr. Vestus Margo, Sr. Racheal Ewebi
Targeted Field clinic	Immunization to children ≤5 years	CHW George Wire
Targeted Field clinic	Field testing of samples and support treatment of villagers.	CHW Mebo, Nelson, Awane, Hayata
Kiunga hospital laboratory	Haematology analysis and blood slides examination	Mr. Geawi Giriha, and the team of laboratory assistants

Nature of assistance	Contribution	Name and title
Participants in health survey and clinic	Community participation and benefit from the health outreach program The measure of health indicators	**Rural Ningerum villages**: Ok Tarim, Tenkgim, Tarakbits, Ningerum Tamaro, Menumgrupe and T'moknai
Participants in health survey and clinic	Community participation and benefits from the health outreach program Measures of health indicators	**Fly River villages:** Erekta, Moian, Karemgo, Membok, Kukuzaba
Participants in health survey and clinic	Community participation and benefit from the health outreach program Measures of health indicators	**Strickland River villages**: Tamivi, Pari, Ogayabom
Participants in health survey and clinic	Community participation and benefits from the health outreach program Measures of health indicators	**Nomad villages**: Fuma, Baniso, Lake Campbell, Somokopa, Hesalibi
Participants in health survey and clinic	Community participation and benefits from the health outreach program Measures of health indicators	**Lake Murray** Kapikam
Participants in health survey and clinic	Community participation in and benefits from the health outreach program Measures of health indicators	**Kiunga town village** - Mepu **Informal settlements Kona -** Sauga, Seven, Sare, Menumsore, and Last Kona
Traditional Balimo sago processing	Balimo way of sago making demonstration photographs by Kiunga hospital compound families	Balimo girls and women Kekela Family of Kiunga Hospital
Traditional Sepik sago processing	Sepik way of sago making demonstration photographs	Mrs. Kambo, Kiunga hospital

Nature of Assistance	Contribution	Name and Title
Townsville Soroptimist club members who were JCU students obtained ex hotel bed linen and towel for charity purpose allocated to support this fieldwork.	Principal investigator distributed the bales of towels and bed linen to Kiunga and Rumginai Hospital. In patients received and took home as hospitals had no laundry facilities.	Medi Reta and Ms. Judy Hunter, Soroptimist club, Townsville, QLD AUST. Shipping provided by Starwest construction company contractor to OTML
Prof Norman assisted me to reactivate my PhD as part of DWU staff development	Prof Pamela Norman initiated communication with Prof Sandra Harding of the Postgraduate school of JCU and appointed Prof John Burton of DWU Postgraduate Studies to assist the principal investigator.	Prof Pamela Norman, Vice President Academic Affairs, Professor of Education, Divine Word University, Madang, Papua New Guinea.
Improving quality of study sites maps of Western Province	Study site maps were upgraded onto OTML based maps and checking references	Prof John Burton, Australian National University
Two posters created by principal investigator for teaching, shared during DWU open day and 2018 PNG medical symposium poster presentation.	Poster 1on Sago induced intravascular haemolysis outbreak and poster 2 on the pathophysiological changes of SHD	Academic enabling environment of DWU.
Value add teacher training at DWU and enhanced my confidence to refocus to complete and submit this PhD thesis to JCU	Graduated with postgraduate certificate in higher education teaching and learning validating my academic advancement as a teacher	Prof Pamela Norman improving quality of DWU teaching staff development program.
Malaria case detection and bed net distribution by OTLM and the global fund	Constant surveillance long term data showed maximum reduction of malaria burden	OTML Vector control section Principal investigator worked as a public health coordinator

This work was supervised by A/Professor Jeffrey Warner and Professor Bruce Gummow as my primary and secondary advisors respectively. Dr. Andrew Greenhill assisted with early writing and accompanied me during the initial fieldwork. All three provided editorial and critical feedback that facilitated the thesis writing.

Laboratory support was provided by Ms. Sandra Pollard and Dr. Marshall Feterl. Thisenabled analysis of clinical samples and implicated sago in disease.

Financial support for this project was provided by Ok Tedi Mining Ltd as a study grant to James Cook University and managed by A/Professor Jeffrey Warner as the Primary Advisor of my candidature.

Fieldwork logistical assistance was provided by Ok Tedi Mining Ltd in the early part of the study. The main fieldwork requiring and access to rural remote villages in and outside of the mine impact villages was provided by Mr. Robin Moaina CBE**,** as the community relation manager in Talisman Energy Niugini Ltd.

Rumginae, Tabubil, Kiunga and Daru hospital staff supported the study. The health team consisted of independent medical practitioners and government health workers including nursing officers, community health workers and laboratory personal. Clinics conducted in the village ensured remote villages received clinical evaluation with health care advice and treatment for all segments of the population (children ≤ 5 years old, school children, out of school children, adolescents, reproductive age group, and older adults).

Village health care facility staff also helped with the communication, clinic and kept surveillance of new cases of sago poisoning outbreaks.

Village elders and leaders welcomed the study team and supported our sustenance for the duration of stay varying from 3-5 days depended on the population size of each village visited.

Our safety and security were assured through the village leaders and the community relation officers of the various companies operating within the regions where the villages were located. The study team was instructed to stay safe by not engaging in any unsafe practices that would endanger the life of others on the team whilst living in the remote villages.

DECLARATION OF ETHICS

Relevant research reported in this study received approval from the Papua New Guinea Medical Research Advisory Committee (MRAC Number 6.29) and human ethics approval from James Cook University ethics review committee (human ethics number H5401).

ACKNOWLEDGEMENTS

The clinical epidemiology of Sago induced haemolytic disease study had been lengthy and challenging but was achieved through the assistance and excellent logistical support provided by resource developers, Ok Tedi Mining Ltd and Talisman Energy Niugini Ltd. Both companies operate in the Western Province of Papua New Guinea. Ok Tedi Mining Ltd had been operating the copper mine in North Fly District for 3 decades and Talisman Energy Niugini Ltd, a new oil and gas exploration company began its exploration activities in Western Province in 2010.

Former CEO of Ok Tedi Mining Ltd, Mr. Keith Faulkner approved and provided the study grant to James Cook University to support the principal investigator as a PhD student to study the clinical epidemiology of Sago poisoning, a disease that affected rural remote communities in Western Province.

I thank the Managing Director of Ok Tedi Mining Ltd, Mr. Keith Faulkner who believed in my work as a medical doctor for the Ok Tedi Mining company and wholeheartedly supported my intention to research the cause of sago poisoning. It was anticipated that the results of the study would benefit the sago eating communities, the health fraternity and those organizations that work in Western Province. As a parting employee's exit strategy, I offered my time to investigate this baffling and unrecognized disease that affected remote communities of Western province. The company assisted communities with medevac for medical emergencies including sago related diseases where the affected cases either were transported to Tabubil or Kiunga hospital for treatment. A PhD study was considered as an independent, open, transparent, and diligent way to research an illness with an unknown aetiology affecting sago eating communities in Western Province.

James Cook University was selected due to the principal investigators prior contact with the team of sago researchers' and ongoing work on the microbiology of sago. The two paths crossed when the principal investigator presented Ok Tedi Mining Ltd's experience of management of clinical cases of sago poisoning cases during the mini sago symposium undertaken in Port Moresby in September 2005 where it was obvious that there was a wide gap in the existing knowledge of Sago Haemolytic Disease as a disease entity. Whilst the laboratory scientists supported themicrobiological study of the sago starch, a clinical epidemiological study was lacking therefore, discussion were centered on the 1975 case series study described by clinicians Taufa and Donovan. This prompted me to highlight the need for this study to Mr. Keith Faulkner, who wholeheartedly supported me with the funding and the logistic support for the fieldwork, and freedom to choose a

university for my PhD study. The project was named Dr. Miila Gena Sago Project. Naturally, I chose James Cook University and the team of sago researchers to assist and supervise this academic endeavor.

I would like to thank my principal supervisor, Associate Professor Jeffrey Warner who supported me through this lengthy study to finally reach this point of completing the thesis. I appreciated all the support as I had to overcome many obstacles to reach the end of the PhD journey. My clinical epidemiological and internal medicine knowledge carried me through to do justice to glean the intricate details of describing sago poisoning in its entirety, a satisfying accomplishment on my part.

To my second supervisor, Professor Bruce Gummow, thank you for your professional input, guidance and editorial assistance that provided the final boost needed in my progression towards the finishing line.

To Dr. Andrew Greenhill, thank you for the assistance provided to me at the start of my PhD journey and for accompanying me on the initial fieldwork to Western Province where we updated the community on your PhD results, microbiological results on sago starch and introduced my study. I benefitted greatly from your superb editing skills in Chapter 5 on the retrospective review of Sago Haemolytic Disease cases. The least I could do was try to use that as a guide in writing even though it may not be evident in the thesis.

Community health assessment was an impossible task to undertake by one person. As the population consist of different segments of children, adolescents, adults, it required a team of health professionals to fully engage and evaluate the communities. As such I acknowledge and thank all the health professionals that spent their time helping me as we travelled and lived in remote communities whilst we conducted a comprehensive health assessment on all members of the remote villages visited in Western Province. This important fieldwork was supported by Mr. Robin Moaina, the CBE, community relation manager for Talisman Energy Niugini Ltd, a new oil and gas exploration company. Without TENL's logistic, security and workplace safety practices, and allowing me to engage a team of independent medical practitioners, I would have no means to reach these rural remote communities and provide the health talks, medical checks, immunizations whilst living for short periods of time in these rural remote communities. To be able to fly by helicopters with our team and supplies into remote communities were simply the best approach ever. My immense gratitude offered to Talisman Energy Niugini Ltd and Mr. Moaina. The health

team hoped that Talisman Energy Niugini Ltd accomplished their deliverables towards community benefits through the medical team efforts.

The health team consisted of both independent medical practitioners and government health workers of Kiunga and Daru hospitals. Dr. Delma Natera, an experienced private practitioner, Dr. Fred Wurr, obstetrician, and gynaecologist experienced in providing health care to communities impacted by resource developer operations, Dr. Nicholas Mann, paediatrician, and Dr. Bage Yominao, an ophthalmologist with extensive experience serving primary eye services in Papua New Guinea and internationally.

Kiunga hospital was central to this Sago Haemolytic Disease study as it was the birthplace. Health extension officer, Ms. Georgina Tendike managed cases with Sago poisoning and was supported by Dr. Julius Pilunduwo and other emergency physicians based in Kiunga hospital. The presence of emergency physicians made a positive difference to the survival of sago poisoning cases.

Nursing officers Rachael, Dilidi, Vesthy, and Maureen assisted doctors in conducting children, school medical, adolescent and women's health clinics. Community health workers, George Wire maintained cold chains and provided immunization for children whilst Debele, Awane and Nelson provided treatment to those evaluated by the doctors.

Special mention of Mrs. Galeva Sere, a dental therapist based at Daru hospital provided much needed dental care that stressed the importance of keeping permanent teeth for life not only for chewing, for intake of nutrition but also to maintain quality of speech and particularly to keep smiling with confidence for as long as one lived. Dental health talks were certainly entertaining, engaging and drew a roar of laughter from the villagers.

Valuable assistance was provided by Kiunga hospital laboratory technicians, Geawi Giriha, Thomas Mebo and Bigam Kiram who collected, sorted, and examined blood films. They also analyzed blood and urine samples and organized storage of sera for analyzes at James Cook University. The results of the samples provided objective evidence of the health status of the remote communities.

With a diverse team, we were able to ensure all members of the communities were evaluated, conditions diagnosed, provided treatment and advice to each segment of the population. Children under ≤5 years old were immunized, 6-12 years, adolescent, school medical; women's health and adults were clinically evaluated and treated for any illness that they had. The principal investigator,

also a physician conducted a medical clinic for adults and recruited study subjects for evaluating baseline health of adults of the Sago poisoning endemic population described in the thesis.

To all the communities that were visited, I thank one and all for their understanding, enthusiasm, and consent to participate in the study which also required the collection of blood and urine samples. Their eagerness and willingness to be involved in the study was much appreciated.

To establish an open dialogue with remote communities, the health team provided health education talks which were thoroughly enjoyed by the remote communities and I thank each of the health workers who had the difficult task to adjust their health talks to be understood by the village people. Each health worker improved their delivery of health talk topics by leaving out unnecessary technical details and concentrated on just explaining physiology in layman terms. The principal investigator constantly reminded health workers that these health talks were not for nursing or medical students and therefore needed preparation and practice. Many practice sessions improved the content of the health messages to the communities. The study delivered a total of 23 health programs, 184 health education talk, and 161 clinics. A total of 1,549 adults were evaluated and vaccinated 502 children in these remote communities.

To Ok Tedi Mining Ltd, I thank the company for all the support provided from the beginning to the end of the study, especially the logistics support in reaching the remote communities during the long period from the initial community engagement and the dissemination of the results of the study to health workers in North Fly District and community relations officers of the company to inform the Fly River communities. The results were presented to the executives of Ok Tedi Mining Ltd. Two posters produced on the epidemiology and pathophysiology of SIHD was emailed to the CEO of the company that explained the evidence of effects of sago poisoning.

For the third and main field work, I was stranded and abandoned in Kiunga, unable to proceed to the study site, remote village of Suki to assess the health status of rural remote communities that was affected by sago poisoning. A solution was offered by Talisman Energy Niugini Ltd, a gas and oil exploration company. To Mr. Robin Moaina CBE of Talisman Energy, I thanked and appreciated you for trusting my clinical skills to accord me as a team leader to provide health care to communities impacted by the oil and gas explorations. This allowed me to finally measure the health of rural remote communities.

The health team appreciated the protection, safety arrangements and the logistics provided by Ok Tedi Mining Ltd and Talisman Energy Niugini Ltd during the fieldwork conducted in the most

remote parts of Papua New Guinea. Without their support the generously funded Ok Tedi Sago Project undertaken by the principal investigator remained impossible.

To ECPNG church, I thanked them for the upkeep of village airstrips allowing safe landings of aircraft and appreciated the ECPNG communities' hospitality as a model community for keeping a clean village environment with such admirable group cohesiveness that maintained regular scheduled clean up days by the community. ECPNG deserved the public health prize for sustainable community improvement. I thanked colleagues, Dr. Daniel Priest and Dr. Adeline Sitther, whom I knew and worked with prior to my PhD study. It was gold to have Dr. Kath Donovan's original manuscript on the case series of Sago Haemolytic Disease handed over to me by Dr. Priest to continue the investigation into the unsolved medical emergency disease affect sago eating communities in Western Province. The doctors of ECPNG Church at the Rumginai hospital operated a default North Fly District hospital for many years as they take on referrals and conducted emergency surgeries additional to their walk-in cases a role not met by the government service. I appreciated their support in access to patients and medical records during my study.

To the following villages that hosted the health team, I thank the people of rural Ningerum region villages of Ok Tarim, Tengkim, Tarakbits, Ningerum, Menumgrupe, T'moknai; Fly River villages of Erekta, Moian, Karemgo. Membok, Kukuzaba; Strickland villages of Tamivi, Pari, Ogayabom; Nomad region villages of Fuma, Baniso, Somokopa, Hesalibi, Lake Campbell and Lake Murray region village of Kapikam. The experience was enjoyable and humbling as the health team parted knowing that it may be unlikely to return to these remote communities ever again.

To the health workers of Kiunga hospital, I thank them for the shared experience of working with them and enriched my medical experience, diagnosing, and treating medical conditions in patients that also included sago poisoning. Together we strived to improve patient care, an unbelievable clinical experience that clarified my view on the plight of rural remote communities need to access health care during medical emergencies situations and also education services.

To the Kekela family and the team of Balimo women, I thanked them for demonstrating the Balimo way of sago making and processing at the Kiunga hospital compound that provided the photographs for this study. To Norman Kambo's family, I thanked your wife for demonstrating the Sepik way of processing sago. The video of the traditional sago making has been uploaded onto YouTube to inform and educate the wider audience.

This work was dedicated to all rural health professionals that strived to provide health care to communities in the most difficult of circumstances. The level of care provided was limited by the knowledge and resources available in the rural hospital or aid post setting. Knowing exactly what to do depended on available knowledge of diseases accompanied by the ability to recognize and have an action plan to execute the treatment and or referrals. This work will enable you to know the symptoms and signs of Sago poisoning, recognize it to make immediate plans for referral, or start the blood transfusion without delay and ensure the patients received intravenous rehydration and to be confident to hold back on the use of diuretic in sago poisoning cases even though the standard protocol for any blood transfusion states to administer a diuretic.

To my children, Mege, Konara, Christina and my foster children, Abraham, Ulia and Jeremiah, I thanked you for being the focus of my life and made me a proud mother through your achievements. To Kristopher Vagi, my son-in-law, I appreciated and thanked you for the care and support you provided to Ulia and Jeremiah during my long absence during this study.To other families that have supported and cared for my children, I thanked my sister Josephine, Maryku, Kiape, as well as John and Bage Vince.

To my father, Gena Yalmene Petrus Olam, the hospital orderly, the first Dr. Gena captured my interest in medicine during my childhood. Through a plethora of observations such as observing him work on the paediatric ward, supervised sick children fed meals cooked by the nutrition team, hearid names of diagnosis, witnessed the accident emergencies cases rushed into Kundiawa hospital, watched patients forcefully trying to jump out of windows after they ate mushrooms were intriguing encounters in my childhood. To my mother, Meke Erekina Yongwa, shy, resourceful, loving, caring yet firm provided a home environment conducive to study. To both my parents, I thanked them for preparing me to serve others and this study was the ultimate test, a study conducted in remote communities of the Western Province, an impossible task finally concluded with improved health outcomes for all stakeholders.

'It seems impossible until it is done 'by Nelson Mandela.

ABSTRACT

Sago induced intravascular haemolysis, commonly known as sago poisoning by the lowland communities in Papau New Guinea, is presumed to be a lethal food borne disease causing severe anaemia. It is largely unrecognized by many health workers in Papau New Guinea. The broad objective of the current study is to explore the epidemiology of this condition in different communities in Papau New Guinea including the natural history, clinical features, and pathophysiological effects in affected individuals so to gain insight into disease aetiology.

A clinical epidemiological study of outbreaks of sago poisoning was carried out to assess the clinical and pathophysiological characteristics of the disease and interrogate the presumed association with sago consumption. The study included localities and seasonality of outbreaks and investigated whether the disease was contagious. A parallel cross-sectional study to assess the endemic health status of the lowland rural communities in North and Middle Fly communities was used as a control. Hypotheses were tested by Chi-squared tests, t-tests and regression analyses as appropriate.

Sago poisoning was confirmed as a food borne toxicosis, which only affected those that shared a common meal of sago pancake as the point source without any secondary cases. The clinical case definition had an emetic phase 8-12 minutes after a meal, accompanied by a feeling of lightheaded, dizziness and weakness, progressing to recumbency and unconscious with red urine before death or admission to hospital for blood transfusion as treatment. A 35% case fatality favored males despite females being affected with equal severity. Early deaths occurred in young male children and adults. Late deaths occurred on the third to fourth day of illness due to volume depletion and dehydration prompting acute renal failure. After blood transfusion, patients recovered fully, without any focal neurological deficits. Haematological findings showed intravascular haemolysis with haemoglobinuria, low haptoglobin, elevated lactic dehydrogenase and reticulocyte count and markedly reduced pre blood transfusion haemoglobin. This suggests that a preformed microbial toxin, may play a role in causing the exponential haemolysis of erythrocytes.

The findings of this study can be used to inform communities about safe sago storage and that storing sago starch in a perpetual fermented state avoids microbial contamination and can thus prevent foodborne toxicosis outbreaks. Furthermore, this study identified clinical features and laboratory findings that can be communicated to healthcare workers in Papua New Guinea so that they may more readily recognise and diagnosis Sago Haemolytoic Disease and appropriately manage and treat affected individuals.

ABBREVIATIONS

ECPNG	Evangelical Church of Papua New Guinea
CEO	Chief executive officer
CHW	community health workers
Dept	Department
Govt	Government
G6PD	Glucose 6 phosphate dehydrogenase
HEO	Health extension officer
NO	Nursing officers
NFD	North Fly District
MFD	Middle Fly District
MCM	Monforte Catholic Mission
MCV	Mean cell volume
MCH	Mean corpuscular haemoglobin
MCHC	Mean corpuscular haemoglobin concentration
OTML	Ok Tedi Mining Limited
PNG	Papua New Guinea
MAF	Mission Aviation Fellowship
SHD	Sago haemolytic disease
SIIH	Sago Induced intravascular haemolysis
SFD	South Fly District
Sr.	Nursing Officer, Catholic religious order for female nun
TENL	Talisman Energy Niugini Ltd
VHF	Very high-frequency radio

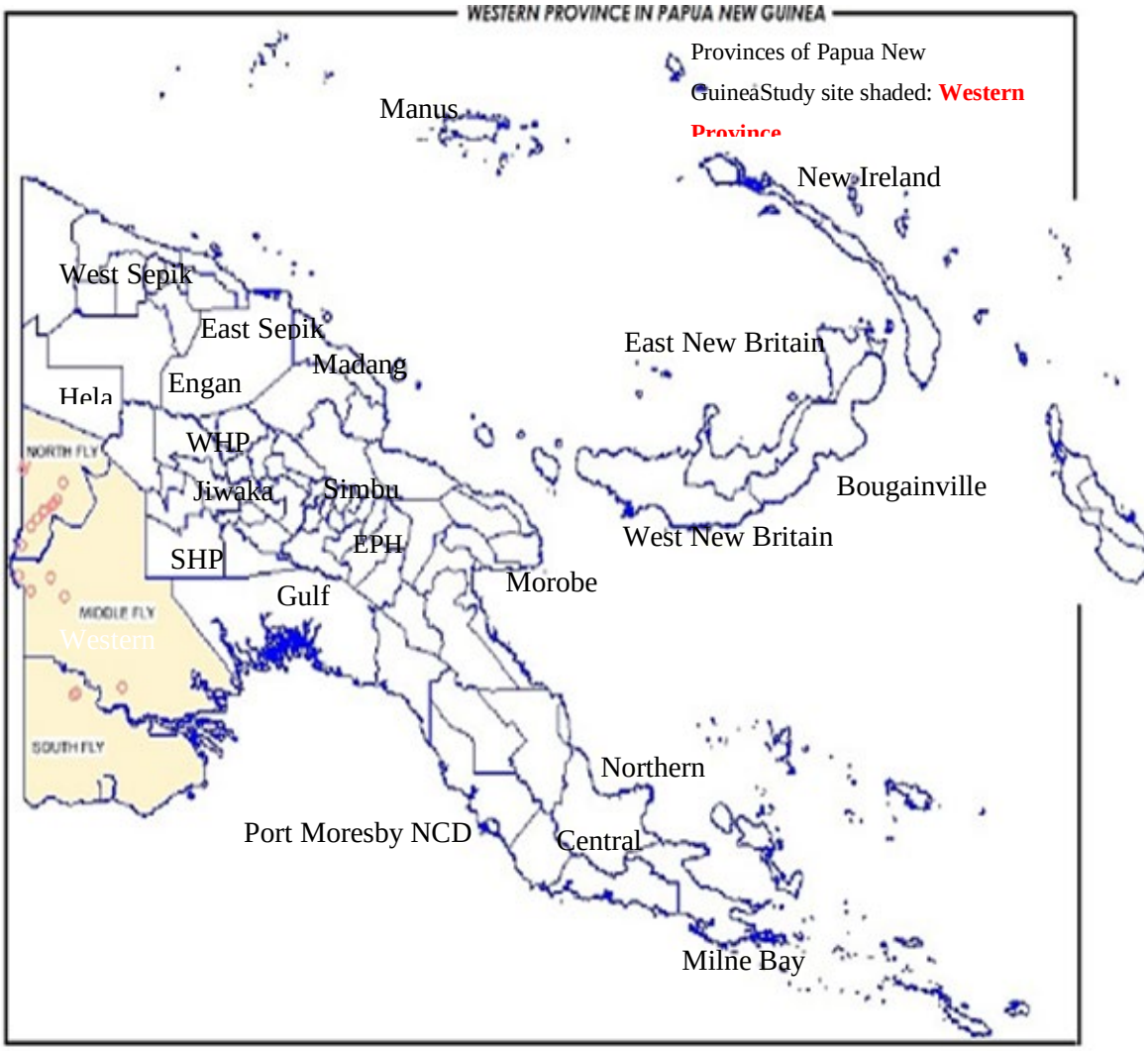

Figure iii. Map of Papua New Guinea – SHD outbreaks at study sites

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1 Chapter 1 Introduction and Background

1.1 Statement of the problem

Rural hospitals in Western Province Papua New Guine (PNG) have historically received patients that suddenly became unwell after consuming a meal of sago (Dr M Gena personal observations; Taufa 1974; Donovan et al. 1976). Their relatives reported that affected individuals passed red urine as they lay down, were unable to sit up or stand and remained recumbent soon after consuming a meal of sago pancakes. Fatal outcomes were reported among those who ate the same meal of sago. This natural history of the illness reported by clinicians and family members lacked important epidemiological features which necessitates a complete case definition.

This disease has historically affected sago eating communities of the East Sepik and Western Provinces of Papua New Guinea as reported by (Taufa 1974; Donovan 1974) where sago is widely consumed as their staple food, unlike other provinces where sago is consumed during food scarcity. Two clinicians highlighted the presumed link of this haemolytic condition to sago consumption. The first report was by Dr Tukutau Taufa, practising in Maprik hospital of the East Sepik Province (Taufa 1974) followed by Dr Kath Donovan of Balimo hospital of the Western Province (Donovan et al. 19760. They named this condition Sago Haemolytic Disease (SHD) in 1974 and 1976 respectively. Since this time, it had been a neglected condition lacking further epidemiological investigation. There was no clinical case definition to fully characterise the disease entity and no description of the pathophysiological findings in affected individuals. Such studies are important to confirm the diagnosis and aetiology of the condition. Case series reports have been the only source of clinical data with limited pathological evidence and response to treatment data. Taufa first reported 7 cases of SHD from Maprik communities of East Sepik province in 1974 (Taufa 1974). Similarly, Donovan reported 14 cases from communities of Western Province in 1976. The case fatality rate was 19% for the 2 case-series reports with a total of 21 cases. Moreover, both Donovan and Taufa reported the presumed association between stale sago consumption and SHD without conducting an outbreak investigation to confirm the suspected relationship (Taufa 1974; Donovan et al. 1976).

Awareness of SHD by health professionals (including community health workers, nurses, health extension officers and doctors) was and is limited. Management of known medical

emergencies are detailed in a standard treatment book which is widely distributed to health workers of all categories to use when evaluating patients for treatment. SHD is a medical emergency of rural remote communities, however this disease is not included in the standard treatment book due to lack of awareness by many health professionals and decision makers in national government health administration (Dr M Gena personal observations). Therefore, health workers must assess patients with acute anaemic hypoxia without guidance to start emergency treatment with oxygen supplements, intravenous rehydration, and ultimately blood transfusion to save these patients. Rapid response by early transfer of suspected SHD cases to hospital remains a critical first step to successful treatment as blood transfusion was a hospital-based treatment. Any delay experienced in the transfer of cases can lead to a fatal outcome. Death occurred in SHD predominantly in males who seemed less tolerant of acute severe anaemia with hypoxia compared to females. Death occurred at two different time intervals: either early within 4-12 hours of disease onset or on the $3^{rd} – 4^{th}$ day of the illness. Due to the exponential haemolysis, patients became debilitated suddenly by the presence of an acute anaemic hypoxic state forcing anaerobic cellular respiration by increased lactic acidosis as a cause of acute metabolic acidosis. Early death occurred in those less able to tolerate such a severe physiological derangement. The later death occurred in cases with severe illness for a prolonged period without blood transfusion and severe dehydration over time. Being unconscious led to dehydration as they were unable to rehydrate. Dehydration and severe acute anaemia were a lethal combination in SHD cases. This is because hypotension potentiates the effects of profound hypoxia that disrupts the acid-base balance further with deleterious effects on physiological functions. The severity of acute anaemia seen was caused by the primary effect of SHD's rapidly intense severe intravascular haemolysis. This led to the depletion of the red blood cell population in patients as evidenced by the massive haemoglobinuria. The generation of excess free haemoglobin exceeded the binding capacity of the haptoglobins causing it to be excreted through urine. Haemoglobinuria is a known cause of acute renal failure as a result of free haemoglobin impacted in the renal tubular cells, causing necrosis (Chugh et al. 1977; Chow et al. 2001). Dehydration led to hypotension and that further reduced renal perfusion and precipitated acute renal failure, more often as a terminal event (Kumar et al. 1973; Koffler et al. 1976; Needham 2005). Treatment for acute renal failure with peritoneal dialysis and renal dialysis were not available in Papua New Guinea during this study.

The locals' name for SHD is sago poisoning due to how they witnessed the disease being associated with the sago meal. This information was not appreciated by health professionals as they remained unfamiliar with SHD. In the past, familiarity with SHD was confined to a restricted group of health workers and doctors that worked in Maprik, Balimo and Rumginae hospitals due to existing local knowledge and history of management by their clinicians. Beyond this, the disease remained unknown to many health workers and doctors in Papua New Guinea including the principal investigator.

This, in part, explained the lack of awareness hence SHD is a neglected disease that affects remote communities that depend heavily on sago as their staple diet. Poor health and lack of access to health care are compounded during medical emergencies experienced in the rural remote setting where there is a lack of not only coordination but also efficient and effective transport required to transfer patients to receive life saving hospital-based treatment.

1.2 Anecdotal reports of sudden deaths

There have been anecdotal reports of SHD of sudden deaths in remote villages, refugee camps and hospitals in the Western Province. Communication undertaken by the principal investigator with Bishop Gilles Cote confirmed these abrupt deaths occurred amongst the refugee camps and other isolated villages. In 2012 a discussion with Dr. Evelyn Lavu, a haematologist from Port Moresby General Hospital, a teaching hospital, highlighted the sudden deaths among the Porebada villagers following a meal of sago. With dominant cultural beliefs, the communities related these deaths to sorcery. Therefore, they were unlikely to discuss them unless health professionals took a verbal post-mortem and inquired about meals consumed preceding the deaths. Councillor Titus Telua of the remote village of Fuma in the Nomad area disclosed the deaths of several families living in a single household followed a dinner consisted of sago cooked with oily red pandanus nuts (conedium) cooked in a mumu, in an earth oven of hot stones. He reported that no one survived (Dr M Gena personal observations).

Compensation payments were sought from Ok Tedi Mini Ltd by the villagers over the sudden deaths that occurred in communities affected by mining activities. They believed that the mining operations were responsible. This was expected as the mine had been blamed for various other reasons too, as reported by the Flew health assessment study of Fly River communities (Flew 1998).

1.3 Challenges related to this study

1.3.1 Health workers access to medical literature

Access to the medical journals, internet, and research by health workers in remote rural areas of PNG was non-existent at the time of commencement of this study (Dr M Gena personal observations). Therefore, only some health professions were aware of Taufa and Donovan's case series reports that described the clinical features and management of SHD. Furthermore, health professionals may not encounter SHD cases as their practice locations may not be in SHD endemic lowland areas where sago consumption as a staple diet.

1.3.2 SHD remained unrecognized by health professionals

The lack of clinical reports on SHD cases did not reflect its absence but was related to the lack of prior knowledge of SHD by health workers. This accounted for the lack of recognition of cases and fatal outcomes of cases fortunate to reach hospital. Moreover, the vital epidemiological data that characterized and linked SHD to lowland communities' staple food of sago remained unexplored. This occurred even though stale sago was suspected by early reports (Taufa 1974; Donovan et al. 1976). Grieving family members were dissatisfied over the sudden deaths of cases in hospital. They showed open aggression, physically assaulted health workers, and damaged the hospital over their disbelief that members of the family that were well that day had died in a matter of hours. Doctors who feared for their safety following such confrontations by distraught relatives consequently abandoned their posts at Kiunga hospital. This thereby deprived the hospital of doctors for many years. These episodes were confirmed by the hospital matron and longest-serving senior health workers and nurses like Siapan Sagi; who worked extensively in Western Province and were now stationed at Kiunga hospital (Dr M Gena personal observations and personal communications).

1.4 Air Transport for medical retrieval

Mercy flight was and is the main source of transport for effective and efficient medical retrieval of patients. A lack of access to efficient transport led to a delay for cases arriving at hospitals to receive urgent blood transfusion. The delay in travel time contributed to increased deaths experienced as late as day seven of travel. The use of a canoe - a traditional form of transport- required physically paddling over long-distance contributed to treatment delay and led to the deaths of cases. Furthermore, a lack of road networks prevented the use of motor vehicles as well as failure to improve efficient river ambulances. Availability of effective and efficient small fixed wing aircraft, motorized river ambulances transport and reopening village

airstrips will ensure medical emergencies cases timely access to urgent blood transfusion (a hospital-based treatment) and consequently, lower or prevent the higher mortality experienced by SHD cases. Isolated rural remote communities depend heavily on efficient fixed-wing aircraft or helicopters provided by resource developers and dedicated international charity organizations such as the Mission Aviation Fellowship (MAF). These mercy flights contributed to saving the lives of those unfortunate to be affected by medical emergencies (Dr M Gena personal observations and personal communications). MAF provided air-transport and hope to rural remote communities that have an operating village airstrip, as they can potentially reach the hospital in time to receive a life-saving blood transfusion or emergency surgery. The use of efficient transport optimizes opportunities to save lives in isolated remote communities that remain on the fringe and beyond the reach of existing health services. During colonial days, twin otters and cessnas were flying to most districts. Talair airline with the highland warrior insignia was owned and operated by Dennis Buchanan. This service was a logistical solution to the difficult terrain of PNG but no longer exists.

1.4.1 Operational status of rural airstrips

A critical link to early medical retrieval by air was the existence and operational status of rural village airstrips. Many rural airstrips were not maintained except for those that were operated and maintained by church organizations. Villagers can easily travel short distances by river or road to the nearest airstrip to allow planes or helicopters to land and transport patients to the nearest hospital for treatment. Villagers reported that they do travel to the nearest operating airstrip. Kapikam villagers informed the principal investigator that they were ready to allocate and clear land for an airstrip as that will help them with transport for patients and school children to access heatlh and education needs of their community.

1.5 Objectives of the study, research questions and study design

This overall objective of this study was to characterize SHD, including its epidemiological features, natural history, clinical features, and pathophysiological effects to determine its aetiology. This study also included the task of training health workers and communities to recognize the disease. This involved familiarizing health workers with the management of SHD and assurred communities of the best treatment, as blood transfusion which was only available at the hospital. Medical emergencies such as sago poisoning patients must arrive at the hospital as early as possible. Improved disease surveillance and rapid transfer of cases to the hospital for investigation and treatment of SHD improved the survival of cases. The

principal investigator established an open dialogue with all stakeholders, health workers, and communities. Through this, more health workers became familiar with and treated sago poisoning cases with the urgency required to save lives.

1.5.1 Study objectives

The specific objectives of the study and their respective locations in the thesis are presented in Table 1.1.

Table 1.1 Study objectives

Study objectives	**Chapters numbers**
1. Determine the natural history and clinical course of SHD.	6 & 7
2. Compare gender difference in disease severity	6 & 7
3. Compariegender difference in mortality	6 & 7
4. Compare number of complications associated with SHD	6 & 7
5. Determine incidence of the SHD among in affected community	5
6. Test all clinical samples	8
7. Identify risk factors and comorbidities of SHD	5, 6, & 7
8. Testing of hypotheses Nutrition & SHD Contaminated sago and SHD Anaemia of SHD compared to other types of anaemia	5, 6, 7, 8
7. Determine health status of rural remote communities	5
8. Compare access to health service by rural communities of Fly River and periurban communities around Kiunga Township	3
9. Provide evidence for logistic challenges confronting communities to access healh care by rural communities.	3, 4, 5, 6, 7, 8
10. Determine if fixed wing aircraft are suitable for delivery of goods and services into rural communities in order to piggyback medical retrievals from the remote villages.	3, 4, 5
11. Make recommendations to government agencies and standard treatment based on study findings.	9

1.5.2 Research questions

Table 1.2. shows specific research questions aligned with null hypotheses and the Chapters that relate to addressing these research questions.

Table 1.2 Research questions

Research questions	**Null hypothesis**	**Chapter numbers**
1. Do consumers of contaminated sago develop symptoms and signs of sago poisoning (life threatening acute intravscular haemolysis)?	1. Consumption of Consumers of contaminated sago do not develop sago poisoning.	6 & 7
2. Does gender of patients with sago poisoning determine the severity of illness?	2. There was no gender difference in the severity of sago poisoning between males and females	6 & 7
3. Is there a gender difference in mortality experienced by sago poisoning cases?	3. There was no gender difference in deaths between males and females.	6 & 7
4. Was there a dose response effect between the quantity of contaminated sago consumed and level of pre blood transfusion haemoglobin?	4. There was no measurable dose response effect between quantity of contaminated sago consumed and the reduction in the pre blood transfusion haemoglobin.	6 & 7
5. How is anaemia of SHD different to other anaemia in SHD impacted communities?	5. There is no difference between anaemia of SHD and of other causes in SHD affected communities.	5
6. Is there an association between nutritional status and severity of SHD?	6. There is no relationship between nutritional status and severity of SHD.	8
7. Is consuming contaminated sago truly associated with SHD?	7. There is no relatioship between consuming contaminated sago and SHD.	5, 6, 7

1.5.3 Study design

Different study designs were utilised for different purposes and at different times. Details of each study design and the duration of data collection are included in the respective Chapters.

1.5.4 Location of study

Extensive travel was undertaken during this study to villages in North, Middle and South Fly districts. All villages impacted by the Ok Tedi Mining Ltd. Project located along the length of Fly River from Kiunga to estuary were visited. This included the North banks as well as several of the South banks and Kiwai villages within the estuary of the Fly River. Figure 1.1 shows the location of the villages and hospitals visited to conduct SHD awareness education with health workers. to disseminate awareness and educate communities and health workers about SHD, specifically it's signs, symptoms, treatment, and the need to initiate early communication and medical retrieval of cases to the hospital.

Health education talks on SHD awareness and other common diseases were delivered to these communities located along the Fly River and Nomad region of Western Province. Provision of education and information created an environment that enabled the communities to participate in the prospective active surveillance. This allowed them to identify, report, and refer sago poisoning cases with the remaining implicated sago early to the hospital where the study could obtain pertinent data to achieve the overall objective of the study.

During the study most medical referrals were received by hospitals located in North Fly District. Kiunga government hospital received the most cases followed by Rumginae and Tabubil. Balimo hospital in the Middle Fly district also received cases when there were doctors in residence. Daru hospital was not visited during the study based on the pattern of transfer of medical retrieval northward.

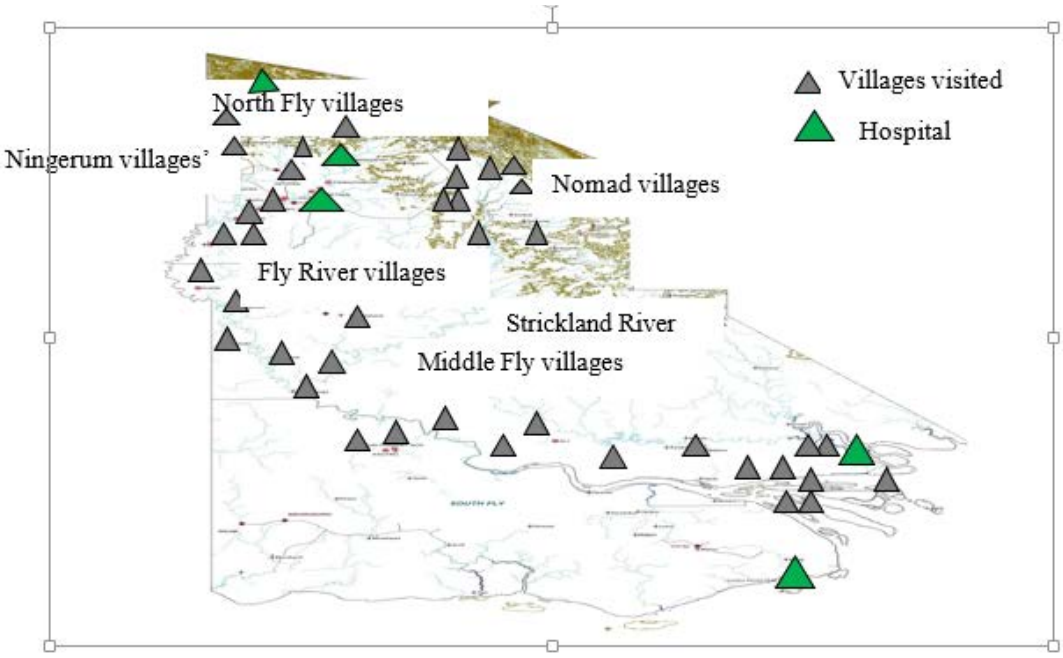

Figure 1.1 Villages visited for SHD awareness in the Western Province. Map by M Gena

1.6 Key findings

Chapter 2 is the Literature Review of SHD. It reviews other epidemiological studies, and the resources used for the successful completion of those studies in Papua New Guinean communities. The current study compared the strength of support of the technical team and resources used in those studies to the challenges of the SHD study undertaken among remote communities of Western Province.

Chapter 3 Methods and Methods describes all methods used to collect data for this study. It includes information about the location of 5 hospitals in Western Province, their respective health care providers, geographical areas of coverage, communication networks, aspects of travel and transport and methods to prepare sago. It also describes procedures for accessing medical records, the types of clinical and laboratory results accessed and methods for statistical analyses.

Chapter 4 provided the results of measuring the acess to health care provided by the government health care to residents of the peri urban informal settellers and the Catholic health care services provided to the Fly River villagers south of Kiunga town. Some of these villages existed near the Indonesian border. Proxy health indicators were compared between the communities with and without access to healthcare to assess health gains between these two groups that are described in Chapter 5.

Chapter 5 described the results of premorbid health assessment of SHD endemic communities. This baseline health assessment would a follow up to past studies done by Ok Tedi public health teams many years ago during the beginning of the mine operations. Results demonstrated the effect of treated bednet use and access to health care on burden of malaria types, microfilaria and nutritional status and biochemical health profile of these remote communities.

Chapter 6 consisted of a retrospective review on a case series study of SHD cases admitted to Tabubil, Rumginae, Kiunga, and Balimo hospitals and their clinical outcomes with and without treatment. This review provided the clinical features that establish a rudimentary case definition to guide the epidemiological study to be refined by the end of the study.

Chapter 7 describes a prospective study of sago poisoning outbreaks and identifies epidemiological characteristics of disease outbreak, the implicated food items, the incubation period thereby establishing the temporal relationship between the time of exposure to the time

of onset of the first symptom of disease and additionally the dose response relationship with disease presentation and outcome.

Chapter 8 identifies the specific changes in the pathophysiology of SHD which revealed effects of the disease that were not known previously. It discusses the additional treatments to reduce the severity of SHD and prevent early deaths.

Chapter 9 is the General Discussion and discusses the general findings of this study and results of hypotheses testing including mathematical modelling of dose response effects. A strategy to identify the aetiology of this disease is proposed and importantly this suggests ways forward to improve health and access to health and education for rural communities in Papua New Guinea.

The results of this study provided the evidence required to improve the clinical diagnosis and targeted treatment of SHD cases. As discussed above, a further objective of this study was to include SHD as a medical emergency condition in the standard treatment book to guide health workers in PNG. The results of this study were anticipated to educate government administration on the health requirements of medical emergencies that affect remote communities. Furthermore, this study highlighted the urgent need for efficient logistics such as fixed-wing flights and motorized water ambulances to facilitate rapid access to urgent hospital-based healthcare for vulnerable and disadvantaged remote communities.

2 Chapter 2 Literature review

2.1 Introduction

2.1.1 Overview of the health of Papua New Guineans

Papua New Guinea had a population of 7.2 million in 2006; of which 40% of the population was school-age children, the majority of whom were not in school. Only 23% of male and 17% of female children completed grade 7 or more according to the demographic health survey of PNG and world health report (PNG govt 2006; WHO 2014).

The overall health of Papua New Guinea was reported as poor due to considerable childhood and maternal mortalities that exceeded those of neighbouring countries in the Pacific. Papua New Guinea's reported mortalities included an infant mortality rate of 58 deaths per 1000 live births, a neonatal mortality of 29 deaths per 1,000 live births, < 1-year-old mortality of 29 deaths per 1, 000 live births, and 74 deaths in children < 5 years old per 1000 live births. Similarly, maternal mortality was reported at 733 deaths per 100,000 deliveries (PNG Government 2006). Women and children were reported to have poor nutrition and that reduced their level of health, rendering them more susceptible to infections. Lack of access to health care was a major contributing factor explained by various factors. Many communities existed beyond the reach of existing health services or were deprived of health care access by the closure of their village health facility. This was compounded by the blatant lack of dedicated transport required to deliver health care to disadvantaged communities (Kolehmainen-Aitken 1992; Connell 1997, 2005). There were existing examples where a lack of knowledge on other serious health issues also lead to fatal outcomes, such as the death of women during childbirth (Mola & Aitken 1984; Gillett 1991) and the high mortality of children (Duke 1999; Duke et al. 2002). There was also a lack of adequate means of travel within the villages to encourage early travel to the hospital. This deprived pregnant woman access to supervised delivery practices, hence accounting for the high maternal mortality. Those requiring urgent operative delivery needlessly die (Johnson 1971). These poor indicators of childhood and maternal health were reported in the 2006 demographic health survey undertaken by the National Statistics Office of the PNG Government (Rutstein 2000; PNG govt 2006; Black et al. 2008) and had also been eluded to by earlier reports (Johnson 1971; Mola & Aitken 1984; Duke 1999; Duke et al. 2002). This study further confirmed that 87% of the population of Papua New Guinea live in rural areas. They therefore had no access to running water or electricity, and had poor sanitation compared to urban populations.

Moreover, rural areas lack community-based or public health interventions that can improve health on a population-wide scale. Communities required open dialogue and meaningful communications and interactions with government extension services to have sustained health gains (Duke 1999; Black et al. 2008). Improvements were possible but must be accomplished by improving the communities understanding of health, enabling them to adopt practices that will sustain their health over time, this required multiple strategies (Health & Services 1990; Rychetnik et al. 2002; Pearson et al. 2003; Brownson et al. 2009; Brownson et al. 2010).

The main focus of the Government of Papua New Guinea's National Health Plan of 2001-2010 was on public health, emphasizing greater access to quality health care and improving skills of all categories of health workers. It also encouraged greater cooperation between organizations interested in public health interventions and health care delivery. They were encouraged to register with the government to operate in the country, resulted in an influx of non-government organizations engaged in providing health care, some embedded within the government health delivery systems (Gilson et al. 1994). Written reports and publications were abundant on the health of Papua New Guinea. Long term surveillance of central highlands communities affected by Kuru and Pig-bel were undertaken by interested researchers in close collaboration with veterinary scientists. The Kuru and Pig-bel studies utilized community-based activities and legislation to improve the villagers' knowledge on health issues affecting their population and enforced prohibition of cultural practices involving transumption to control the transmission of Kuru. The Pigbel epidemic was controlled by the government administration who prevented people from consuming the contaminated pork meat. Policemen and health workers were instructed to find stored pork meat from the villages' huts and burn it in bonfires. Long term control was achieved by vaccinating the affected population of children with the Pig-bel vaccine (Murrell et al. 1966; Alpers 1979; Murrell 1982; Murrell 1983; Murrell & Walker 1991; Alpers 2005; Murrell 2005; Alpers 2008). The Papua New Guinea government lacked focus on a planned and dedicated logistic solution for rural transport. This prevented rural communities from having access to hospital-based treatments for medical emergencies during epidemics. Hadoc transport assistance provided by government extension services and churches compensated for this gap. Without government presence in these remote communities, logistics requirements are shared by the Mission Aviation Flight (MAF) or a resource developer operating in the area. These organisations responds to calls for transport of sick people or mothers and

children to the nearest hospital to receive treatment (Moser 1989; Bracht & Tsouros 1990; Stone 1992; Botes & Van Rensburg 2000).

2.2 Review of community baseline survey of rural people

The greatest burden of morbidity and mortality were due to infectious diseases which have been challenging to treat and contain. This includes tuberculosis, with a burden further compounded by the emergence of multidrug-resistant forms in Western Province and other centres of PNG (Gilpin et al. 2008; Ballif et al. 2012). Concurrent poor nutrition and the burden of human immunodeficiency virus (HIV) infection set to increase other infectious diseases not only locally, but also globally (Jain & Mondal 2008). Moreover, hospital-based data revealed emerging non-communicable diseases and trauma-related injuries that were an additional strain on health-workers in hospitals (Benjamin 2001, 2007). Contrary to the accuracy of hospital-based data, there was a lack of village-based data that profiled the baseline health status of communities to determine their pre-morbid health status. This may establish risks to health that needed to be mitigated, highlight a need to boost the immune system or to aid individuals with metabolic syndrome. Premorbid health indicators help determine and prioritize a targeted plan of intervention to mitigate particular health risks prevalent in these communities (Brownson et al. 2010).

Health is an interaction between human behaviours and the environment. Therefore, health conditions must be studied in the people living in particular communities so community-based interventions can be conducted. (Rychetnik et al. 2002; Brownson et al. 2009; Brownson et al. 2010). Prevailing poor nutrition and poor access to health care by remote communities reduced their capacity to respond to other insults, such as the effects of SHD. This consequently increased the likelihood of fatal outcomes without rapid intervention. Minimizing the duration of time between the onset of illness and treatment determined the successful outcomes for medical emergencies such as SHD. Prior knowledge of any prevailing comorbidities and the baseline health of rural communities has contributed positively towards formulating plans or guides and assesses interventions to treat health risks with benefit for the overall health of communities (Ashwell 2008; Brownson et al. 2009; Ashwell & Barclay 2010; Brownson et al. 2010). Populations can collectively improve the health of their community by adopting and implementing specific strategies to reduce or eliminate identified risks so to lessen the burden of infectious, non-communicable and

foodborne diseases at the source because prevention is better than a cure (Feachem 1986; Currie et al. 2003; Coote 2004).

2.3 History of Sago Haemolytic Disease (SHD)

A total of 21 cases of SHD were reported in two case series by Taufa and Donovan from Maprik of East Sepik province in 1974. These reports preceded the Suki and Pangoa Island outbreaks in Western province that reported four deaths respectively, resulting in a case fatality of 19%. Taufa reported 7 cases in 1974 from Maprik hospital whilst Donovan reported 14 cases in 1976 from Suki in South Fly, and Pangoa Island of Lake Murray, in the Middle Fly Districts of the Western province (Taufa 1974; Donovan et al. 1976, 1977). Clinical features reported by Taufa and Donovan were vomiting, generalized physical weakness, fever, headache, mental confusion, drowsiness, and loss of consciousness accompanied by severe anaemia with pallor, jaundice, dark red urine and rapid fatality. The premorbid state of those patients was not clearly described, but their reported illness was sudden in onset. Evidence attributed to intravascular haemolysis by earlier reports was based on circumstantial evidence of severe anaemia, jaundice, and bilirubin in the urine. This was accompanied by dark brown discolorations of serum as a presumed indicator of methaemoglobin and the dark red colour of urine with an absence of erythrocytes on urine microscopy was assumed to be haemoglobinuria. Treatment with blood transfusion improved and alleviated patients' symptoms of physical weakness and they regained consciousness. Cases considered non-severe were treated with iron and folic acid tablets to stimulate red cell production and they gradually improved over 2 weeks, regaining their strength and mobility. Such reversibility of symptoms and signs confirmed these as effects resulting from patients having severe anaemia with critically low haemoglobin. These cases experienced a longer duration of morbidity as they made a slow but gradual improvement to regain physical strength and full mobility. The scarcity of blood transfusion in rural hospitals and multitude of cases were additional reasons to adopt a conservative management plan.

A historical record of SHD in a village register dating from 1961 was discovered by Taufa whilst on village health patrol in the East Sepik province in 1974. It recorded an incident of conflict among members of the community following the sudden death of 3 adult members of one family that was linked to a meal of sago. Police and patrol officers intervened to keep the peace. Moreover, SHD was a name coined by doctors working at Maprik hospital to described cases presented with unexplained acute anaemia that were saved with a blood transfusion, but

clinicians were baffled about the cause. Taufa acknowledged that SHD was specifically mentioned during the handover meetings between incoming and outgoing doctors at Maprik hospital. No antibiotics were prescribed but steroids were administered by other practitioners without any effect. Both Taufa and Donovan hypothesized mycotoxins as an aetiology of SHD (Taufa 1974; Donovan et al. 1976, 1977).

In 1977, Donovan in collaboration with an international laboratory undertook the first microbiological study and mycotoxin analysis of implicated sago to test the hypothesis of mycotoxins as a proposed aetiology of SHD. Implicated sago was cultured at the Port Moresby General Hospital Pathology and isolates were couriered to the Central Public Health Laboratory in London. Organisms were identified as those associated with brewing, tanning and fermentation industries and others were soil organisms. The only two organisms isolated known to produce toxins were *Bacillus cereus* and *Paecilomyces lilacinus* but these were not known to cause such severe disease as SHD. It was therefore concluded that they were unlikely to be the cause. Mycotoxin analyses were also reported as negative. Subsequently, Donovan initiated surveillance of SHD by setting out a flow chart aimed at providing a guide for collections of implicated sago and blood samples of cases for targeted analysis in a new outbreak. Since then, there had not been any reports of SHD until the current study.

2.4 Basal microbial study of non-implicated sago starch

Thirty-two years later, in 2006, Greenhill conducted a detailed investigation of sago starch basal microbial content in non-implicated sago that identified a haemolytic property of filamentous fungi (Greenhill et al. 2007a; Greenhill et al. 2007b; Greenhill et al. 2010b) in addition to overt colonization of sago starch by bacteria and fungi (Greenhill et al. (2005a), 2005b); Greenhill et al. 2006; Greenhill (2006); Greenhill et al. (2007a); Greenhill et al. (2007b); Greenhill et al. (2010b)). The microbiological investigations were conducted on sago samples that were primarily destined for domestic consumption. These studies were unable to conclusively prove or disprove the association of SHD with microbial contamination of sago starch but for the first time showed bacterial and fungal contamination of this staple food that sustains remote communities. These studies confirmed the presence of foodborne pathogens indicative of faecal contamination of sago starch produced by families for consumption that did not have access to alternate food sources. Sago was the only food that was readily available as *Metroxylon sagu* grew in abundance throughout the Western Province in the swampy environment, which was unsuited to other food crops. Consuming faecally-

contaminated sago posed a significant and constant threat to the health of rural populations; whose health was regarded as poor compared to urban settings in Papua New Guinea (Gillett 1991; Connell 1997; Duke 1999; PNG govt 2006).

2.5 Characterization of haemolytic compounds in sago starch

Greenhill's identification of the haemolytic activity of *Penicillium citrinum* was confirmed in a later study (Atagazli et al. 2010). The haemolytic compounds were further characterized as fatty acid methyl esters on chromatography and mass spectrometry and identified as free fatty acids of saturated and unsaturated forms designated as C16-C20 on proton nuclear magnetic resonance. Analysis of implicated sago showed a heavy concentration of free fatty acids content at 78,722 mg/kg dry weight (Pue et al. 2008). This was concluded to be evidence for fungal colonization of the sago, but the question remained as to whether this was responsible for causing SHD.

2.5.1 *In vivo* testing of free fatty acids as a cause of SHD

In vivo tests to reproduce SHD in the laboratory were also conducted by adding commercial free fatty acids to sago and fed to rats with either high or low protein diets. A control group was maintained on commercial feed without free fatty acids. Intravascular haemolysis was confirmed with the presence of haemoglobin in the urine of rats fed low protein and sago that included the free fatty acids. The rats were euthanized to obtain tissues for a histological examination which showed the spleen had increased deposits of haemosiderin that were also present in the urine. Any conclusion linking the presence of free fatty acids and SHD needed repetition to determine the bacterial and microbial content in implicated sago. The isolation of the preformed natural toxin(s) produced a secondary alteration in erythrocyte membrane function, this was postulated as the mechanism of haemolysis as proposed by this study (Weed & Reed 1966). Furthermore, the haemolytic effect in SHD cases can be studied by labelling red cells used in blood transfusion and quantifying both red cell destruction and survival of red cells and then relate this to the concentration of preformed toxin (Braga et al. 2000).

2.6 Lack of clinical and pathophysiological data on SHD

Central to the high mortality of SHD was the lack of understanding of the epidemiological details needed to characterize the disease and facilitate the study of its aetiology. Consequently, there was no specific treatment that can be administered such as antimicrobial

agents or antitoxins. In the absence of specific treatment, supportive symptomatic treatment remained central to improved outcomes. This included replenishing the red cell population of SHD cases as a medical emergency intervention. Early researchers suspected the disease to be a mycotoxicosis and treated it symptomatically by correcting the anaemia with blood transfusion whilst maintaining good hydration and also administered iron and folate to those that were not severely affected, led to gradual recovery (Taufa 1974; Donovan et al. 1977). Irrespective of the few people who knew about the disease, many health workers in lowland communities were unaware of SHD signs and symptoms and its status as a medical emergency condition that required urgent resuscitation to improve survival of cases. The intention of this study was to fill the gap with the results of case definition, pathophysiological changes that explained the clinical features and provided the evidence-based treatment with blood transfusion whilst investigate the aetiology by clinical epidemiological investigation of the outbreaks.

2.7 Lack of robust epidemiological data on SHD

In addition to the absence of a detailed aetiology for the disease as well as incomplete clinical and pathophysiological knowledge, there is inadequate epidemiological data for SHD. The lack of data is a major impediment to our understanding of the illness, to a point where we were unable to confirm the suspected temporal association between stale sago consumption and the development of SHD. There was a notable absence of timeline of exposure (yet to be identified) to the time that the first symptom appeared to accurately determine the incubation period. This would enable a correlation between the illness and sago consumption as the exposure establishes a temporal relationship. Furthermore, a dose-response effect relationship could not be adequately determined from the available literature on SHD. There was no description of the severity of illness in comparison to the quantity or quality of sago consumed preceding the outbreak. Essentially, the SHD clinical description remains unchanged from the early reports (Taufa 1974; Donovan et al. 1976, 1977).

2.8 Review of epidemiological studies of rare diseases in PNG

Boutique illnesses such as Kuru and Pig-bel from rural communities of the central highland provinces of PNG were intensively described when sufficient resources were available. They have been extensively studied by clinicians of regional hospitals and supported by scientists of the Papua New Guinea Institute of Medical Research. Both the research institute and regional hospital are conveniently located in Goroka, Eastern Highlands which were connected by an

extensive road network within its province as well as to other highland and coastal provinces by the Okuk highway of PNG. The Western Province has a vast area but little to no road system. In its place, the extensive river system serves as their roads. Unless modern transport was used on the river ways, traditional canoes would be the means of transport. The mining town called Tabubil located in the extreme north. Sago haemolytic disease affected isolated rural remote communities that have poor access to health care depend on mercy flights by fixed-wing planes or helicopters to transport cases to hospitals in Western Province. As there were no road networks that connected these villages to the hospital except for the 140km Kiunga -Tabubil private road operated by Ok Tedi Mining Ltd. Moreover, there was no research institution in the Western Province to aid the investigation of SHD. The decline in health as reported post-reform throughout PNG has had a detrimental effect on the Fly River Government administration's ability to maintain effective health service delivery to inhabitants of remote communities in the Western Province. A progressive and sustained closure of government-operated aid posts in remote communities has led to collapse of the government health care delivery system. Over many years of neglect, the communities have been heavily dependent on church health services and resource developers to continue to provide health care in the Western Province (E 1990; Kolehmainen-Aitken 1992; Connell 1997; Duke 1999; Connell 2005). Government hospitalswere continued to be supported by both Ok Tedi Mining Ltd. and AusAID. The PNG government mandated decentralizing was a myth for community development (Schoeffel 1997). Without the presence of a research institution and no proximity between health care delivery and research, this study was undertaken as a PhD project to investigate causative factors of SHD at James Cook University. The university functioned as the research institution, alongside a technical team of researchers consisting of A/Professor Jeffrey Warner and Professor Bruce Gummow. Both are familiar with conducting research in remote areas of the Western Province and mine impact on animal health respectively. Inevitably, with the clinical acumen of the principal investigator a research team was formed on the common interest of SHD to finally identify the causative factors by conducting this study.

2.8.1 Investigation of other boutique illnesses in PNG

The Papua New Guinea Institute of Medical Research (IMR) was located in Goroka, Eastern Highlands Province. Its close proximity to Goroka Hospital facilitated discussion and collaboration between the clinicians and researchers which led to improvements in clinical care for patients. The interplay between the researchers and their proximity to the point of

care was evident during the study of Kuru - a transmissible spongiform encephalopathy among the Fore people of Eastern Highlands Province and Pig-bel (enteritis necroticans) that affected all the highland provinces of PNG. In contrast, the investigation of SHD was undertaken by interested clinician not aligned with research institutions and collaborated with scientists not aligned with clinical practice. Such malignment of interested researchers resulted in the disjointed research that lacked the continuity to study all facets of this disease. As such, there has been a prolonged period where no research was conducted into sago haemolytic disease and there was an absence of publications in the medical literature. This contributes to SHD's high mortality due to the lack of recognition by health workers and doctors practicing in the lowland region of PNG.

Where researchers and clinicians aligned and communicated well the collaborations produced intended results. The establishment of the IMR in Goroka played a critical role in providing proximity to clinicians at the Goroka Base hospital. This allowed the researchers to progress their investigation into Kuru and was followed by laboratory studies that proved the transmission of the prion inducing Kuru in chimpanzees (Alpers 1979; Hadlow 1995; Alpers 2005; Collinge et al. 2006; Alpers 2008; Collinge et al. 2008; Hadlow 2008) and Pig-bel(Murrell et al. 1966; Murrell 1982; Murrell 1983; Murrell & Walker 1991; Murrell 2005).

Such a detailed study on Kuru in PNG provided knowledge and insight into the diagnosis, control, and prevention of bovine spongiform encephalopathy globally in the early 1990s. (Epstein & Haywood 1997; Nathanson et al. 1997; Johnson & Gibbs Jr 1998; Ireland 2003; Smith 2003).

2.9 Natural history of Kuru

Studying the natural history of disease provides clues to the possible aetiology, such a study was not done for sago haemolytic disease until now. These required a detailed approach of watching and waiting to study the outbreaks as they occurred to gather accurate epidemiological details to assess the possible cause of SHD. This was done by this study, characterizing it as a toxicosis with an unidentified preformed toxin yet to be identified even after 50 years since the first reports of SHD. Kuru had no treatment, and the researchers had the luxury of time to observe the disease to it's extinction.

The study of Kuru provided an excellent description of the natural history, but it had taken the lifetime of one researcher, Dr. Michael Alpers, to live among the affected communities and

characterize the details of the disease. Collaboration allowed communication between researchers and may quickly contribute meaningfully to advance the research similar to the Kuru study where William Hadlow, a veterinarian, in 1959, informed the Kuru researchers that the brain histopathological changes in Kuru resembled the changes he had seen in sheep suffering with scrapie (Hadlow 1995, 2008).

Kuru was a fatal neurodegenerative disease that progressed to death within 12 months of the onset of physical neurological symptoms. Malnutrition and respiratory disease in the supine position were terminal events (Alpers 1979, 2005, 2008). The absence of vertical transmission was confirmed (Amyx et al. 1981). Early recognition of the similarities between Kuru to bovine spongiform encephalopathy facilitated urgent control measures by culling of contaminated cattle population on farms in United Kingdom. This measure isolated contaminated meat from consumers (Gajdusek & Zigas 1959; Alpers 1979; Trevitt & Singh 2003; Alpers 2005). This was a highly collaborative and effective third world research project used by developed countries to protect the health of population from a new epidemic of bovine spongiform encephalopathy among the meat eaters of developed countries (Alpers; Alpers 1979; Lindenbaum 2008).

Anthropological studies indicated that exposure was associated with mortuary practices (Lindenbaum 2009) and the trend was captured by a long term surveillance system to include the period from inception to completion (1957 to 1961). Researchers observed the time line of the old and new cases and monitored deaths to reveal a trend in mortality of 1000 deaths in the first 5 years, this declined progressively which indicated the end of the epidemic (Alpers 2008). The lack of new cases meant the affected community observed the law that prevented their mortuary practice, and therefore exposure was eliminated. This community remained under constant surveillance to monitor for the appearance of new cases. The only non-medical intervention that effectively interrupted Kuru transmission (Collinge et al. 2006) was the colonial administration law that prevented the handling of dead humans as food. The colonial administration enacted legislation to prevent cannibalism and those practicing it were punished by the law. A non-medical and a public health measure such as the one legislated ultimately ended the Kuru epidemic amongst the Fore tribe. Alpers used the term human transumption rather than cannibalism due to its inherent negative connotation of the word cannibalism. A global pandemic affecting meat eaters in the developed world was prevented using the findings of the Kuru study led by Dr Michael Alpers. He introduced a group of third year medical students from UPNG (that included the principal investigator) to the Kuru

patients in their houses during a field visit at Okapa in the Eastern Highlands Province of PNG.

Experiments in laboratory animals confirmed the infectivity of the prion the critically needed evidence base to prevent transmission and contamination of meat production permanently on a global scale. The farm practice of producing animal feeds from remnants of the animals in abattoirs was exposed as the transmission point that contaminated the meat produced for human consumption. The production of animal feeds induced animal cannibalism. Measures were taken to prevent the transmission of prion in the cattle meat. Cattle on farms were culled and burnt and animal feed production was changed to avoid feeding same-species feed to farm animals (Bradley & Wilesmith 1993; Nwankiti et al. 2013) Additionally, butchery practices were improved to prevent cross contamination of meats with neural tissues. All meat were tagged to ensure tracking from the farm to shops to plate (Fisher et al. 2005). There had the potential for similar benefits to humans to be derived from a detailed study of SHD.

2.10 Natural history of Pig-bel

Pig-bel or enteritis necroticans affected highlanders of PNG but has been reported in other third world countries. It historically affected famine-stricken communities in Europe during the post-war famine period, therefore it was the resurgence of an old disease provided the background of poor nutritional of affected population.

Pig-bel (a local pidgin name) meant pig in the stomach or abdomen. Technically, Pig-bel is known elsewhere as enteritis necroticans. It commonly affected children of the central highlands in PNG. The name is derived from the diseases association with pork meat ingestion that was prevalent during the pig festivals which are regular traditional community celebrations (Murrell et al. 1966; Murrell 1982; Murrell 1983; Murrell & Walker 1991; Murrell 2005). The multiple risk factors of ingesting highly contaminated meat (a rich culture media for *Clostridium perfringens*) by a predominantly vegetarian population with low secretions of pancreatic proteolytic enzymes was a lethal combination (Murrell et al. 1966; Lawrence & Walker 1976; Lawrence 1979; Lawrence & Cooke 1980).

Pig-bel was closely associated with the traditional pig festival in the highland communities of PNG. This was a significant cultural activity that maintained the family and tribal linkages, social cohesion, competitiveness, and cooperation that sustained village life for peace and respect and maintained their tribal differences. The ban imposed on the pig festival as the

source of contaminated pork meat effectively permanently eliminated a traditional social and cultural network (Murrell et al. 1966). *Clostridium perfringens* in pork meat was not neutralized or killed by proteolytic enzymes in the predominantly vegetarian population because a vegetarian diet of the central highland population in PNG did not stimulate the production of these enzymes. The ingestion of this enriched culture media of *Clostridium perfringens* caused acute inflammation and necrosis of the entire length of the small intestine. Laboratory studies revealed that the rapidly necrotizing effect on the intestine were due to a toxin. The severe effects of this disease in affected individual, prompted drastic measures for treatment, prevention, and control. Surgeons were forced to remove large sections of the intestines of cases to improve survival. Police and public health workers were dispatched into villages to build bonfires and burn all meats stored from the pig festival. Without a pig festival, the traditional village singsing (traditional group dancing) ceased. The epidemic of Pig-bel was controlled with mass vaccination of children against Pig-bel in the affected regions of the central highlands (Murrell et al. 1966; Lawrence et al. 1990; Murrell 2005).

SHD is an acute illness like Pig-bel but differs in its underlying pathology. SHD presents as an acute anaemia with systemic symptoms of profound hypoxia without a focal infection. In Pig-bel a focus of infection in the small intestine occurs that rapidly kills the entire small intestine, giving rise to fulminant septicaemia and death in young children (the main feature of Pig-bel). Through the collaborative efforts of clinicians and researchers, they identified important contributing factors in the epidemiology of Pig-bel. Future epidemics were prevented by vaccinating children against Pig-bel However, vaccinations were not sustained and there was no program to improve nutrition, Recently, there have been reports of a resurgence of Pig-bel among children in the highlands (Poka & Duke 2003). This readily highlights the need for public health interventions that addresses the root cause of the disease.

It was proposed that the vegetarian diet needed to change to accommodate a regular intake of protein to stimulate the production of proteolytic enzymes by the wider communities rather than the current dangerous episodic exposure. The cooking of pork is predominantly done through steam created by pouring water over food placed on heated stones (called a mumu). This is a ground oven constructed by digging a hole in the ground. The holes are deeper and may resemble a drain depending on the quantity of food to be cooked. The hole is laden with firewood splinters to ignite the fire. Above the hole a heap of firewood is stacked like a double layer bridge, then medium rounded size rocks are placed in a well-rounded heap. The fire ignites the wood in the hole which burns the pile of timber holding the rocks, this in turn

heats the under-surface of the rocks. The bridge collapses with the rocks and more firewood is added to increase the heated surface on the top of the rocks. When the firewood has completely burnt into ashes, the stones are ready. The hole full of heated stones is encircled with banana leaves, with more leaves placed over the hot rocks. A cradle bed of banana leaves is placed to prevent the food from burning. Layers of food are then placed on the hot leaves, separating the food from the hot rocks. The food is encircled with more leaves so a pile is created. When this is completed, water held in containers of long bamboo pipes is held over the pile of food and poured down, so it travels through the food onto the hot stones to generate steam. More and more banana leaves are layered over the mumu to securely trap the steam and cook the food well. After two hours the leaf wraps are removed, and the cooked food is served out to members of the community. The rocks are left in the hole for storage until the next cooking session when they will be dug out for reuse. Should the stones be under heated, they can transfer heat resistant bacteria into undercooked meat, or the food may only be partially cooked. This can therefore produce a rich culture media allowing bacterial growth which infects those that consume the meat (Murrell et al. 1966; Murrell 1982; Murrell 1983; Murrell & Walker 1991; Murrell 2005).

2.10.1 Unknown natural history and epidemiology of SHD

There was no epidemiological data available on SHD to shed light on associated factors except the presumed association with sago consumption when the disease was first described (Taufa 1974; Donovan et al. 1976, 1977). Despite Donovan establishing a plan to investigate new cases of SHD, there was no existing system to conduct an intensive laboratory investigation in the Western Province. The rural laboratory microbiological services were absent as were haematological and biochemical tests on clinical samples. There was little to no objective scientific basis with which to measure the effects of SHD or investigate the microbiology of clinical and implicated sago. Clinicians working in such remote settings had neither research support nor a public health reporting system that investigated unusual diseases. To improve greater collaboration, the principal investigator (a clinician who was familiar with SHD) sought funding from the Ok Tedi mine to join scientists at James Cook University to study SHD clinical epidemiology. This was to fill in the existing knowledge gaps and contributed to improvedg clinical outcomes of cases whilst investigating SHD and its aetiology. The collaborative team finally conducted a study on SHD's clinical epidemiology in the Western Province.

2.10.2 Long term surveillance and collaboration

There was a need for a long-term surveillance system as described for the Kuru study. Appropriate collaboration between researchers and clinicians was also needed as demonstrated in long term studies. Collaboration allows communication between researchers and may quickly contribute meaningful advances in the research similar to the Kuru study by William Hadlow in 1959. Such interactions enriched and facilitated the laboratory investigation that proved prions as the transmission agent for Kuru (Hadlow 1995, 2008). On a positive note, for SHD, Dr Kath Donovan's original manuscript of cases was given to the principal investigator by Dr Daniel (Priest of Rumginae Hospital) during my field work formed a continuity from the past to the incoming researcher.

There has not been long term surveillance of SHD since the first report 50 years ago by concerned clinicians, Taufa and Donovan (Taufa 1974; Donovan et al. 1976). Thirty-one years later, Greenhill conducted a basal microbiological study of non-implicated sago that identified haemolytic compounds. Thirty-nine years later; Pue characterized the haemolytic compounds as free fatty acids in an unpublished thesis. Forty-one years later, this study fills the gaps in epidemiology and pathophysiology of SHD to fully characterized the disease and shed more light on its possible aetiology in addition to establishing the premorbid or baseline health of SHD endemic communities as its source population.

2.11 Pathophysiology

2.11.1 Anaemia

The normal red cell life cycle is 120 days. Bone marrow produces new red cells to replace the loss of senescent red cells that have reached the end of their lifespan. These old red cells are degraded in the spleen and liver and components of the red cells are recycled. A balance always maintained between the quantities of old red cells removed and the release of new red cells into the circulation. Increased production of red cells in bone marrow occurs only when that equilibrium was disturbed, such as during increased red cell loss due to haemorrhage or haemolysis and reduced production of red cells by the bone marrow (Hall 2010). Anaemia can be sudden with an acute onset or gradual and chronic. The steady-state of the body maintains a haemoglobin between 144-166 gm/L for men and 122-147gm/L for women (Gomella & Haist 2004). The body exerts a tight control by breaking down and recycling components of haemoglobin. This involves removal of 1-2% of senescent red cells and salvaging components of globin, iron, and bilirubin for recycling and replacing with an equivalent quantity of 1-2 %

reticulocytes (Hall 2010). Hypoxia activates the kidney to release erythropoietin that stimulates the bone marrow to produce new red cells (Eckardt et al. 1989; Ge et al. 2002).

2.11.2 Bilirubin metabolism

Free haemoglobin released into the circulation during intravascular haemolysis is toxic. It is removed through binding to haptoglobins and hemopexin which are recognized scavengers that transport it to macrophages and monocytes within the reticuloendothelial cells. These catabolize the free haemoglobin into individual components of iron, globin, and bilirubin to be recycled in the synthesis of new erythrocytes. A depletion or absence of haptoglobin indicates significant intravascular haemolysis (Hall 2010). Additionally, the free haemoglobin converts to ferric haemoglobin upon oxidation and binds to hemopexin. This is then transported to the liver for metabolism and recovery of ion, globin and bilirubin (Rother et al. 2005).

The globin component is released to be reused in the production of amino acids. The iron binds to transferrin and is transported to the bone marrow to be incorporated into new red cell production and is tightly controlled for recycling. The efficiency of iron recycling is disrupted because of severe intravascular haemolysis as it leads to the renal excretion of haemoglobin with intact iron into the urine. This subsequently leads to iron deficiency, anaemia, and stimulates the bone marrow to regenerate new red cells to compensate for the depleted red cells population. The insoluble bilirubin binds to albumin and is then transported to the hepatocytes (liver cells) where it is converted to conjugated bilirubin and excreted into the bile. Under normal physiological conditions, the normal values for total bilirubin are 5.1-17mmol/L, direct bilirubin is 1.7-5.1mmol/L and indirect bilirubin 3.4 -12mmol/L (Gomella & Haist 2004).

2.11.3 Biochemical markers of haemolysis

Biochemical markers defined the type of haemolysis as either extravascular haemolysis when red cells are broken down in the macrophages in the liver and spleen, or intravascular haemolysis when red cells destruction occurred within the circulation. Elevated levels of lactate dehydrogenase (LDH) were common to both types of haemolysis as released by the haemolysed red cells. Therefore, the quantity correlated to the population of red cells destroyed as described in inherited diseases such as sickle cell disease (Kato et al. 2006; Kato & Taylor 2010; Christensen et al. 2011; Kupesiz et al. 2012). It was common to see an increased reticulocyte count in response to anaemia due to blood loss as haemolysisof red cells (Mehta 1994; Tefferi 2003). Jaundice occurs during extravascular haemolysis and only

appears in intravascular haemolysis if there is delayed excretion of bilirubin (Neale et al. 1958). Recurrent haemolysis intermittently over many years such as commonly associated with sickle cell disease, the resulting gall stone formation or cholelithiasis as a recognized complication that presents as recurrent right upper quadrant pain. Other complications of a folic acid deficiency and bone pain with enlargement of frontal bones and the maxilla observed in both thalassemia (Vichinsky 1998; Galanello & Origa 2010; Haidar et al. 2011) and sickle cell disease (Diggs 1967; Lee et al. 1981). Haemoglobinuria, haemosiderin in the urinary sediment, free plasma haemoglobin, and depleted haptoglobin levels found only in intravascular haemolysis in addition to increased LDH and reticulocyte response, which are common to both types of haemolysis (Hall 2010).

Haptoglobin levels were usually present as 100mg/dl but this is drastically reduced to low or absent in accelerated haemolysis as it binds the toxic free haemoglobin and is transported to the liver to be detoxified (Neale et al. 1958; Körmöczi et al. 2006), hence its low or depleted level which can indicate the intensity of the intravascular haemolysis. Free haemoglobin binds to nitric acid to form nitrate and methaemoglobin whilst the remainder is reabsorbed by renal tubular cells. When all haemoglobin scavenging mechanisms were saturated, haemoglobinuria with haemosiderin occurs (Brus & Lewis 1959; Jelkmann & Metzen 1996). Tissue hypoxia produced by acute anaemia during haemolysis stimulates erythropoietin release from the kidney which stimulates erythroid hyperplasia of the bone marrow to increase both red cell production and the release of reticulocytes (Jelkmann & Metzen 1996). Newly formed red cells take 5- days to enter the circulation, a delayed response needs to be considered in cases that have severe intravascular haemolysis. They will require an urgent blood transfusion to alleviate hypoxic effects and re-establish aerobic cellular respiration to normalize acid-base balance and prevent fatalities (Finch & Lenfant 1972).

2.11.4 Clinical features of acute anaemia in SHD

The clinical features of SHD included headache, dizziness, global weakness, drowsiness, unconsciousness, and death. These signs in SHD were indicative of severe hypoxia with potential acid-base disturbance because of deficient oxygen supply to cells to sustain cellular respiration under anerobic conditions. Without adequate oxygen supply, a direct result of severely depleted red cells numbers, there was a critical reduction in capacity to transport and deliver oxygen to cells. This results in cellular hypoxia which adversely affected cellular respiration and had the potential to produce altered myocardial function by decreased vascular response to catecholamine, which affects the flight or fight response (Fishman 1976;

Goligorsky 2001; Curtis & O'Keefe 2002). The rapid loss of red cells and haemoglobin through rapid and severe intravascular haemolysis leaves the body vulnerable to prolonged hypoxia. This can cause irreversible damage to the integrity of cells and their viability, ultimately leading to organ damage or fatal outcomes. Studies have shown that hypoxia regulates cell metabolism by downregulating metabolic demand to match low energy levels (Wheaton & Chandel 2011).

2.11.5 Homeostasis under hypoxic condition

Hypoxia has varying consequences on the body; it reduces energy production, diminishes physical activity, can render loss of consciousness, and even lead to death of the affected individual. The body's approach for adapting to profound hypoxia is to increase the delivery of oxygen to cells by a compensatory increase in the heart rate and stroke volume to maintain perfusion to cells. A depleted oxygen transport system that cannot be sustained by compensatory mechanisms is unlikely to supply sufficient oxygen to maintain normal cellular respiration and other physiological functions and will therefore lead to fatal outcomes. Oxygen is essential to cellular respiration and optimizes maximized energy production to sustain life (Saikumar et al. 1998). The presence of oxygen allows oxidative phosphorylation for efficient production of adenosine triphosphate (ATP) which is dramatically reduced during anaerobic cellular respiration. Without sufficient ATP, the adverse physiological effects of acidosis develop and this compromises homeostasis through the acute prolonged state of hypoxia. Glycolysis under anaerobic cellular respiration leads to the accumulation of pyruvate and convertsed to lactic acid which reduces pH and produces metabolic acidosis. This condition was easily reversed when oxygen delivery to cells reaches a sufficient level. This presence of oxygen drives oxidative phosphorylation to improve energy production and reverses other adverse physiological effects of metabolic acidosis. Its effect on the acid-base balance ceases, allowing it to return to normalize the pH range.

2.11.6 Oxygen haemoglobin dissociation curve.

Appreciating the oxygen dissociation curves in Figure 2.1 and Figure 2.2 will enhance the understanding of the optimal state metabolic functions in human and contrast that to that of a pathological state that directly enhances it function by efficiently transporting oxygen to cells to meet the the energy required by the physiological status of the body. It can hold back on the release of oxygen when the energy need is reduced such as resting. Erythrocytes have a threefold function; as oxygen deliverer, a remover of carbon dioxide and keeping the balace of

the acid base system that are critical to life (Sanghavi 2023), hypoxia of confine space environment, and high altitude (Smith 2005; Singer 2011; Basnyat 2003).

Haemoglobin has several functions; the first and foremost is oxygen binding and delivery to tissues to maintain aerobic cellular respiration and kept in tandem with the extraction and transport of CO2 to the lungs for exhalation. An equally important function of carbonic acid chemical reaction that occurrs within the erythrocytes in order to maintain acid-base balance. Moreover, the kidneys and lungs also play important roles in eliminating acids and waste products. The lungs exhales carbon dioxide and draws in oxygen for haemoglobin to bind and transport to cells as a rapid response system to reduce acid build up while the kidneys ensure sustained response (Smith 2005; Singer 2011). A compromised kidney and lung function adversely affects the oxygen dissociation curve (Bruce et al 2000; Chow et al 2001). When there are high carbon dioxide levels and an increase in hydrogen ions, the delivery of oxygen is increased through the Bohr Effect, where the oxygen dissociation curve is shifted to the right as oxygen is delivered to tissues at a low partial pressure of oxygen. Similarly, the Haldane effect describes the production of carbon dioxide produced from the dissociation of oxygen within the erythrocyte; carbon dioxide produced from the carbonic anhydrase reaction is transported to the lungs in exchange for oxygen. The presence of carbon dioxide and oxygen affects the haemoglobin's affinity to bind or release oxygen and carbon dioxide's ability to restore pH (Loeppky et al. 1983). The factors that induce changes in the oxygen dissociation curve as depicted in Figure 2.1 below shows increased release and utilization of oxygen by a right shift of curve in such conditions includes being ill with a febrile illness, respiratory infection or failure, a state acidosis, or anaemia or a combination of these. Figure 2.1, Figure 2.2 and Figure 2.3 demonstrated the left shift of the curve with low oxygen demand, thereby, increased the affinity of oxygen as in hypothermia, alkalosis, and displacement of oxygen binding by carbon monoxide in Figure 2.3.

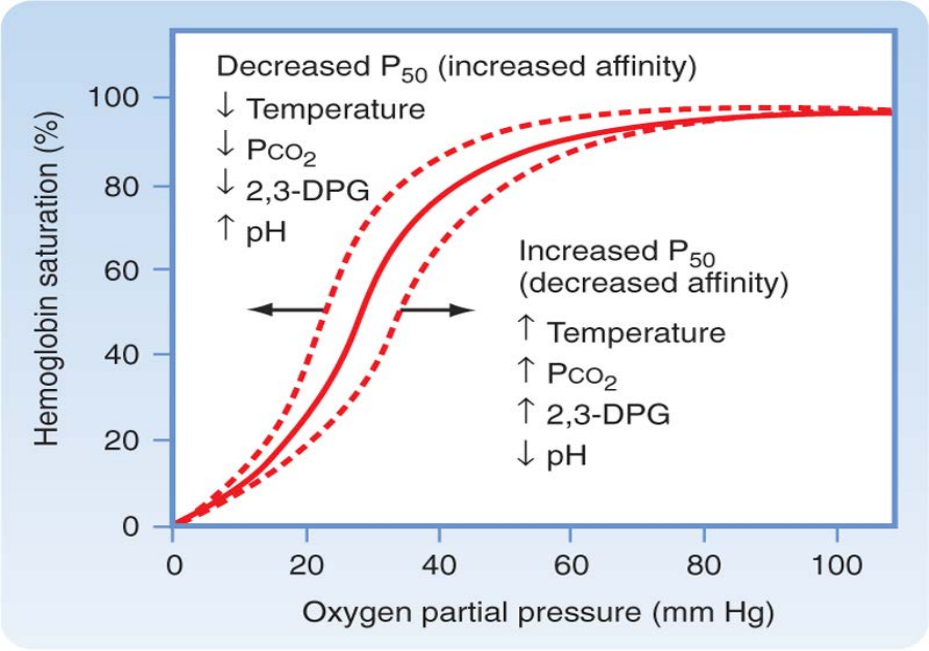

Figure 2.1 Oxygen dissociation curve would shift to the right in SHD. Sourced from Berne and Bevy Physiology 6th Edition online.

The affinity of oxygen for binding to haemoglobin is efficient, and it can utilise a cooperative effect where oxygen draws even more oxygen to bind onto haemoglobin for delivery to tissues. The conditions that promote loose binding of oxygen and haemoglobin allows greater release of oxygen to tissues in conditions of acidosis resulting in low pH, presence of fever, and increased levels of 2, 3 diphosphoglycerate (Stringer et al. 1994).

Oxygen is tightly bound when the opposite conditions are present that raise the pH such as hypothermia. A reduced partial pressure of carbon dioxide contributes to metabolic or respiratory alkalosis. Another cause of oxygen being tightly bound is foetal haemoglobin extracting oxygen from the maternal circulation for the foetus.

Monitoring by pulse oximetry shows the oxygen saturation, but oxygen delivery at the cellular level is reflected by the area of the steep inclination of the oxygen binding site. Here the rapid loading or offloading oxygen at the cellular level would be more efficient despite reduced oxygen saturation readings by the pulse oximetry.

Oxygen is critical to life and is reversibly bound to the haemoglobin contained in and transported by the erythrocytes to cells, with cellular metabolism as the endpoint. After this, the haemoglobin binds carbon dioxide (a waste produced by the cells) and removes it on the

return journey by offloading it into the lungs to be exhaled. As such, the excess reserve capacity of haemoglobin to attach a greater quantity of oxygen to support the body's physiological function can be appreciated. Moreover, carbon dioxide dissociates to acids that are weak and not harmful to sustaining physiological reactions when a normal pH, 7.35-7.45 is maintained. Such a fine balance maintains the normal narrow range of the pH and depends on several factors including the number of erythrocytes, the level or concentration of the haemoglobin and the circulating blood volume as well as the oxygen content in the environment. A sudden reduction of any one or more of these factors will adversely affect physiological function thereby leading to acute hypoxia and acute metabolic acidosis and resulting in a fatal outcome.

In SHD, the abrupt onset of exponential haemolysis of the red cell leads to a critically low number of red cells as well as reduced haemoglobin. This drastically reduced the oxygen delivery triggers the anaerobic cellular respiration produces a build-up of lactic acid. This leads to the onset of sudden metabolic acidosis which may account for the greater number of deaths in the first 6 hours of illness. Without arterial blood gas analysis, the evidence of metabolic acidosis would not be measured in the rural settings where SHD is endemic. However, this study postulates that extreme severe hypoxia and acute metabolic acidosis are unlikely to be physiologically compensated thereby causes the early deaths in SHD.

The oxygen dissociation curve is shifted to the right to readily offload oxygen for cellular respiration. In the presence of a sudden critically low haemoglobin, the transport and delivery of oxygen to sustain cellular respiration becomes markedly reduced in addition to the critical loss of buffering capacity. Below are two figures (Figure 2.2, 2.3) of the oxygen dissociation curve that demonstrates the normal sigmoid curve and the sigmoid curve in anaemia. The flatter or more horizontal curve demonstrates carbon monoxide poisoning where CO is irreversibly bound to the haemoglobin. This may depict the oxygen saturation most likely to be present in cases of sago poisoning, where the erythrocyte population is depleted through massive intravascular haemolysis leading to extreme acute anaemia with hypoxia. The only option that is available to reverse and normalize the acute anaemic hypoxic state is by an urgent blood transfusion that will restore the oxygen dissociation curve to save life based on the understandaning Figure 2.1 and 2.2. Without this intervention death is inevitable as witnessed in sago poisoning cases. In Figure 2.2; sago poisoning cases, the oxygen transporter depleted to near flat line therefore oxygen saturation capability cannot exist. Replenishing erythrocyte population is urgently required by blood transfusion. Oxygen staturation requires

the presence of the oxyhaemoglobin; without it is understandably life ends. The initial acute anaemic hypoxic effects can worsen over the hours as cases beomes dehydrated from the inability to take in oral fluids to rehydrate. In this situation death occurs on day 3 from the onset of acute kidney failure in patients with haemolysis and dehydration.

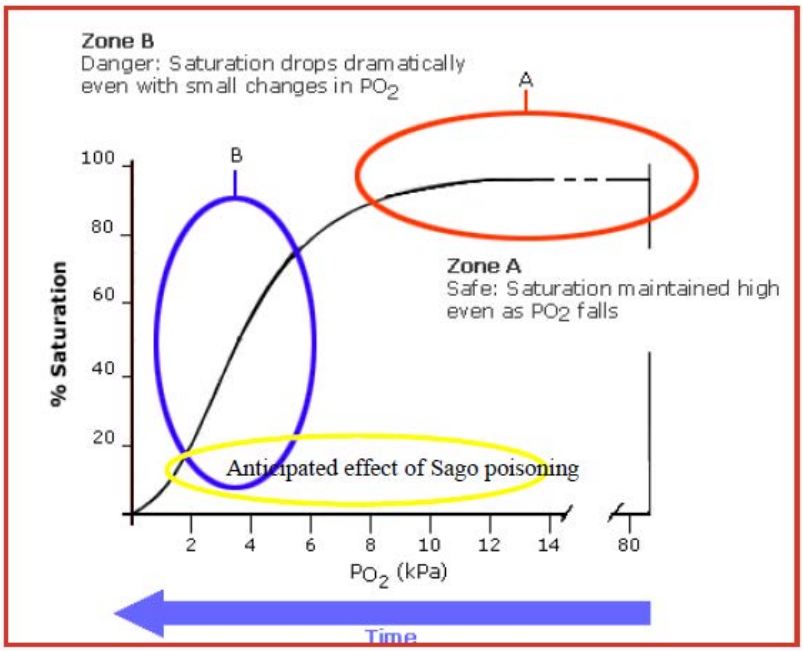

Figure 2.2 Oxygen delivery by the haemoglobin content in the number of erythrocytes. Oxygen dissociation curve Adapted from e-safe-anaesthesia.org online image.

Figure 2.2 shows the potential effect of severe acute anaemia to explain the inability for oxygen saturation to be sustained in the absence of erythrocytes that contain haemoglobin.

The greater reserve for oxygen carrying capacity in haemoglobin protects against hypoxia by maintaining the oxygen saturation curve. This protection or safety margin is lost when the haemoglobin is reduced to a critically low level as a result of loss of erythrocytes. In sago poisoning cases with a critically low number of erythrocytes the oxygen perfusion pressures can only be maintained by having a normal blood pressure. An intravenous rehydration will maintain blood pressure and protect against dehydration. A naso-gastric rehydration can also be accomplished, but both procedures are not practical at rural aid-posts. The critically low oxygen supply becomes inadequate to maintain cellular respiration and normal physiological functions of voluntary muscles and brain cells. Therefore, sago poisoning cases remain

recumbent and unconscious. These two clinical effects were alleviated by urgent blood transfusion.

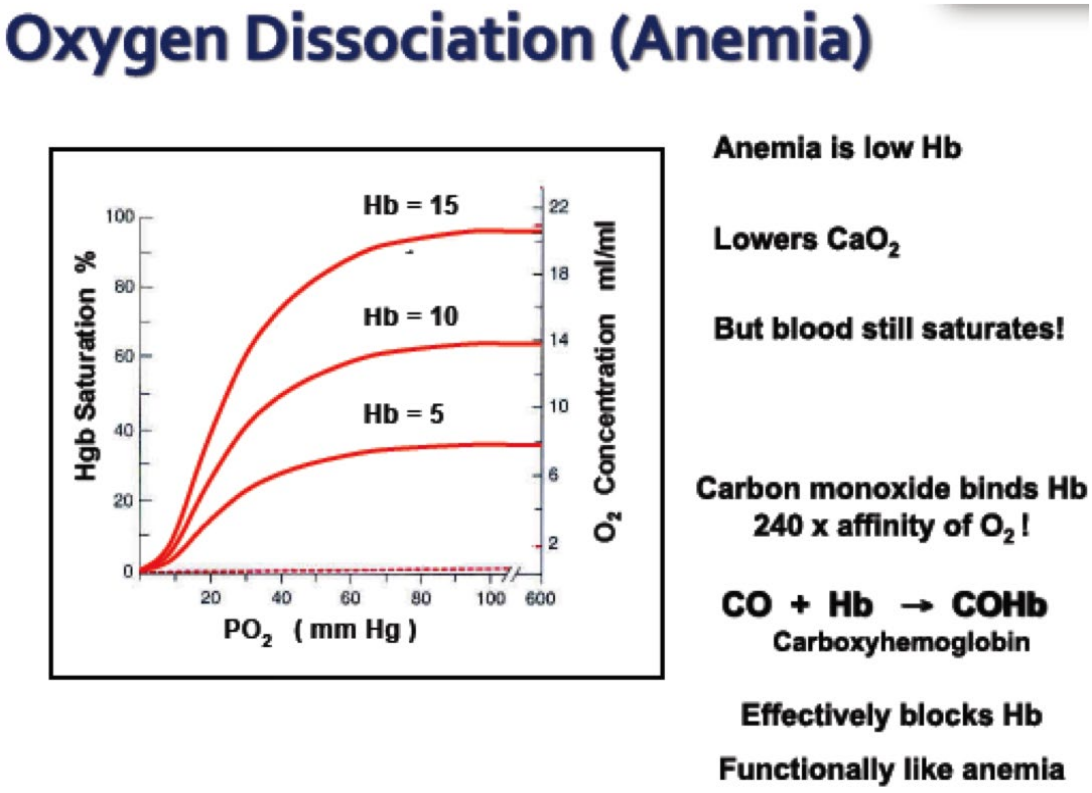

Figure 2.3 Anaemia and oxygen dissociation Adapted from http://classconnection.s3.amazonaws.com/686/flashcards/955686/png/anemia1335114542348.png

Anaemia can result from a loss of erythrocytes in the circulation through rupture of blood vessels or from the failure of the bone marrow to regenerate sufficient quantities (Figure 2.3). Carbon monoxide poisoning mimics anaemia of acute sago poisoning due to its irreversible binding with haemoglobin, making the haemoglobin unavailable to bind with oxygen. In this case the oxygen dissociation curve doesn't reduce but instead flattens, renders patients hypoxic with fatal outcomes.

The presence of sufficient haemoglobin is required for cellular respiration as haemoglobin binds and transports oxygen from lungs to tissues, binds to acids, carbon dioxide, and hydrogen ions produces by cells. Carboxy haemoglobin carrying the carbon dioxide diffuses

out of the lung following the concentration gradient from high to low and is exhaled. Whereas the hydrogen binds with bicarbonate in the plasma to become water and carbon dioxide.

2.12 Acid-base balance

2.12.1 Physiological control of pH 7.35-7.45

The body's acid-base balance is reflected by the pH which has a small range from 7.34-7.45. This range creates an optimal environment for normal physiological functions and cellular metabolism to facilitate enzymatic and cellular reactions. The acid-base balance is maintained by buffer systems namely protein, haemoglobin, phosphate, bicarbonate, and pancreatic fluid and this is supported by the respiratory and renal systems. Different diseases can disturb this narrow balance and adversely affect physiological function. Therefore, recognizing its presence, cause, and use is rational to treat and eliminate disturbances. This is usually done by treating the underlying condition (Singer & Hastings 1948; Adrogué & Madias 1998).

2.12.2 Buffer systems

Buffering capacity is what maintains the narrow pH range. It is supported and maintained by erythrocytes, respiratory and renal functions. The immediate buffering response is mounted by chemical buffer production (of which bicarbonate is the major source) through the carbonic acid reaction. This immediate buffering response is undertaken in the circulation within the erythrocytes. This water and carbon dioxide reaction produces carbonic acid $H_2CO_3^-$ which is further broken down into HCO_3^- and hydrogen ions (Sirker et al. 2002).

2.12.3 Compensatory buffering by respiratory and renal organ system

Reduced pH is immediately detected by the respiratory centre in the medulla, which stimulates the lungs to increase the rate and depth of respiration. This is so carbon dioxide (acid) is expired in greater quantities for pH to return to its normal level. This compensatory mechanism takes seconds to minutes to be affected by the body. Furthermore, the reduced pH also stimulates the kidney to increase acid excretion to return pH to normal, but this takes hours to days to have effects. Kussmaul's respiration is the clinical compensatory respiratory effort in diabetic ketoacidosis and can occur in acute renal failure (Aoyama & Kolff 1957; Trang et al. 1992; Yamada & Nonaka 1996; Klahr & Miller 1998; Chiasson et al. 2003).

2.12.4 Clinical evidence of normovolaemic anaemia

Obvious common causes of acidosis would relate to diseases of the compensatory organs such as those of the lungs and kidney. Experimental evidence in humans has been done to assess

the effects of normovolaemic anaemia through removing blood and replacing it with the equivalent amount of fluid and this showed no adverse clinical effects (McLellan et al. 2003; McLellan & Walsh 2004; Harder & Boshkov 2010). In SHD, the sudden loss of a great number of red cells through rapid haemolysis resulted in a high number of deaths in the first 12 hours of illness. This supports the idea that the underlying cause of death was likely to be severe hypoxaemia and or metabolic acidosis in patients. Significant metabolic acidosis was shown to exist in patients with severe malaria-related anaemia where intravascular haemolysis also occurs (Day et al. 2000). Other unlikely causes of sudden loss of consciousness were methanol intoxication, uraemia, and diabetic ketoacidosis were most unlikely. Furthmore, exposure to drug intake of iron, isoniazid and salicylates for rural remote communities were nearly impossible as were exposure to intake of ethylene and propylene glycol.

3 Chapter 3 Materials & Methods

3.1 Location of 5 hospitals in Western Province

Figure 3.1 is a map of Western Province showing the locations of the 5 hospitals, 3 of which are in the North Fly District. These are principal localities for records of past/retrospective and receive prospective cases of sago poisoning reported during the study period. The only Ok Tedi Mine Ltd. mine operated a road link between Kiunga and Tabubil to connect the 3 hospitals, Tabubil Hospital, Rumginai Hospital and Kiunga Hospital. There are no other significant road systems that connect remote villages to key locations such as towns and hospitals. The extensive river systems do allow remote communities to travel using traditional canoes with paddles, some will use an outboard motor to increase the speed of travel. Rumginai and Kiunga Hospitals receive patients traveling downstream from upper Fly River villages and the other mountainous areas. Tabuil Hospital receive medical refferrals by road between hospital and by air. These hospitals sometimes have support of road ambulances that retrieve patients from the airport or the wharf.

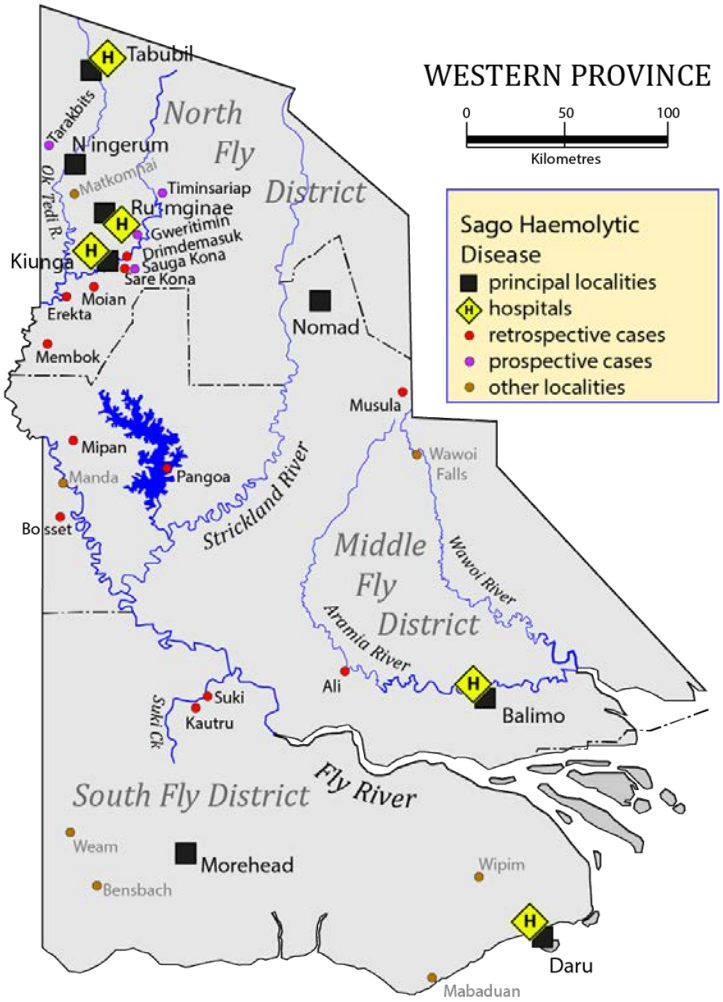

Figure 3.1 Villages, sites of new and old SHD outbreaks. The maps were obtained from Ok Tedi Mining Ltd and Microsoft Word insert shape functions was used to a create dot mapping of SHD outbreaks for Western Province. The geospatial maps showed specific features of rainfall and river system that were associated features of the location of outbreaks of sago poisoning. Prof John Burton, formerly of Divine Word University provided the Ok Tedi maps and the geospatial maps were provided by Dr Marcello Agen, a geologist with geospatial expertise. Map prepared by Miila Gena & John Burton.

3.2 Study design

Four study designs were used for the current study, these were retrospective, case control, prospective and cross-sectional studies respectively. As discussed previously the overall objective of this study was first to epidemiologically characterize the natural history of sago

poisoning cases and identify the determinants of outbreaks in the cases compared to the controls as well as identifying the environmental factors contributing to the outbreaks. Collectively, these findings would contribute to improving the understanding of sago induced poisoning and subsequent management and treatment.

A case definition for sago poisoning needed to be established. This would be used to make a clinical diagnosis to guide the investigation and treatment of new cases. This case definition was created from clinical details and data extracted from the medical records. These details included demography, history of illness, clinical features, laboratory results, treatment, and the clinical outcomes. Additionally, survivors and relatives were interviewed to cross check details of the history.

The case definition was communicated to health workers and the community so that they would be well informed and facilitate early medical retrieval of survivors to reach hospitals. Transport remained a challenge for these remote communities. The risk of mortality by gender measured as an odds ratio was investigated using a case control study design. The risk of exposure was 100% when a meal was prepared using contaminated sago flour. There was no way of predetermining the contamination of sago flour.

A cross-sectional study design was used to measure health status by conducting health surveys of remote communities.

A prospective study design was used to establish the temporal association between exposures to different food types, incubation period and onset of illness. These were vital observations of the timelines that needed to be made during an acute outbreak of sago poisoning. In preparation to collect such detailed information for a timeline in new cases, the principal investigator communicated with prominent individuals such as survivors, nurses, village counsellors and elders in these remote communities. The principal investigator inquired about sudden deaths that occurred within a family or families of one or more people who died at the same time. A verbal post-mortem was asked to determine symptoms of illness and health prior to death. This also included determining the type of meal consumed prior to illness or death of family members as well as requesting them to consider the time from meal to the time of illness and or death. The time of a recent meal to the time of illness was to be described as crude as morning, afternoon or night. Survivors were asked to recall the types of food eaten, particularly to quantity the number and the sizes of sago pancakes consumed. The communities and key individuals received information during health talks and through the

description of past cases. This prepared them to report timelines and food intake history accurately for future outbreaks.

3.3 Health and education providers to rural remote communities

3.3.1 Major health care providers

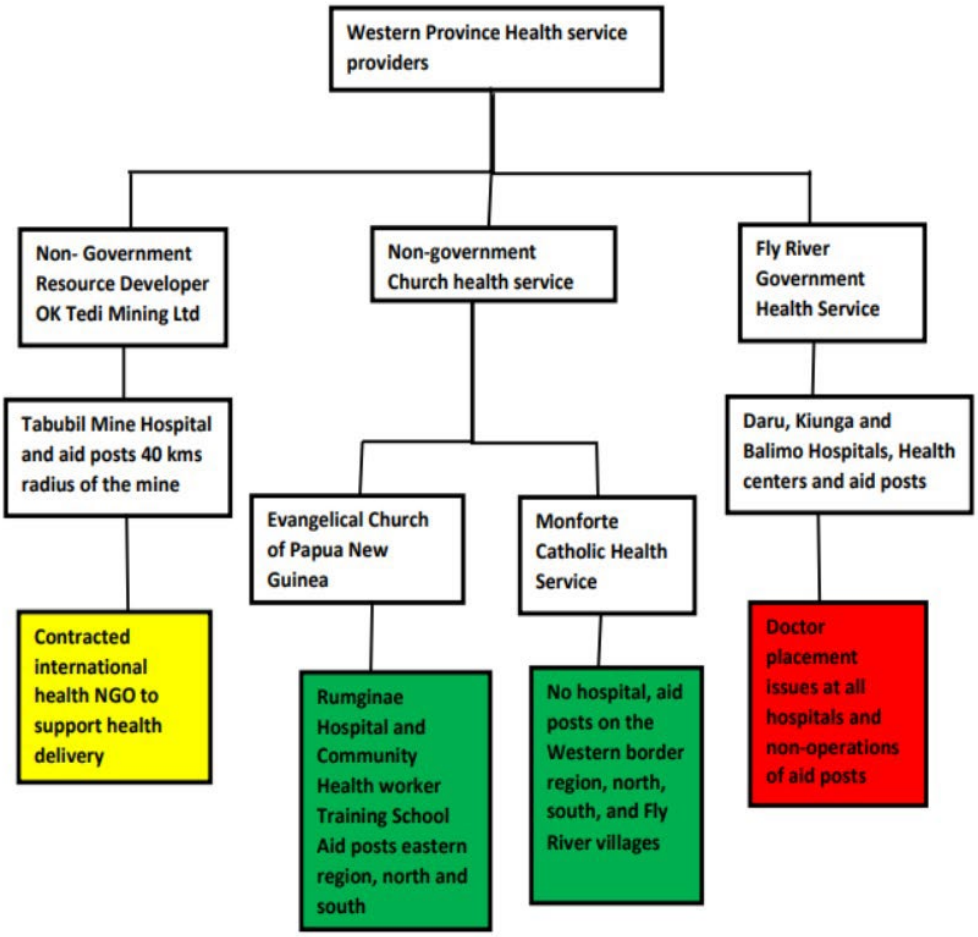

Figure 3.2 Western Provinc Health service providers and issues. Image prepared by Miila Gena.

Western Province has a vast area where remote communities occupy and live on their own traditional land; therefore, the population remained out of reach of government services. Church organizations provided health and education needs to these communities using their

own logistics or by partnering with logistic organizations (such as the Mission Aviation Fellowship) that operate single and twin-engine fixed wing aircrafts. The dominant providers of church health services are the Monforte Catholic Mission and Evangelical Church of Papua New Guinea (ECPNG Church). They championed the provision of health and education services to these remote communities who belong to their congregations.

3.3.2 Resource developer as health care provider

Ok Tedi Mining Ltd. is a significant health care provider in North Fly District. It also serves as a referral hospital to the surrounding hospitals in addition to areas designated by Ok Tedi Mining Ltd., including the Telefomin and Oksapmin area of the West Sepik Province. It is not unusual for people working in North Fly District to bring in their relatives from other provinces in PNG to receive hospital-based care in the Tabubil Hospital due to the presence of specialists in all major disciplines of medicine, surgery, obstetrics, and gynaecology.

3.3.3 Fly River Provincial health services

Whilst the church health service and Ok Tedi Mining Ltd. provided health care to their congregations, mine employees, their families, mine impacted villagers, and others, there continues to be an apparent lack of visibility of government health services due to closure of government health facilities located in remote communities. The government hospital in Kiunga lacked doctor-based clinical service on a long-term basis until Ok Tedi Mining Ltd. intervened with the placement of Ok Tedi Mining Ltd. employed doctors at the hospital. The principal investigator was the first company-employed doctor who provided medical support to the Kiunga Government Hospital, which became the home to the study on sago induced intravascular haemolysis.

3.4 Communication methods used by remote communities

3.4.1 Radio communication

Radio communication was used extensively by the remote communities. Very high frequency radios or VHF were provided by the churches, government, and the Ok Tedi Mining Ltd. to their respective communities thereby linking them for direct communication. The extensive radio communication was instigated by the Papua New Guinea National quarantine NAQIA. It was to be used as an animal health surveillance system to report on outbreaks of animal disease but embedded as a communication system to be used by health care providers to human.

3.4.2 Mobile phone network

Mobile phone communication was introduced in 2000. The network coverage does not reach all remote communities.

3.4.3 Local communitiy communications

The use of runners who come to the hospital to inform the ambulance service was witnessed where patients can be collected from the roadsides or the waterfronts where canoes are moored. During the prospective study on the outbreak, it was fortunate that the ambulance transported the case from the Sauga Kona, an informal settlement for those people originating from the Northern Province. Councillor Jonathan Boru, a resident of Sauga Kona, was able to provide vital information to the study on the sago poisoning cases that affected his extended family. Rumginae ECPNG church hospital received many patients including sago poisoning cases from the outbreak in Timingondok village; they paddled downstream in their canoe to arrive at the waterfront of the hospital. Upper Fly River villagers travelled downstream to the Kiunga wharf and transported to the hospital by ambulance. The lower Fly River villagers paddled upstream to Kiunga. The villagers may elect to travel by road to Rumginae hospital should they prefer church health service rather than the Kiunga government hospital.

3.5 Location of hospitals in the North Fly District

The North Fly District hospitals were located along and connected by the Tabubil-Kiunga Ok Tedi Mining privately owned and operated road. Different health care providers operate in different areas that aligned with their church operational activities to serve their congregation. The Catholic Church Health outreach services reached villages located along the Fly River as well as the border villages located to the North and the south. ECGPNG church health services reached remote villages located to the Northward, Northeast, Southward and South-East towards the nomad and Southern Highlands Province whilst also covering Middle and South Fly Districts. The government health service based in Kiunga Hospital had aid posts that have ceased operations many years ago.

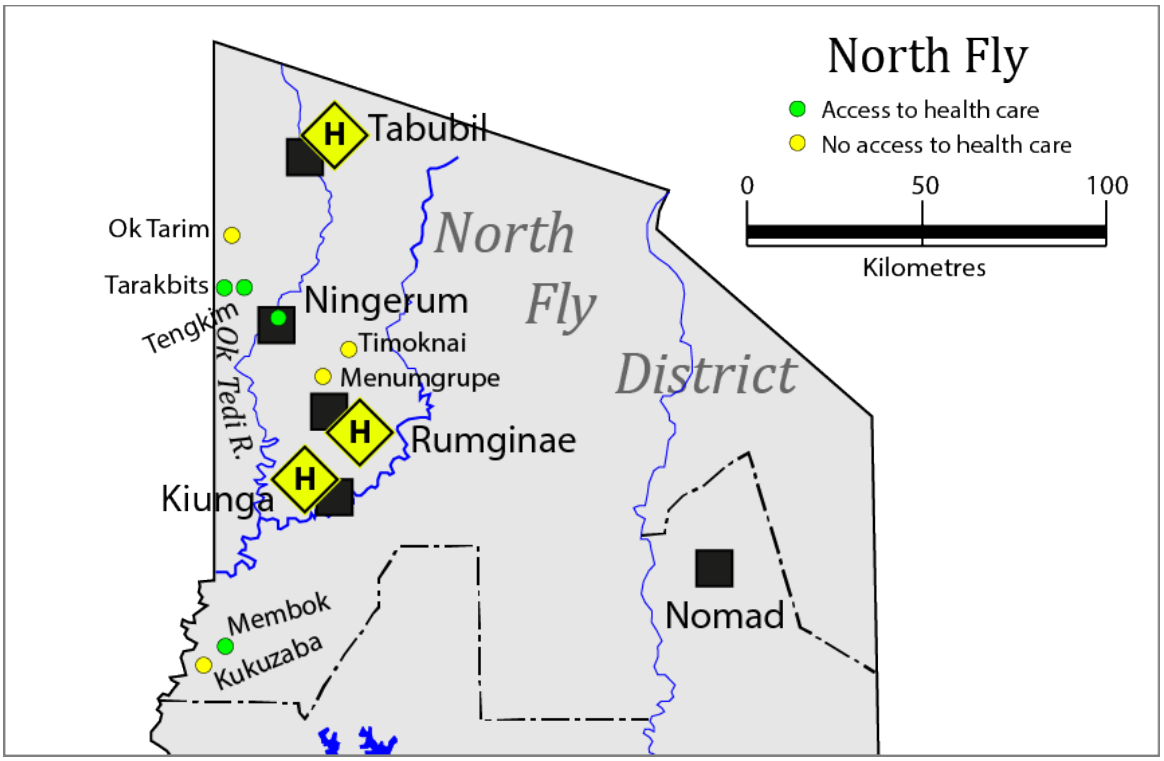

Figure 3.3 North Fly District hospital locations and aid posts. Image by Miila Gena & John Burton

3.6 Travel logistics into rural remote communities

3.6.1 River transport

Western Province has an extensive river system that allowed travel from the highlands to the flood plains. These extensive river systems were used by people to travel using traditionally built canoes and paddles. Canoes are used as part of travel with journeys often completed on foot. During the colonial era, the government had boats or ships travelling on the main riverways of the Fly River to deliver goods and services. Since PNG gained its independence on September 16th, 1975, certain logistical systems that were efficiently operated during the colonial era could not be maintained and or sustained. The remote communities informed the health team that the last time they received any medical attention of this scale was during the colonial era.

3.6.2 Air transport

Whilst the Mission Aviation Fellowship (MAF) flights were used consistently for health and education purposes to remote communities, often, they provided emergency medical evacuations in response to call outs received from rural remote communities. The

requirements were for airstrips to be maintained to a standard where landing and taking off was deemed safe by the pilots. Churches maintained their villages' airstrips with their congregations at a cost. The Monforte Catholic Church lost their pilot priest in a plane crash at Membok village along the Fly River and have not maintained their airstrips since. Commercial flights do not use village airstrips except those approved by the Department of Civil Aviation. The ECPNG Church congregations throughout the Western Province maintain their communications and airstrips allowing MAF flights to serve their communities. Travel by air is the most efficient travel method but required operating village airstrips to meet safety standards set by Department of Civil Aviation.

3.6.3 Road ambulance

Five hospitals are located at the extreme northern and southern end of the province. Access to the hospitals occurs by air for most remote communities. Others travel by canoes using the river ways going downstream. Those travelling upstream require use of motorized dingy or canoe. The mine road from Kiunga to Tabubil is used by communities who can reach the road system to access the hospitals. All hospitals have road ambulances and drive out to calls from villages reachable by road, or transport patients from wharves to the hospitals.

3.7 Access to health care

The map below showed the peri-urban informal settlements of rural populations migrating to the township of Kiunga who created and built informal settlements as their homes. These informal peri-urban settlements were known as Kona by the locals and each Kona belongs to specific people from a rural village. They function as transit homes for the rural villages for health and education services. Chapter 4 compared access to health care between the Fly River villages downstream from Kiunga Township shown on the map (Moian, Erekta, Karemgo, Membok and Kukuzaba) to the peri-urban informal Kona settlements surrounding the Kiunga town. The comparative study was deemed fair as the Catholic Church health service kept the aidposts operating for the Fly River communities despite closure of the government aid post.

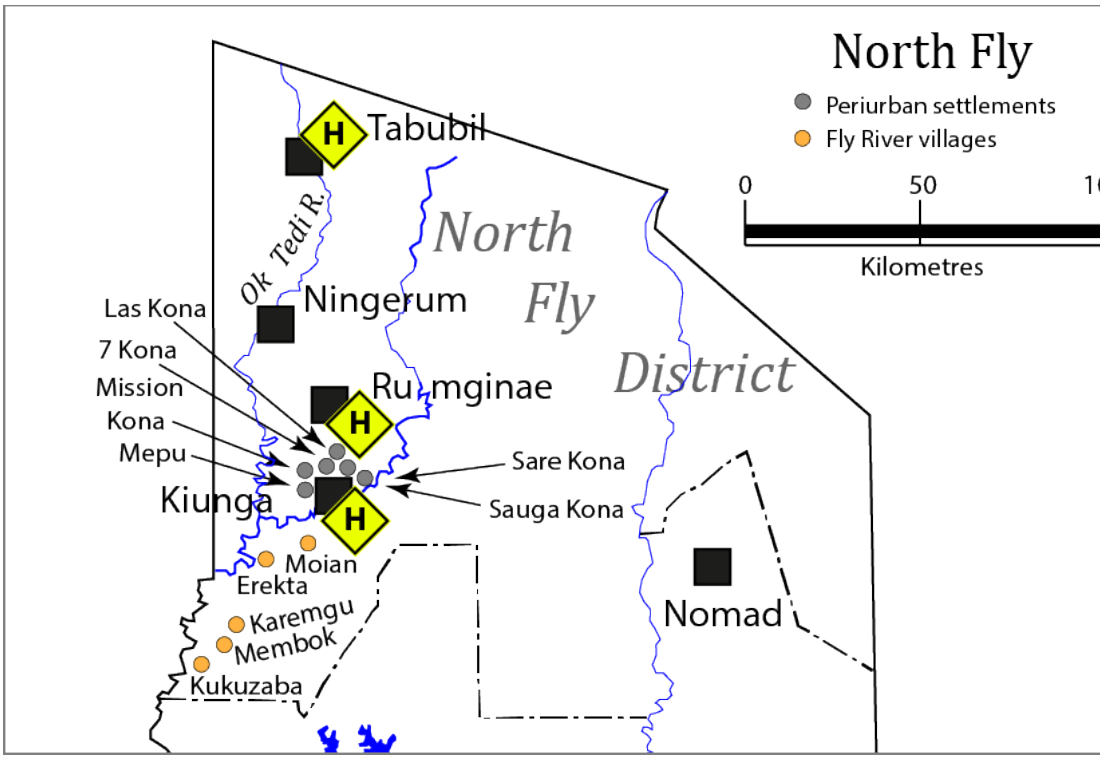

Figure 3.4 Peri urban settlers and Fly River villages. Map by Miila Gena & John Burton

3.8 Sago poisoning medical record retrieval from hospitals

The medical records sago poisoning cases stored at Tabubil, Rumginae, Kiunga, and Balimo hospitals were retrieved and reviewed for the point of origin, demographic details, clinical features and the final outcome of cases. The case notes were written freehand and did not follow a checklist therefore paucity of records was anticipated. The written notes were those of health workers managing the cases and not necessarily a doctor. Incomplete history and physical examinations were anticipated, sometimes, the thought processes of clinical care providers remained obscure. It was imperative to seek the assistance of the survivors and relatives of cases to recheck the history, quantity of sago pancake, and other food items consumed on that day. Exposure level, timeline of meal to illness as well as the sequential documentation to the patient outcome was recorded. It was particularly difficult to extract accuracy of the timing of observable events from the implicated meal to hospital arrival and death. Whilst this made the review of retrospective cases challenging, this critical information was well documented in the prospective cases, A list of probable causes was ruled out based on the survivor and relative interviews on history of snake bites, ingestions of beans,

mushroom, fish, and other food items. Village leaders and counsellors were interviewed specifically about sudden deaths in their respective communities. These remote communities live in isolation away from access to shops or services that may predispose them to other causes from modern world associated diagnoses contained in the acronym of MUDPILES (i.e. methanol, uraemia, diabetic ketoacidosis, propylene glycol, isoniazid reaction, iron overload, ethylene glycol and salycilates overdose). Lactic acidosis in sago poisoning was secondary to the anaerobic cellular respiration because of critically low level of oxygen, easily corrected by blood transfusion so the increased erythrocytes population will bind and transport oxygen to the cell to switch over to aerobic cellular resiration.

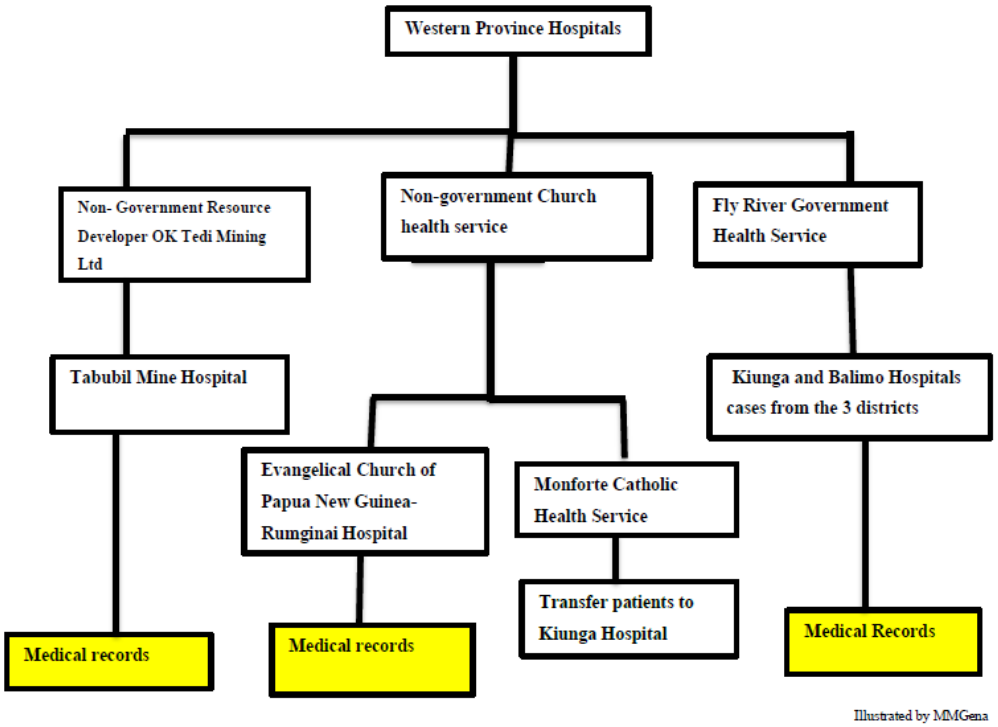

Figure 3.5 Sampling frame used to retrieve medical records of sago poisoning cases showing transfer of sago poisoning cases to Balimo and hospitals in the North Fly District.

3.9 What is sago?

Sago starch was harvested from the trunks of the Metroxylon sagu palms that grew in abundance in the swampy regions of Western Province (Figure 3.6, Figure 3.7).

Figure 3.6 Bags of sago starch on sale at the Kiunga market.

Water was required to dissolve and extract the starch during sago processing. Figure 3.7 shows an image of a sago processing site using swamp runoff water at T'moknai village. Women and girls must carry the macerated sago pith in bags to the water source to extract the sago starch contained in the pith. Traditional implements were used to macerate the fibrous pith. Furthermore, a traditional milling setup was constructed at the processing site as seen in Figure 3.7.

Figure 3.7 T'moknai village water source for drinking, washing and sago processing.

A tripod made of sticks allows the hollow base of the sago palm receptacle to have leaves placed on it. The sago receptacle leaves are placed at a downward inclination and stabilized into a collecting vessel that stores the water containing the sago starch to sediment overtime.

The freshly macerated sago pith is mixed with water and squeezed by hand at the higher end near the tripod stand, the water containing the sago starch flows downward towards a collecting vessel to form sediment. The pith is then discarded onto the ground by the stand which can be seen as light brown colour in the image above. Water is essential for sago extraction and water sources and quality differ in different regions from use of groundwater, well water, running river water, or swamp runoff water as shown in Figure 3.7.

3.10 Sago starch harvest using reticulated water

As part of this study, two methods of traditional sago processing were undertaken by health care workers families at Kiunga Hospital. The demonstration of sago palm harvest and sago starch extraction was done by Balimo women and young girls in the Kiunga Hospital

compound at the residence of Mr and Mrs Kekela. These images show the cleaning and stripping of the bark of sago palm to reveal the inner fibrous core. A traditional tool is used to strip and macerate the pith. Water is added to the pith to dissolve the starch then squeezed to release the starch. The water containing the sago starch is then allowed to collect in a vessel for sedimentation. After several hours, the water is poured out exposing the sago sediment which is collected and packed into storage bags. At this point, the sago is ready to be cooked and consumed. Modernisation of sago processing is evident in this demonstration. The images show the use of reticulated water, plastic drums, plastic canvas to create a pool for the sago sedimentation, and a rubber water hose. Extracting the dissolved starch in the macerated pith require pressure to be applied. Cultural differences were evident in the image showing the Sepik way by hand-squeezing the macerated pith and the use of foot pressure on grass basket of watered macerated pith by Balimo women. The Kiunga town water supply was used to process the sago.

Saudama John and Balimo women demonstrated their way of harvesting sago starch whilst the Sepik way shown by Mrs Kambo. This study credits their participation in the study (Figure 3.8-3.12).

Figure 1 Saudama John cuts the bark to exposes the fibrous interior..

Figure 2.9 Pounding action applied to macerate the pith into thin strips of fibres..

Figure 3.10 A grass basket filled with thin sago fibres soaked in water compressed by foot.


Figure 3.11 A well of brown coloured water saturated with dissolved sago starch..

Figure 3.12 Mrs. Kambo hand washed sago fibres to dissolve sago starch granules.

3.11 Data collection and presentation of data and results

Tables were used frequently to present results throughout the thesis. Images were used to demonstrate the harvesting and processing of sago starch as practiced by local communities, Maps were used to reveal the locations of past sago poisoning and prospective outbreaks as well as the health survey sites. Graphs were used to visually compare variables and groups. Graphs were prepared in Excel and GraphPad.

3.12 Statistics used in analysis

3.12.1 Descriptive statistics

Descriptive statistics (%, frequencies etc) were used for comparisons as appropriate.

3.12.2 Use of Chi- square and T tests

Chi-square and t tests were used to test hypotheses and compare groups across all data sets as appropriate.

In Chapter 4 there were two distinct groups of population those that were urban based and those that lived in the remote villages. Their access to health care was determined by their residence, the urban based settlers were able to access town-based health service. Those living in their remote villages depended on their village aid post was operational. Based on this, the Chi-square test of independence was used to tests frequency of self reported utilization of

health care between rural and urban residents. The self reported symptoms of an illness affected them over the past 2 weeks; any use of inpatient service in past 6 and 12 months in the past year. In Chapter 5 Chi square tests were used to test for the burden of malaria detected in the urban and rural communities. The number of visitations, the number of blood slides read as positive or negative are descrete varables as such Chi square test was appropriately used to test for relationship between the locality and reported illness by gender between the urban and rural groups.

The independent two sample t-tests was used to test means of continuous data as such t tests were used to detect differences in the mean of groups of variables as appropriate. The health assessment (Chapter 5) measured biochemical and haematological parameters of the population that had access to health care and those that did not. This study's baseline health assessment measured the impact of these public health interventions and provided evidence of any improvement in the health indicators measured that included body mass index. This data was tabulated and graphed by village. The levels of biochemical and haematological profile were used to search for burden of parasitic disease malaria and filariasis; prevalence of anamia; emergence of non- communicable diseases, and the presence of end organ damage in presence of renal or liver diseases. The independent two sample t test was used to detect any statistically significant differences in biochemical profile by gender of results between these two stated groups. For example, to identify if there was a statistically significant difference existed between the mean of cholesterol for men with access to health with men who had no access to health care. This was similarly done for women who had access to health care and those that did not.

In Chapter 6 t-tests were used to look for mean differences in biochemical and other parameters in relation to sago poisoning. For examples haemoglobin levels between males and females affected by sago poisoning.

3.12.3 The use of regression analysis

Simple and Regression analysis was doing usingExcel/GraphPad in Chapters 6-8 to test relationships using. For eacmple a simple linear regression analysis was used to demonstrate the relationship between the dependent or response variable (pre-bloodtransfusion haemoglobin) to the independent or predictor variable (the quantity of contaminated sago consumed). Mathematical modelling predicted the severity of the intravascular haemolysis to the quantity of contaminated sago consumed in Chapter 7.

3.12.4 Measure of the odds of an event

GraphPad statistical software and Medcal online software were used for calculating the odds of an event across Chapter 6-8). For example, odds ratio calculations were used to show the odds of death outcomes in males and females affected by sago poisoning and the odds of death in SHD outbreak by gender. These tools were also used for odds of events as exposure or death with and without blood transfusion, gender differences in the disease outcome and attributable risk to developing sago poisoning.

3.12.5 Other statistical tools

The incidence of sago poisoning was calculated using the number of hospitalized cases per 100,000 population in Chapter 7.

3.13 Case definition for SHD and hypothesis testing in new outbreaks

The principal investigator collected clinical edpidemiological data by comparing the the timeline between meal to the appearance of the first and the subsequent symptoms. This time period not only to confirm an incubation period but also captured the temporal relationship that connected the exposure as sago meal consumption the first and subsequent symptoms. This provided the evidence to refute or accept the hypothesis of the implicated food item being sago and establishes the natural history of the disease and to contribute towards identifying the aetiology. This study defined a case of sago poisoning to be 10-15 minutes after the meal complains headache or dizziness progresses to become profoundly physically weak and loses consciouness inaddition to passing red coloured urine. This occurs suddenly and affects all those who ate the sago meal, the point source of the outbreak. This study sounds an alarm where a group of cases may easily trigger the diagnosis of sago poisoningo it can affect individual patients who alone ate a sago meal. Chidlren may present in an unconscious state because they were fed the sago meal due to food scarcity. Health workers need to be diligent in looking for and suspect acute sago poisoning so progress to check a full blood count and proceed with crossmatching blood and transfuse as soon as possible. An accurate case definition will be accomplished to

included clinical, epidemiological and pathophysiological features during the prospective outbreak investigation in Chapter 7.

3.14 Seasonal effects on SHD outbreak

Other factors influenced the occurrence of sago poisoning were investigated including the weather, seasonal effects, temperature, and rainfall. The mean temperature and rainfall were calculated with data obtained from the Papua New Guinea weather Bureau. These were used to produce graphs demonstrating the mean temperature and rainfall per calendar month, whilst also showing the reported SHD outbreaks by the calendar month.

Communication and transport played a critical role in accessing hospital-based care in a timely manner. The use of different types of communication and modes of transport (usually a combination of different modes) are tabulated in Chapter 6. Medical records were reviewed for past case history; physical findings, laboratory tests, treatment, and clinical outcome for each case were retrieved. Survivors, family members, and councillors were also interviewed to verify details of the illness and outcomes such as deaths that occurred outside of the hospital.

3.15 Epidemiological factors of SHD

Chapter 7 is a prospective study of new sago poisoning outbreaks. This was critical to the study, as an accurate disease timeline was needed to identify the exposure that preceded the onset of illness. The chronological appearance of the symptoms was key to establishing the incubation period, as the time taken from a meal to the time of the first symptom (and subsequent symptoms) appearing reflects the underlying pathophysiological process. Together, this will confirm the temporal relationship between exposure and the onset of illness. Due to the remote nature of the communities involved, the natural history of sago poisonings plays out as patients sought transport to reach hospital. Upon arrival at the hospital the history of exposure, onset of illness, clinical evaluations, biochemical, and haematological tests conducted on the patients revealed the pathophysiological changes relating to the effects of sago poisoning as described in Chapter 8. The pathophysiological changes will explain the severity of effects, complications, and fatal outcomes. This evidence can drive the efforts of primary prevention measures for affected communities, including first aid and specific treatments for sago poisoning cases.

3.15.1 Challenges of epidemiological studies in PNG

The literature review in Chapter 2 sought to reveal the difficulties of conducting an in-depth epidemiological study in Papua New Guinea. It's especially considered the functionality of hospital and laboratory services that existed in these rural remote areas, and difficulties regarding their involvement with past research activities undertaken in the country.

Papua New Guinea was home to renowned ground-breaking research on diseases that affect the regional indigenous population through their cultural practices. There are two important examples which stand out. The first of these is Kuru, a disease that was difficult to diagnose as it was a neurological disease. Sharing of evidence between the medical researchers and veterinary scientists in conferences was able to highlight the similarities of Kuru to scrapie-like illness found in the sheep. This enlightened the medical researchers on Kuru and allowed them to finally identify a prion as the infective agent. This was proven by injecting laboratory animal with infective brain tissue transmission to produce Kuru-like illness in the animals and allow recovery of the prion from the animal tissues post-mortem. Secondly, Pig-bel pathological changes appeared to resemble a past disease associated with European famine, which resurged in the indigenous vegetarian population that suddenly had increased availability of pork meat meal during intervals of the cultural pig festival. Without effective preservation methods, the pork meal was equivalent to eating culture media infected with clostridium perfringens. This disease was named pig-bel the local name linking the implicated food item to the site of disease, the small intestine which is also properly known as enteritis necroticans.

Both types of research were conducted in the central highlands of PNG, nearer to the Goroka Base Hospital and the PNG Institute of Medical research. These studies were supported due to the locality of the research institute and the clinicians based at the Goroka base hospital.

Conducting research in Western Province is unheard of unless it was supported by organizations that have logistic services operating in Western Province. The principal investigator was part of a mining initiative to assist the Kiunga government hospital clinical service to upgrade to a doctor based clinical service. As such, this study was strongly supported by the CEO of Ok Tedi Mining Ltd, Mr. Keith Faulkner, who initiated the mine health outreach program to support the local communities of the North Fly District as well as the mine impacted riverine communities along the corridor of the Ok Tedi River downstream from Kiunga Township.

3.15.2 Expected results from retrospective study

1. Establish the burden of sago poisoning cases that were hospitalized.
2. Calculate the incidence of sago poisoning cases
3. Establish the relationship between weather and outbreaks of sago poisoning
4. Establish the types of transport used in the transfer of sago poisoning cases.
5. Establish the means of communication used to the transfer of cases.
6. Establish a crude case definition for the first time to guide the prospective study

3.15.3 Expected results from prospective study

1. Establish the incubation period of SHD for the first time.
2. Identify the exposure to the implicated food item for the first time.
3. Establish the temporal relationship between the exposures that precede the onset of illness for the first time.
4. Explore the relationship between the level of exposure and the severity of the illness, therefore, establishes dose relationship to severity of disease for the first time.
5. Establish the lethality of the exposure for the first time.
6. Describe the pathophysiological changes of SHD to explain the clinical symptoms and signs.

3.16 Examples of data collection sheets

3.16.1 Data extraction tables

Sago Poisoning data collection record **Evidence recorded as present or absent**	**Present-Yes**	**Absent-No**
Were you bitten by a snake before SHD illness		
Were you bitten by a spider before SHD illness		
Did you eat mushrooms before SHD illness		
Did you take any prescribed medications for malaria before SHD illness?		
Have you had this kind of illness in the past?		
Did your family have this illness in the past?		
On the day you got sick, can you recall how long it took from meal to onset of illness?		
What was the first symptom that made you know that you were sick? Date of illness- Estimate time of illness Date of discharge Condition at arrival at the hospital Ambulant	 Date Date Yes	 Time No

Fully conscious		
Responding to verbal commands Responding to painful stimuli Passed/passing red-coloured urine Presence of fever Received intravenous rehydration Received Blood transfusion Time to return of consciousness and voluntary movement after blood transfusion		

3.16.2 Medical record information extraction sheet

	Review of the medical record of sago poisoning		
	Date of outbreak		
	Date of hospital admission		
	Duration of illness before blood transfusion		
	Date of blood transfusion		
	Time of meal known - guestimate	Yes	No
	Time of the first symptom known		
	What was the first symptom?		
	What was the second symptom?		
	List of symptoms- Conscious state - unconscious		
	Ambulant		
	Recumbent position		
	Passed red urine		
	Did the patient vomit?		
	Did the patient have diarrhea?		
	Did the patient have a fever?		
	Was evidence of skin bleeding?		

	Was evidence of bleeding into the conjunctiva recorded		
	Evidence of pallor recorded		
	Pulse rate on admission		
	Respiratory rate on admission		
	Blood pressure rate on admission		
	What day of blood transfusion was the conscious status restored – Day 1		
	What day of blood transfusion was the conscious status restored – Day 2		
	What day of blood transfusion was the conscious status restored – Day 3		
	What day of blood transfusion was the conscious status restored – Day 4		
	What day of blood transfusion was the conscious status restored – Day 5		
	What day was the patient ambulant – Day 1,2,3,4, 5,6,7,8,9,10		
	Were you able to walk out of the hospital normally without physical assistance on discharge?		

3.16.3 Survivor interview and or relative interview sheet

Sago haemolytic disease survivor interview **Is this a survivor or a relative interview: Circle the appropriate interviewee status**	**Response**	
	Yes	**No**
Were you bitten by a snake before SHD illness		
Were you bitten by a spider before SHD illness		
Did you eat mushrooms before SHD illness		
Did you take any prescribed medications for malaria before SHD illness?		
Have you had this kind of illness in the past?		
Did your family have this illness in the past?		
On the day you got sick, can you recall how long it took from meal to onset of illness?		
What was the first symptom that made you know that you were sick? Did you walk into the hospital when you were ill?		

3.17 Tables for collection of laboratory results for clinical specimens

Data collection tables are shown below.

3.17.1 Results of full blood counts of patients pre blood transfusion

Sex	Age	Haemoglobin	Reticulocyte %	White cell count

3.17.2 Results for haemoglobin indices

Gender	Age	Retics	Hb	MCV	MCH	MCHC

MCV: mean cell volume; MCH: Mean concentration of haemoglobin; MCHC: Mean cell haemoglobin concentration

3.17.3 Results for red cell morphology

Gender	Hb	Howell Jolley body, Bite cells	Microcytes	macrocytes	poikilocytes	Anisocytosis

3.17.4 Results for enzymopathy and haemoglobinopathy

Sex	Age	G6PD	Hb A	Hb F	Hb H

3.17.5 Results for clinical urine samples

Gender	Urine Hb	Bilirubin	urobilinogen	Protein	Sugar	leucocytes

Hb: Haemoglobin

3.17.6 Results for liver enzymes and bilirubin of patients

Sex	Age	Total Bilirubin	ALT	AST	γ GT	Alkaline phosphatase

ALT: Alkaline transferase; AST: Aspartate aminotransferase; γ GT: γ glutamyl transferase

3.17.7 Results for renal function tests

Sex	Age	Creatinine	Urea	Bicarbonate	pH

3.17.8 Results of exposure to heavy metal results

Gender	Age	Lead	Mecury	Arsenic	Cadmium

3.17.9 Microbiology

Microbiology results of implicated sago	Types of microorganisms grown		Toxin isolating and identification
Microbiology set one	Aerobic	Aerobic	PCR testing
Sampe1			
Microbiology set two			
Sample 2			

Microbiology set three			
Sample 3			

3.17.10 Vital signs, oxygen saturation, haemoglobin, and anion gap

Sago poisoning case vital signs, oxygen saturation, pre-transfusion haemoglobin, and electrolytes are tabulated and graphed to reveal trends in the data for further analysis.

3.17.11 Table of results for three males in the prospective outbreak study

Sex	Age	Temp Degree centigrade	Pulse rate	Resp. rate	BP	O2 sat%	Chloride	Blood sugar	Anion Gap

4 Chapter 4 Access to health care by rural remote communities

4.1 Introduction

This Chapter aims to measure the access to health care by urban-based residents of informal settlements surrounding Kiunga and to compare this to Fly River villagers in North Fly District that receive the government and the Catholic Health services through supported aid posts.

The urban dwellers were originally rural villagers who have travelled to Kiunga and stayed in informal settlements on the periphery of the Kiunga town. The main reason provided was to have easier access to the government health and education services as opposed to remaining in the rural Fly River villages. Figure 4.1 below shows where the study participants resided. The different health care providers and their area of operation are are shown on Figures 4.2- 4.4.

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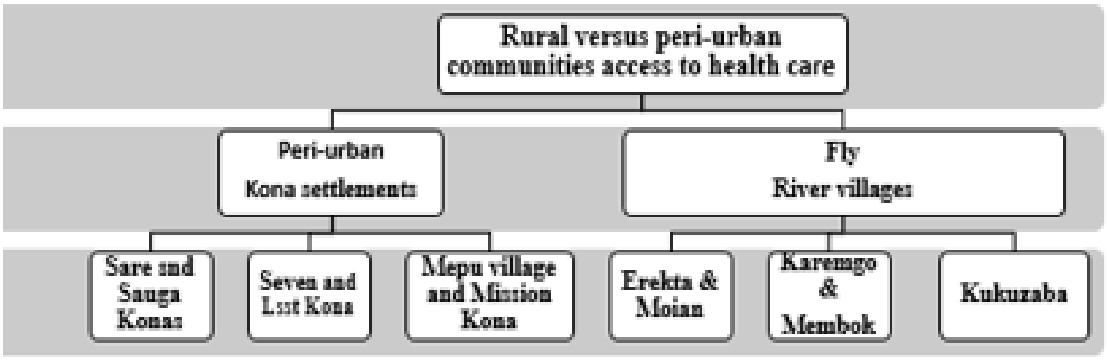


Figure 4.1 Health care access by peri-urban settlements to Fly River villagers. Image prepared by Miila Gena.

Over time these informal settlements known as Kona provided transit accommodation to support family kinships during travels to town or offer boarding to children for education. The map of North Fly District shown below (Figure 4.2) shows the location of the three hospitals. These were the Kiunga government hospital, the Rumginai Evangelical Church of Papua New Guinea (ECPNG) hospital and the Ok Tedi Mine Ltd. Tabubil Hospital. The Monforte

Catholic Church is the main provider of health services through their extensive network of aidposts along the Fly River and towards the border between PNG and Indonesia; they do not operate any hospital. The ECPNG health service operates hospital in addition to aidposts towards the north east region extending to the border of the Southern Highland Province.Their aid posts were operational and participated in the study.The non-operational status of some aid posts were part of government health service.

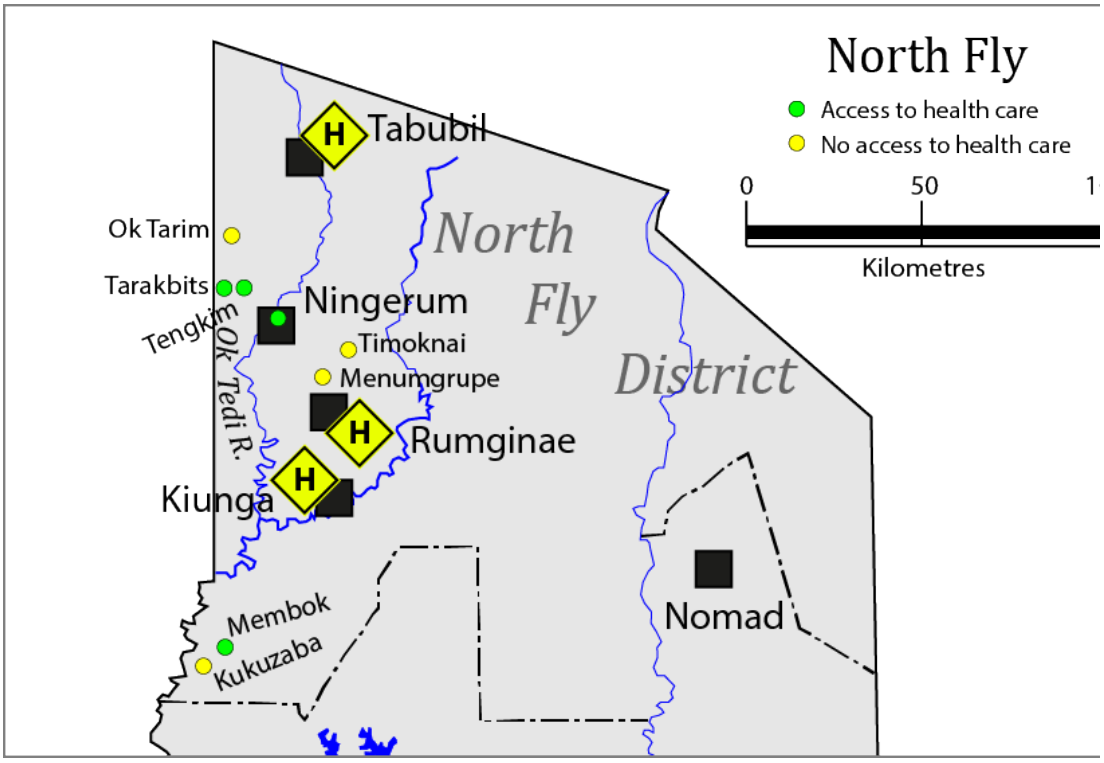


Figure 4.2 Village aid posts operational state in the NFD. Adapted by Miila Gena and John Burton

4.1.1 Background

The access to basic health care declaration of Alma-Ata in 1978 emphasized access to basic health care as a fundamental human right. Despite this declaration, not all developing countries were able to ensure that their citizens received this basic level of care. Papua New Guinea was no exception even in the natural resource-rich area of the Western Province (TO 2003).

Access to health care and access to essential medical emergency treatment in PNG remains uncoordinated and poor, often left up to the communities and more often relatives to accomplish, if they can. Inevitably, preventable deaths occur due to the lack of a formal medical retrieval system that can efficiently transport cases to hospitals promptly for life-saving treatments (Clem & Green 1996). The lack of mechanical ventilators and aircraft required for urgent medical referrals was highlighted during the Tsunami of July 1998 (Maegele et al. 2005).

Timely access to emergency treatments remains critical to saving lives. This requires access to well-coordinated and effective means of communication supported using effective and efficient transport for critically ill cases over a long distance to the hospital to receive prompt treatment. Without such a system, costs were absorbed by resource developers and charity aviation services such as Mission Aviation Fellowships that operate in remote areas of Papua New Guinea such as Western Province (Barss & Blackford 1982). This has therefore led to rural hospital generalist and emergency medicine training of doctors in Papua New Guinea (Symmons & Curry 2007).

The church health services support remote communities of the Western Province. They remain the main health service providers and are operated by the Catholic and Evangelical Church of Papua New Guinea. Additionally, Ok Tedi Mining Ltd. provides health services to the remote communities within the mine lease area and beyond as a referral hospital because of the provision of medical and surgical specialists. The mine also operates aid posts located within the mine lease area. The provincial government is a minor provider where its network of aid posts have ceased operation as well as struggles to maintain an acceptable level of health care at its hospitals, such as the Kiunga hospital that is heavily supported by Ok Tedi Mining Ltd and AusAID (Connell 1997; Duke 1999; Gibson & Rozelle 2003). Due to the vast area of Western Province; each health provider delivers health care to distinct areas without overlapping. There was varying degree of access, from being optimal in communities that had operating aid posts to reduced or non-existent access by those that exist on the fringe and beyond the reach of existing health services respectively. Access to needed health care requires varying travel times and it may take days to weeks to reach aid posts or hospitals.

4.2 Materials and Methods

4.2.1 Medical Ethics approval

Medical ethics approval was obtained from the Papua New Guinea Research Advisory Committee MRAC No. 06.29 November 2006 for the clinical epidemiology study on Sago Haemolytic Disease and further human ethics approval under category 2 identification number H5401 from James Cook University on the 17th of December 2013. Permission to access remote communities was sought through the community relation officers who visited remote communities and held discussions with village elders and the health committee of the villages.

4.2.2 Recruitment of study subjects

This study compares access to health care provided by Catholic and government health service to remote communities of Ningerum and Fly Rivers villagers and peri-urban communities of informal settlers respectively. The population of each village were recorded during census and published by the National Statitical office of Papua New Guinea.

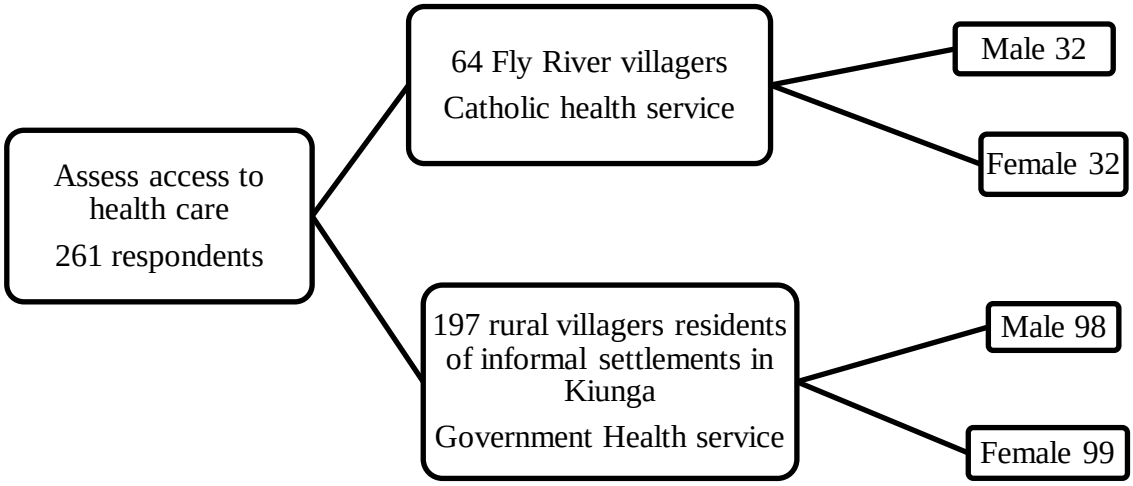


Figure 3 Selection of study subjects by gender by location. Illustrated by Miila Gena

Adult study subjects were recruited during clinics conducted in 5 Fly River villages and 5 informal settlements. Verbal responses were gathered for the questions of access to health

care via health worker consultation over 2 weeks, 6 months, and use of hospital inpatient care for last 2 weeks, 6 months and 12 months. These were recorded as yes or no on the data collection sheet. Responses were categorical variables and X^2 was used to analyse and detect any difference between the two groups with and without access to health care.

4.3 Results

4.3.1 Area of health service by the different health care providers

Figure 4.4 shows the geographical locations of the different health service providers. Figure 4.5 shows the sites of peri-urban settlements and Fly River villages.

The Catholic health services based in Kiunga and their health care coverage extend northward and westward towards the Papua New Guinea Indonesia border, as well as southward along with the Fly River communities. Moreover, this coverage extends northward to Ningerum villages of Tarakbits, Tengkim, Kumgim, Ok Tarim and Eastward towards MatKomnai Catholic station, Menumgrupe and T'moknai. The Evangelical Church of Papua New Guinea (ECPNG) provides health care eastward and southward towards the border villages of Southern Highland Province and into the Middle Fly District. Ok Tedi Health services provide health care to the extreme north of North Fly Districts that extend to beyond its preferred area of Telefomin and Oksapmin in Sandaun Province. The government health services extend from Kiunga hospital northward to Ningerum and along the Fly River and hospital service operated Kiunga, Daru, and Balimo hospitals also supported by OTLM and AusAID. Unlike other health service providers, there government health services regressed in numbers of aid posts due to unplanned closure of aid posts and under performing hospitals due to the lack of doctors.

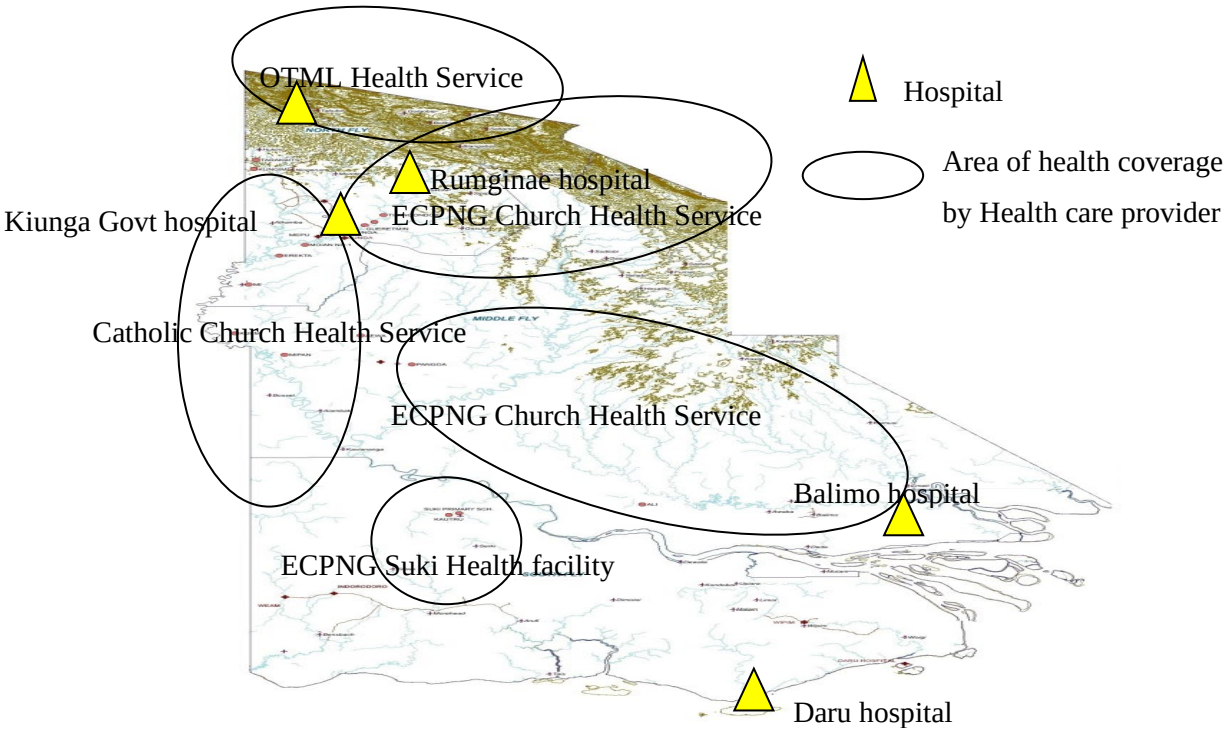


Figure 4.4 Area of health care distribution by health care providers. Imageby Miila Gena

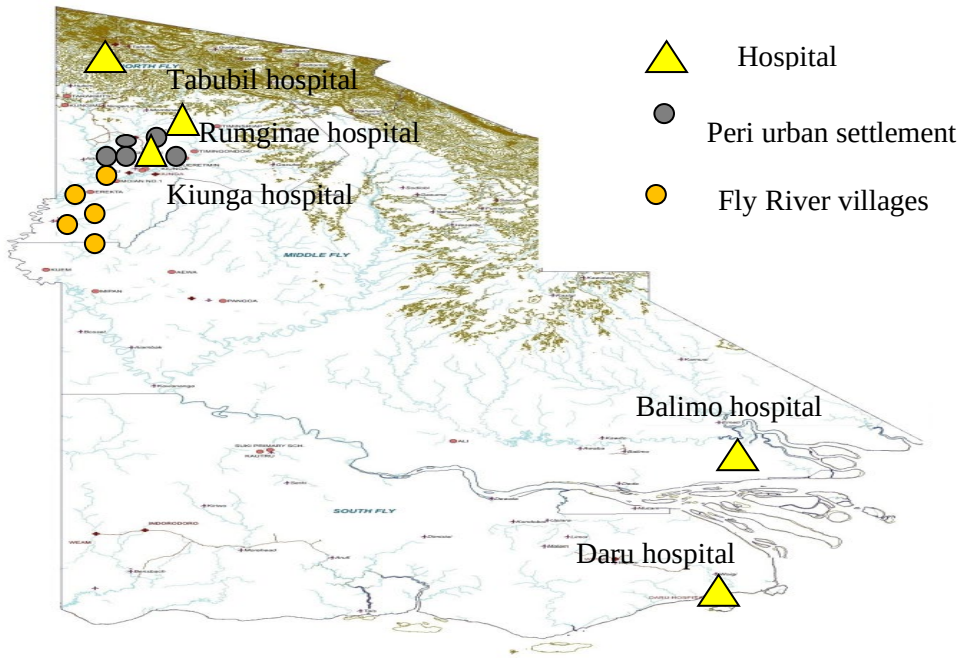


Figure 4.5 Sites of peri-urban settlements and Fly River villages. Image by Miila Gena

4.4 Access to health care by urban and Fly River villages in NFD.

A total of 261 responses were obtained from urban dwellers of 5 peri-urban informal settlements in Kiunga and rural dwellers of 5 Fly River villages south of Kiunga Township.

Chi-square analysis was used to test the difference between the urban and rural dwellers access to health care by their self-reported responses to health worker consultation and use of the hospital as an inpatient in the last 2 weeks, 6 months, and 12 months. There was no statistically significant difference between urban and rural access to health care as measured by their response to the 5 questions in Table 4.1 and both had a similar response to their need for eye care which was measured as an indicator for unmet health needs.

The similarity in access to health care illustrated in Figures 4.6 and 4.7 showed urban dwellers had greater access, more consultation with the health workers and increased usage of hospital facilities for inpatient care compared to rural dwellers. However, the difference was not statistically significant. There was no gender dffierence detected in the utilization of health care.

Table 4.1 Urban and rural communities' access to health care

Measure access to health care	Peri-urban settlers		Rural villagers		Chi-square	Chi-square	X 2
Variable's description	Male	Female	Male	Female	Test statistic	Critical value	P value
Have you accessed health care access last 6 weeks?	20	26	13	17	9.997	3.84 with 1df	1
Have you been an inpatient in the last 6 months?	15	12	4	8	1.642	3.84 with 1df	0.47
Have you been an inpatient in the last 12 months?	26	20	8	10	4.689	3.84 with 1df	0.42
Have you got any problem with your vision?	41	42	25	28	69.979	3.84 with 1df	0.68

Over 6 months rural and remote communities demonstrated similar utilization of health care between urban and rural dwellers as well as by gender.

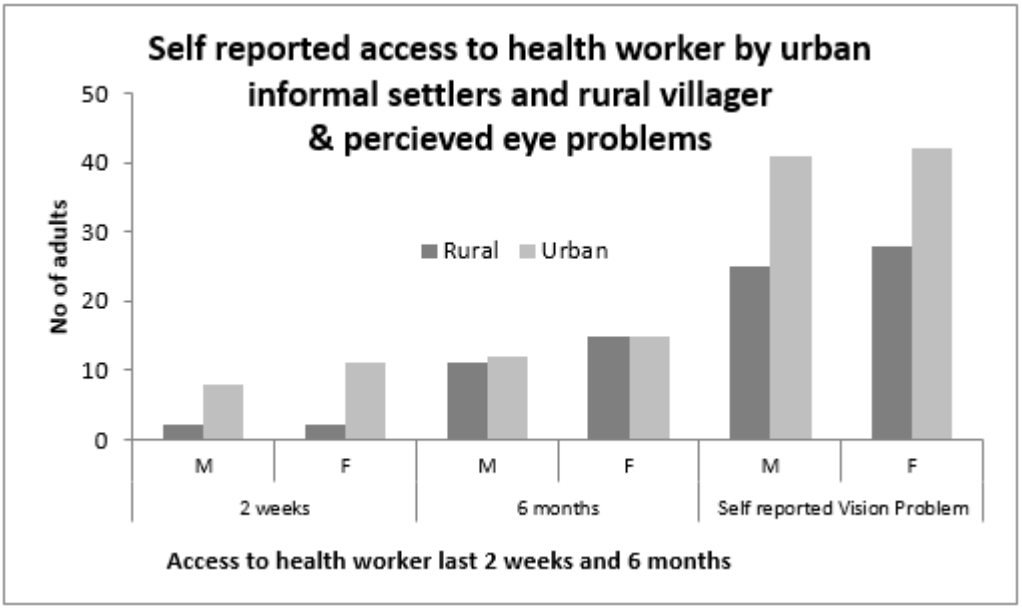


Figure 4 Utilisation of health care by urban and rural dwellers.

Perceived eye care need was used as a measure of unmet health needs between the urban and rural dwellers, but also did not demonstrate a statistically significant difference between the two groups. Primary eye care services are provided by Callan Service at the Monforte Catholic Mission headquarters in Kiunga that provides regular clinic days for eye care.

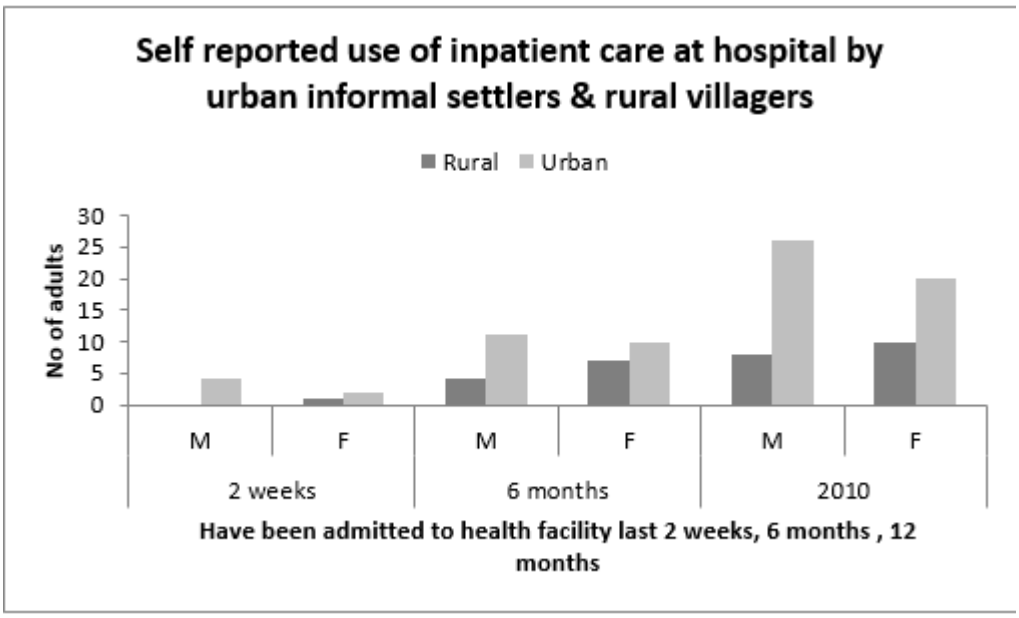


Figure 4.7 Self-reported utilization of hospital facilities by urban and rural dwellers.

4.4.1 Utilization of health facility as an inpatient by urban settlements and Fly River villages

The self-reported pattern of use of the hospital inpatient care for the different times of the past 2 weeks, last 6 months and last 12 months showed higher use by urban-based communities living in close proximity compared to their rural Fly River villages. More urban males used the hospital inpatient care compared to urban females, rural males, and rural females.

Table 4.2 Cumulative frequency of health worker visits by villagers

	Total evaluated	Frequency saw health worker in last 2 weeks	Cumulative frequency	Cumulative %
Sare Kona urban	32	11	11	42%
Mepu urban	80	7	18	69%
Seven Kona urban	20	0	18	69%
Last Kona urban	35	4	22	85%
Moian rural	13	0	22	85%
Erekta rural	7	2	24	92%
Karemgo rural	19	0	24	92%
Membok rural	17	2	26	100%
Kukuzaba rural	17	0	26	100%
	240	26		

The burden of health worker consultation in the last 2 weeks is displayed on the Pareto chart in Table 4.2 and showed that 80% of the health worker consultation was reported by urban dwellers who were residents of Sare Kona and Mepu village. These were followed by rural village residents of Erekta and Membok villages who live close to aid posts at Membok village operated by the Catholic health service. No health worker consultations were undertaken by residents of Moian, Karemgo, and Kukuzaba who live furthest to aid posts.

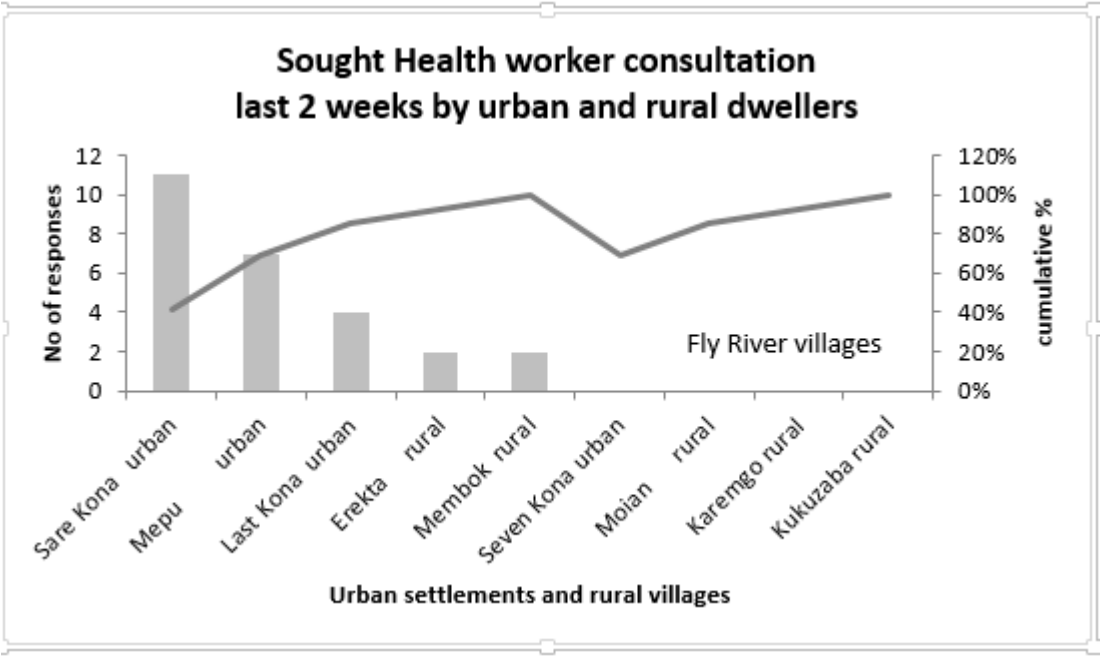


Figure 4.8 Health worker consultations by Sare Kona and Mepu residents.

Figure 4.8 Pareto chart demonstrated the 80;20 rule identified 80% of the health worker consultation was undertaken by urban residents of Sare Kona and Mepu compared to rural Fly River villagers.

Table 4.3 Cumulative frequency of consulting health worker in last 6 months

Urban settlers and Villages	Total evaluated	Seen health worker in last 6 months	Cumulative frequency	Cumulative %
Sare Kona	32	13	13	25%
Mepu	80	10	23	44%
Membok	17	10	33	63%
Kukuzaba	17	5	38	73%
Karemgo	19	4	42	81%
Last Kona	35	3	45	87%
Moian	13	3	48	92%
Seven Kona	20	2	50	96%
Erekta	7	2	52	100%
	240	52		

Table 4.3 data on cumulative frequency of consulting health workers in the last 6 months is presented in the following Pareto chart shows higher consultation of health workers by peri-urban informal settlements in Sare Kona and Mepu village. At Membok village on the Fly River, a Catholic Health Service aid post also reported a higher consultation. This supports high usage of operating health facilities.

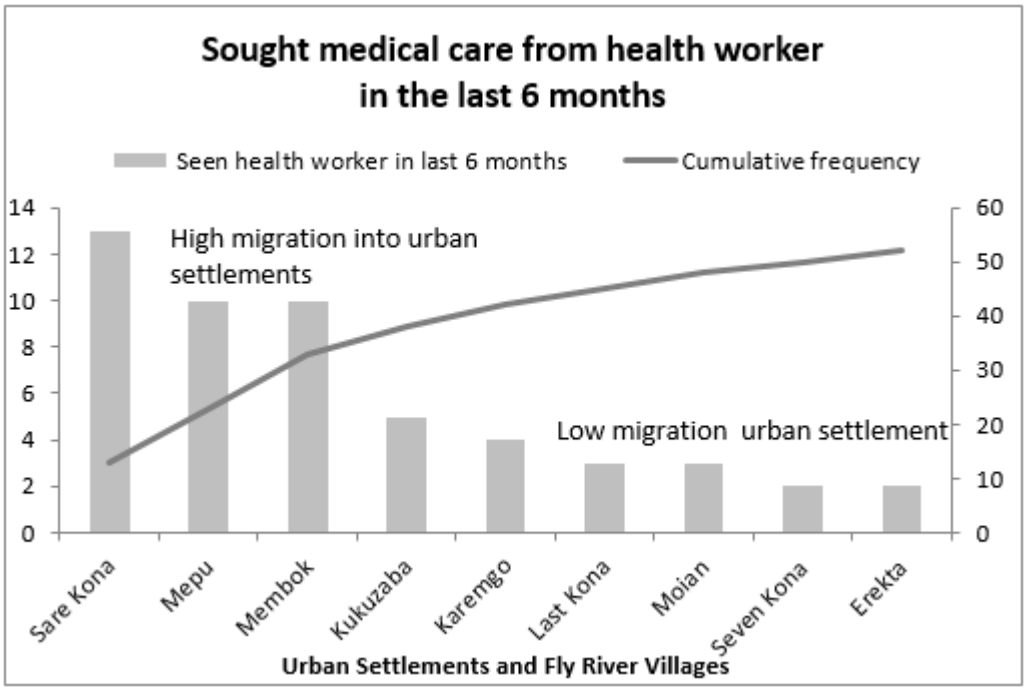


Figure 4.9 High health worker consultations by urban settlers the last 6 months.

The Membok aid post is operated by Catholic Church Health Service and provides health care to villagers of Membok, Karemgo, and Kukuzaba whilst Moian and Erekta villagers travel upstream to the town of Kiunga for health care, travel takes an hour by motorized canoe or dinghy.

Peri-urban informal settlements residents have a walking distance of 20-30 minutes for hospitals and clinics and can request assistance to be transported by ambulance. Remote villagers use traditional river transport such as wooden canoes to travel to the hospital. The Kukuzaba villagers take 2 days of travel on a motorized dinghy or a canoe to reach Kiunga hospital. To access health care at Membok aid post is a 30-minute canoe ride compared to a 10–15-minute walk by the Karemgo villagers. These remote communities bypass the nearest aid post when it is closed or runs out of medical supplies.

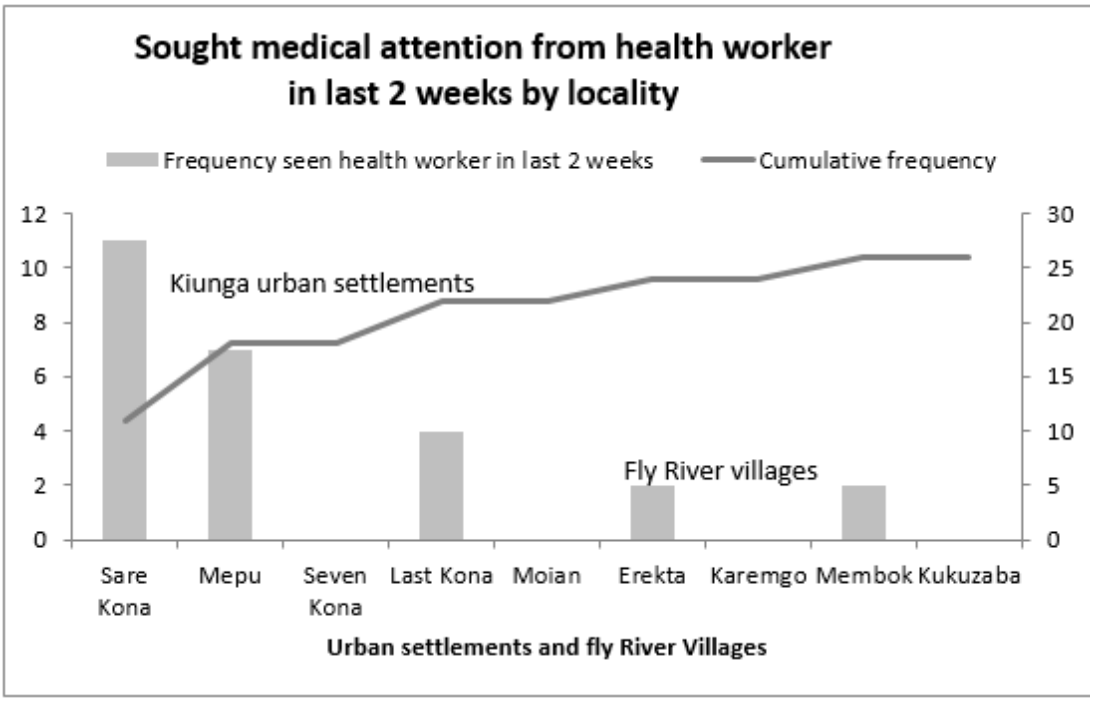


Figure 4.10 Higher health worker consultation by Sare Kona and Mepu residents.

Sare Kona and Mepu villages have a large transitional population from rural areas who sought residence with relatives for their duration of stay in Kiunga. Therefore, health worker consultations could be by the transient remote villagers. Fly River villages receive Catholic health services support and maintain day to day operations of the aid posts, allowing health worker consultation for treatment. Where there is operating aid post, care will be sought by the locals.

The peri-urban informal settlement of Sare Kona showed highest utilization of hospital-based care followed by Mepu urban village, compared to other Kona peri-urban settlements and rural villages.

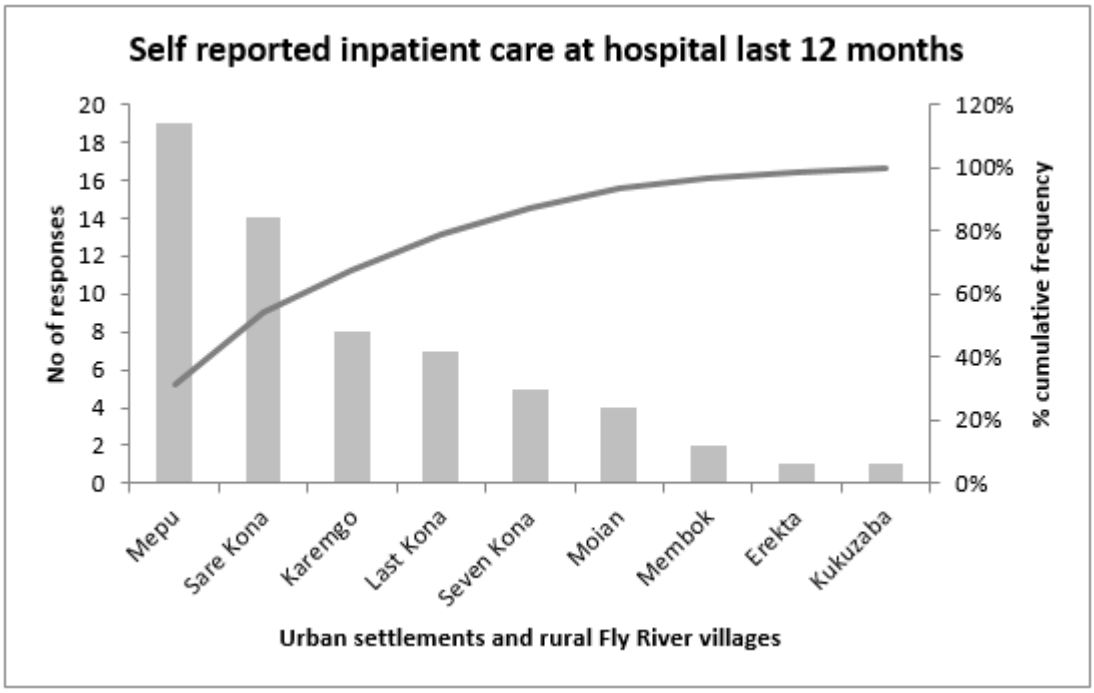


Figure 4.11 Inpatient care usage by Mepu village and Sare Kona residents.

Table 4.4 Frequency of hospital admission in last 6 months by urban and rural dwellers

Urban Kona settlement and villages		Admitted to hospital in last 6 months	Cumulative frequency	Cumulative %
Sare Kona	32	11	11	29%
Karemgo	19	8	19	50%
Mepu	80	6	25	66%
Last Kona	35	6	31	82%
Seven Kona	20	4	35	92%
Membok	17	2	37	97%
Moian	13	1	38	100%
Erekta	7	0	38	100%
Kukuzaba	17	0	38	100%
	240	38		

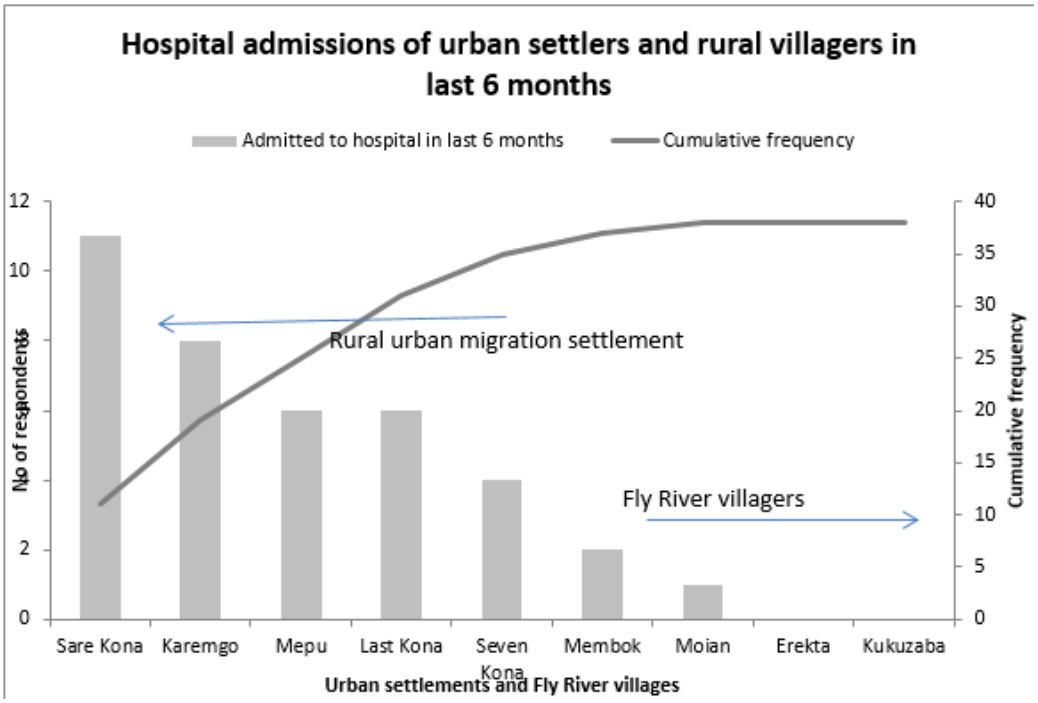


Figure 5 High inpatient care utilized Karemgo rural and urban Sare Kona.

High use of hospital care was reported by the population at Sare Kona (a peri-urban settlement) and Karemgo village on the Fly River. The villagers at upper Fly River north of Kiunga, as well as inland villages of Ningerum and those further towards the border migrate to Sare Kona to be hospitalized at Kiunga Hospital. The villagers on the Fly River travel by canoe to Karemgo to stay with relatives and seek inpatient care at Membok aid post. The increase utilization of health care by kona population reflects the inward movement from villagers preferring to access health care in the town.

4.4.2 Unmet health needs assessment of primary eye care

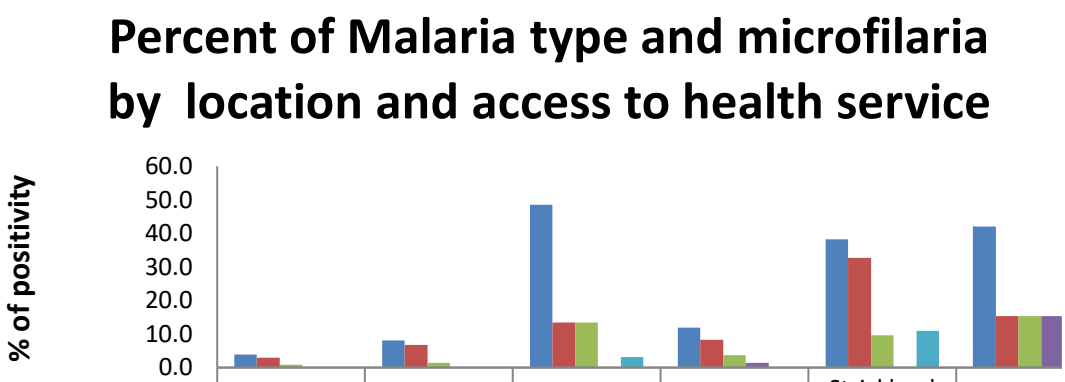
Primary eye care clinics were conducted in urban settlements of Kiunga and Fly River villages to assess the burden of eye diseases and used to identify those that required prescription glasses and/or surgical correction of cataracts and pterygium.

Out of 358 study subjects per urban and rural villages, 78 (21.78%) required treatment, this treatment group consisted of 41 (11.45%) males and 37 (10.33%) females respectively. Prescriptions were issued for reading glasses and 7 cataracts and 4 pterygium cases were

scheduled for surgical correction during the annual eye care program sponsored by Ok Tedi Mining.

4.5 Impact of access to health care and use of treated bed net

4.5.1 Burden of malaria species and microfilaria in remote communities



	Kiunga Township	Fly river villages	Inland lowland	Highland villages	Strickland river villages	Nomad villages
% Malaria	4.0	8.2	48.5	11.9	38.2	42.1
% P.Flaciparum	3.0	6.7	13.4	8.2	32.7	15.3
%P.Vivax	0.9	1.5	13.4	3.7	9.7	15.3
%P.Malariae	0.0	0.0	0.0	1.4	0.0	15.3
% Micorflilariae	0.0	0.0	3.1	0.0	10.9	6.0

Figure 6 Prevalence of malaria species and microfilariae by village.

Inland lowland, highland, Strickland River, and Nomad villagers show the highest burden of malaria and microfilaria. These are the most inaccessible villages and were unlikely to obtain treated bed nets to sleep under to prevent mosquito bites. During the study, bed nets were distributed to the villages for men, women, and adolescent children.

In PNG, Rotary against malaria was the organization that distributed the bed nets as part of the global drive for malaria control. Other organizations obtained a supply of bed nets at a cost to be sold and distributed throughout PNG. Public health sections of hospitals were actively involved in the project. It was up to individuals to purchase from the bed net outlet and in order to take them home to use. Therefore, unless there was a specific drive to transport the bed nets to populations in the in remote communities, bed nets were inaccessible. This meant that these public health interventions would not be used by those most affected by

malaria. The logistics required for distribution would be fixed wing or helicopter airlifts and drop-offs. This study bought and distributed bed nets as part of its health program. Daytime blood slides were collected from Kona settlements to remote communities in the North Fly District, inland lowland of Ningerum and T'moknai and the mountain villages of Tarakbits, Ok Tarim, extending far east to the Nomad villages of Fuma, Baniso, Somokopa, Hesalibi and riverine communities of the Strickland and Fly River. The results of daytime blood slides smears for malaria and microfilaria burden are shown below in Figure 4.14.

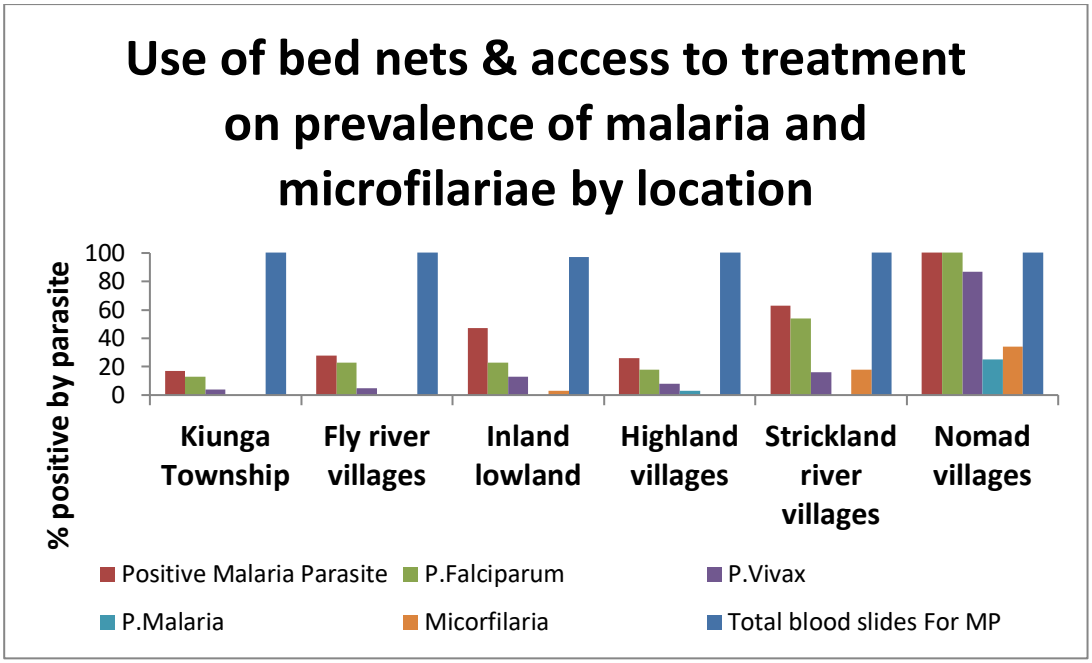


Figure 4.14 Burden of malaria increases as distance increases from the Kiunga Township

Malaria burden is lowest in Kiunga at 4% with similar levels among the villagers located within a day's walk from the town. The highland (8.2%) and inland (48.5%) villages, furthest from Kiunga along the upper Fly River the villagers have a malaria burden of 8.2%. Strickland River villagers (38.2% burden) and Nomad region villagers (42.1% burden) are inaccessible villages reachable only by air. They bear the most burden of malaria and microfilaria infection.

4.5.2 OTML long term case detection surveillance and bed net distribution

Long term sales of bed nets by the Tabubil Public Health Vector Control section was boosted by the Global Bed Net Distribution. The long-term surveillance data showed the greatest reduction was when more bed nets were distribution under the global response against malaria. Figure 4.15 and figure 4.16 showed sustained long-term monitoring of all cases that was treated att he outpatients or inpatient care had blood film examination for presence of malaria parasite. Whilst it was of economic interest for the company, it had other benefit such as further reduction due to bednet distribution by the global fund fight against malaria

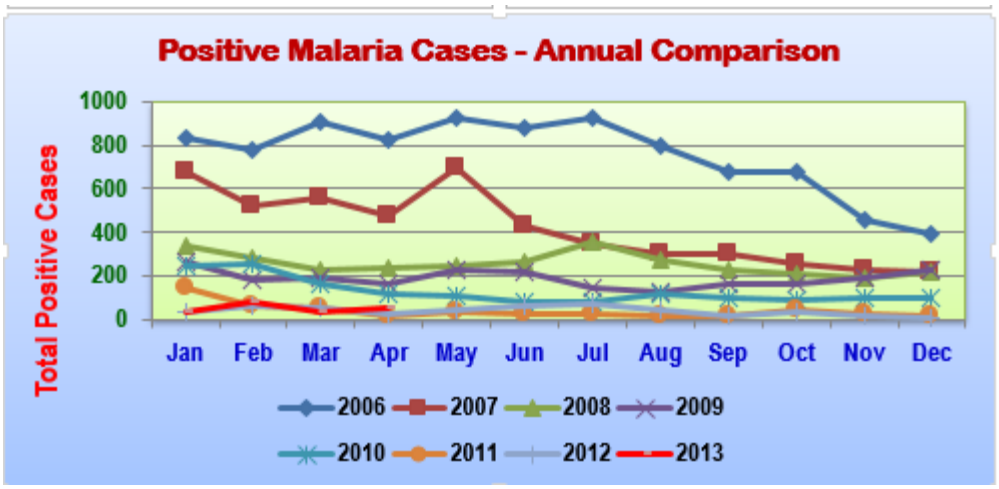


Figure 4.15 Long term malaria intervention and surveillance by Ok Tedi public health .

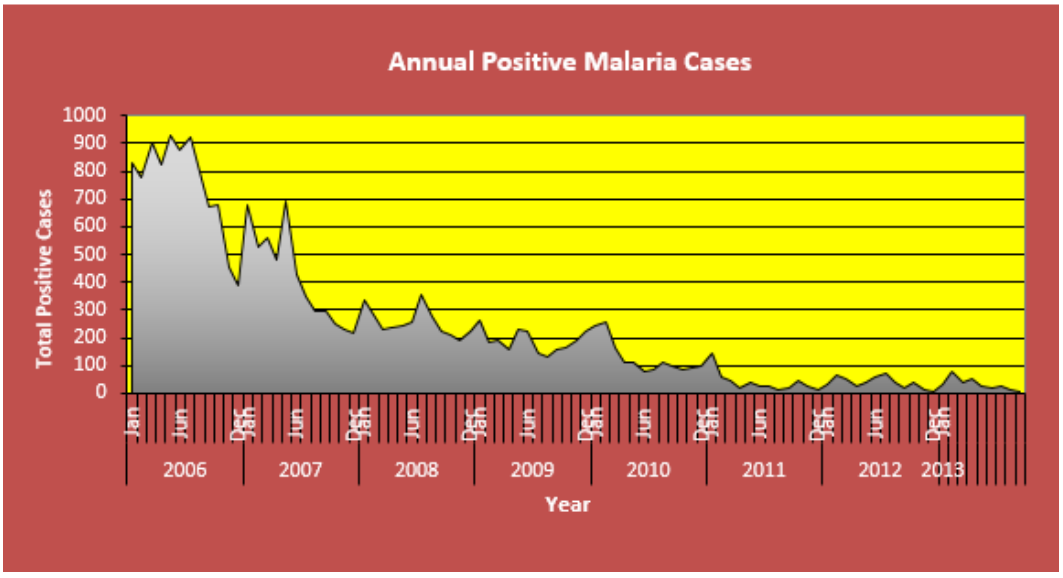


Figure 7 A dramatic drop in malaria case burden by global bed bet distribution.

4.6 Discussion

TThe non-government health services provided the most health facilities such as aid posts and hospitals that continue to remain functional; in comparison, most Fly River Provincial government health facilities remain closed. The reasons given were that they reached retirement and were not replaced or died and not replaced or simply left the facilities. The different health providers operate in different areas of the region, providing wider coverage for rural communities. During the health team interaction with these remote communities,

they collectively expressed their gratitude to the churches for taking care of their spiritual and health needs, and even more for providing schools for their children.

Church health services given by the Catholic and Evangelical Church of Papua New Guinea cover most of the remote communities in North, Middle, and South Fly Districts of the Western Province. Access to health care is important and requires government support for the delivery of bed nets to remote communities. Furthermore, government medical supplies need to reach the rural aid posts operated by Churches to ensure the communities improve their health. The churches operate and maintain the rural village aid posts whereas the government aid posts have ceased operations.

4.6.1 Catholic health services

The map of the Western Province shows that Catholic health services based in Kiunga provides health care to the rural Ningerum area to the north and westward toward the Papua New Guinea (PNG) and Indonesian border as well as southward along with the Fly to Middle Fly District. The following villages benefit from Catholic health service aid posts that operate but not all villages have operating aid posts. In Ningerum rural and Kiunga rural villages located on the Fly River were Erekta, Moian, Karemgo, Membok, and Kukuzaba. The Ningerum rural villages were Ok Tarim, Tengkim, Tarakbits, T'moknai, Menumgrupe, and Ningerum Tamaro along the Kiunga Tabubil mine road with a health centre at Matkomnai. The Catholic health service also provides a clinic for people with disabilities as well as primary eye care services at their Monforte Catholic Mission headquarters site in Kiunga.

4.6.2 Evangelical Church of Papua New Guinea (ECPNG) health services

This organisation provides health care southward towards the Southern Highlands Province and Middle Fly villages as well as the South Fly District. Balimo Hospital was formerly the headquarters for ECPNG health services, this was prior to relocating their headquarters to Rumginae in the North Fly District where they now operate a hospital and community health worker training school. The ECPNG also played a major role in operating a nursing school at Balimo hospital. The principal investigator's communications with Dr. Adeline Sitther pointed out the reason underlying the Churches withdrawal of its headquarters was a major disagreement with the locals which could not be resolved hence requiring them to relocate operations including the health services. A follow up communication by the principal investigator with Dr. Timothy Pyiakalyia from the National government health department, indicated that rural health services were needed desperately by people in all rural remote

setting and indicated the government was disappointed over such withdrawal. By default, Balimo Hospital reverted to the Fly River Provincial Government.

4.6.3 Ok Tedi Mining Limited health services

This resource developer has its own health service provider to serve mine employees as well as the township of Tabubil and the villagers living in the 40km mine radius of OK Tedi Mine operations. There is a definite plan for closure of the mine operations by the Ok Tedi Mine in 2025. They are a major provider of health services and medical retrieval from remote villagers within the mine project impact region, along the corridor of the Fly River. The mine closure is imminent. Since the discussion on the mine closure plan, Ok Tedi Mining has been assisting Kiunga Hospital with a company doctor placement within it to help improve and elevate the clinical service. This was in 2000, when the principal investigator was stationed in Kiunga to provide doctor-based care, supporting the other health workers who had been working without doctor support for years. Most medical and surgical emergencies were transported by ambulance to Rumginae ECPNG Church hospital that had doctors.

4.6.4 The OTML vector control program

The importance of maintaining surveillance or constant data collection and analysis was demonstrated by OTML trained personal where bed net interventions reduced the malaria case burden. This change was dramatically illustrated by their data trends since the mines vector control effect was undertaken to safeguard its employees and the surrounding population located within the 40km radius of the mine. The distribution of bed nets was a constant activity of the Public Health section of the Tabubil hospital. The sudden availability of bed nets under the global fund to eradicate or control malaria boosted their distribution and use which led to a significant reduction in case detections of malaria, demonstrated in figures 4.15 and 4.16. The continuity of this program also extended to the surrounding villages within the within 40 km radius of the mine with data collection and analysis since the mine started its public health program to protect its workers. This was able to show the benefit of bed net use on reducing the burden of malaria and microfilaria monitored successfully by long term surveillance microscopic examination of blood film of all febrile illness cases at the point of care facilities.

4.6.5 Fly River Government health service provider

Government health services are concentrated in the South Fly District. They provide two hospitals; these are Daru Provincial hospital on Daru Island and the Kiunga Hospital in the

North Fly District. It also operates aid posts and health centres in the North, Middle, and South Fly Districts. The government has also had administration over Balimo Hospital since the exit of the ECPNG church when they relocated to Rumginae in the North Fly District. There is a lack of visibility of government services in many remote communities of Western Province.

Kiunga government hospital is plagued by absenteeism of staff when rostered. Only a few dedicated staff work regular rosters despite not being paid their salary and other entitlements. These dedicated staff do take time out to gather food (fishing, trapping prawns, and harvesting sago to feed their families). This was noticed by the principal investigator who was working in Kiunga hospital in 2000 as part of Ok Tedi assistance to provide doctor-based support as a temporary measure to assist and guide medical care for patients. To the team of health workers who normally work without a doctor, it was a welcomed arrangement. Moreover, the company also provided temporary relief to the dedicated health workers by placing them on Ok Tedi salary for 6 months, giving the government time to fix the payment issues. The CEO, Mr. Keith Faulkner, supported this program and communications with him revealed that the royalty paid by the company to the Fly River Provincial Government would last only 2 days in the bank as massive withdrawals depleted the funds. The mining support continues through the engagement of international non-government health organizations to date.

4.6.6 Informal peri-urban settlements (Kona)

The urban settlements provided a convenient transit home to rural villagers that visit the Kiunga Township for various reasons such as sightseeing, school for children, or seeking health care from the hospitals. There was high rural-urban migration into Sare Kona and Mepu village that accounted for the increased use of hospital facilities for inpatients needing medical care.

4.6.7 Operating rural airstrips links to health and education services

This study showed that having access to an operating aid post that is easily accessible to surrounding communities like at the Membok village, utilization of health care had a similar pattern of use as that of urban dwellers The Membok village aid post was accessed by 3 villagers on the Fly River. The Fly River villagers of Erekta and Moian preferred to travel to Kiunga as it is a shorter distance compared to the Membok aid post. Furthermore, the Moian village aid post ceased operating for some time despite the health worker presence in the area.

Access to health care by communities positively correlates to the proximity of users to health facilities and declines sharply with longer distance. This is a recognized phenomenon in Papua New Guinea rural communities and elsewhere in developing countries (Müller et al. 1998; Buor 2003; Noor et al. 2006; Tanser et al. 2006). Another reason that may negate the difference was the use of treated bed nets since the 2009 mass distribution of bed nets to the remote communities. The improvement in the health of communities was evident in this study as reflected in Chapter 5. Communities that existed on the fringe or beyond existing health services were not included in this assessment as they had no access to health care. To overcome the negative effect of long distance on access to health care, new approaches have been undertaken to support governments in their plan to take health service to citizens rather than having citizens travel to access health care (Tanser et al. 2001; Noor et al. 2003; Tanser et al. 2006). Other studies have also confirmed that the burden of disease among communities negatively correlated with access to health care and was an indirect measure of their lack of access to health care. The burden of malaria parasitaemia in communities that did not benefit from malaria interventions was an example of this (Alderman & Lavy 1996; Noor et al. 2003; Feikin et al. 2009; O'Meara et al. 2009; Toikilik et al. 2010; Schoeps et al. 2011).

Hard to reach villages receive the least service due to poor infrastructure development, lack of supplies, or abandonment of posts by health worker. This was associated with the increasing burden of endemic diseases such as malaria and filarial diseases. The Church health service provides support and supplies to remotely located and isolated health workers to maintain the operation of aid posts. It was commonly reported that isolated health workers abscond from their post, depriving remote communities of basic but essential health care (Connell 1997; Gibson & Rozelle 2002; Ashwell & Barclay 2009). During this study, government health workers absconded which led to the closure of government aid posts. Low remuneration packages, lack of professional development, and isolation were identified to contribute to high attrition and exodus of health care workers (Hongoro & McPake 2004; Henderson & Tulloch 2008; Levantis & Jowitt 2009).Despite this, Church health services persevere by operating extensive aid posts among rural remote communities. Another study reported underutilization of health workers in the villages and advocated for the curriculum of health workers to be extended to include more skills. This was so health workers could become more effective in their roles as they needed to do more than being confined to the aid post (Ofosu-Amaah 1983). More often, it is a weakened health service delivery system that contributes to the deterioration and closure of health facilities. Such a scenario can reduce any gains obtained

from programs that improved health outcomes for communities through disease control and health improvement programs (Jackson 1979; Ongugo et al. 2011). Regardless of these hinderances, disadvantaged communities have a right to access health care that can be provided by committed health providers such as Church health services. Regular health patrols with a multidisciplinary team of health professionals can take health care to the remote communities by using an efficient mode of transport. The need to improve the interactions between communities and health professionals (such as doctors and health workers) will allow information exchange and education for communities to consider improving health interventions at the village level. This can include issues such as access to clean water, sanitation concerns on disposing of human and household refuse, reproductive health, childhood and adolescent health, women's health, and men's health. Improving the communities level of awareness and understanding can facilitate uptake of activities to engage in securing health and access to health care (Doerner et al. 2007).

The decline in health and poor access to health care has been extensively studied and reported on that. There is an emphasis on geographical terrain as a major contributing factor and the complete lack of unifying infrastructure that can overcome the geographic challenges. The use of fixed-wing flights in remote communities for medical supplies and medical retrieval for critically ill care improves access to health and saves lives. This strengthens health care delivery in hard to reach remote communities and poor and disadvantaged rural remote communities (Toikilik et al. 2010). It has been shown to work by the church health services and resource developers in the Western Province. Other means of travel are less efficient due to the loss of time spent travelling. A weakened health system perpetuates inefficiency and substandard care (Kolehmainen-Aitken 1992). Improving a regular and efficient system of transport can overcome the physical isolation imposed by geography (Gibson & Rozelle 2003; Allen et al. 2005). Regular use of government boats, trucks, or charter flights occurred during the colonial era to conduct government patrols. Government patrols ceased when Papua New Guinea gained independence in 1975 (Hyndman 1994). Mission Aviation Fellowship provides fixed-wing aircraft to service rural communities and provides medical retrieval services partnering with the Evangelical Church of Papua New Guinea. Church health services have been burdened with a greater patient load since government health services have deteriorated under restructuring and decentralization activities during 1977-1983 (Kolehmainen-Aitken 1992; Smith 1997; Duke 1999).

4.6.8 Rural airstrip revival program by PNG Government

Revival and servicing of rural airstrips under rural development programs has been discussed by the government of Papua New Guinea at a forum on 7th March 2013. This was viewed on the 22nd of July 2015. http://www.inapng.com/pdf_files/CIMC%20Rural%20Air%20Services%20Forum%20Mar2013.pdf. The government included the plan for rural airstrips restoration in the medium-term development plan of 2011-2015 for implementation.

Workplace safety awareness and incorporation into planning and working accordingly in PNG needs prioritizing. A PNG team of medical researchers from the Institute of Medical Research travelling in an aluminium dinghy were lost and never found in 2011. Safety of travel during work is essential and travel by fixed-wing flight to remote areas should be a preferred way of travel. All organizations need to adopt and practice workplace safety in all activities undertaken to prevent incidents that would cause loss of highly trained PNG professional during duty travel to reach fieldwork sites. All organizations must protect employees, and how work is accomplished is controlled by safety policies as a focus to prevent the loss of professionals in any outreach health programs. Assure efficient and safe travel by use of appropriate by fixed wing aircraft or helicopter airlift. This study was fortunate to be fostered by the resource developers' logistical support and safety operating policies known to the principal investigator as a former employee of OTML.

This study provides short accounts of issues that confronted Church health service in Western Province through their interactions with the principal investigator during their 5-year history of working at Kiunga government hospital as an employee of OTML. The Church health services have a strong history of providing health care in Western Province. ECPNG Church health services operated 2 hospitals in Balimo (previously pioneer missionary) and Rumginae and operated a Nursing school in Balimo. Personal communication between Dr. Adeline Sitther and the principal investigator revealed that due to landowner conflicts that proved to be unresolved without government assistance, ECPNG moved its headquarters to Rumginai where it operates a community health worker school and enlarges its Rumginai hospital facilities. Rumginae hospital was functioning as the default North Fly District hospital for many years when Kiunga government hospital was plagued by a lack of doctors. The Fly River Government Hospital constantly refer cases to Rumginai Hospital.

Personal communication with Sr. Lois, former head of Catholic health service revealed they had adopted a proactive approach at Kiunga Hospital by sharing the hospital roster with their nurses. The government employed nurses failed to work their roster and increasing numbers of nurses from church health service had to work the roster. This affected their health outreach program into the villagers as they no longer had staff to send out. Sr Lois withdrew to ensure their health patrol outreach program continued. The weakened government health care system was then supported by Ok Tedi Mining Ltd in the North Fly District, but this is a phenomenon that is widespread throughout Papua New Guinea.

4.6.9 Statistical testing on the burden of malaria

Long term malaria surveillance program by the Ok Tedi Mining Ltd had contributed to protecting the employees and their families as well as the communities surrounding communities. The use of bed nets and vector control program had impacted on the prevalence of burden of malaria. Blood slides were collected from the urban Kiunga population as well as rural villages. These slides were examined at the Kiunga hospital. The results were read as positive or negative for malaria parasite. Kiunga urban had 429 blood slides examined of which 17 were positive for malaria, 412 were negative. The Strickland villages had 165 blood slides examined and 63 of the blood slides were positive for malaria. The Chi- square test of independence was used to test if the results were significantly different between the urban rural communities.

A null hypothesis was based on the prevalence of malaria being the same for both the Kiunga urban and rural population of Strickland River. . The alternate hypothesis was that the prevalence of malaria was different between the urban and rural population. The Chi-sqaure test of independence was used to test for relationship between malaria burden between urban and rural residents. The test statistic was 119.79 which were greater than the Chi- square critical value of 3.841 with 1 degree of freedom. The null hypothesis of no difference in the prevalence of malaria between the urban and rural population was rejected and accept the alternate hypothesis of the burden of malaria between the urban and rural village of Strickland community was statistically significantly different.

4.7 Conclusion

Western Province health services depend greatly on non-government organizational health services. The ECPNG Church health services and Ok Tedi Mining Ltd provided two hospitals in North Fly Districts that have specialist doctors working, in addition to operating aid posts

throughout their respective regions. The Monforte Catholic Health service has no hospital but operated aid posts along the border villages in the north and south, and also along the Fly River. Given that the rural aid posts were operating in the communities that the study surveyed, their access to health care was like that of urban dwellers. These urban dwellers had easier access to two hospitals operated by the government at Kiunga hospital and the ECPNG Church at Rumginai as well as one urban clinic operated by the Monforte Catholic Mission in Kiunga.

The proximity of the aid posts and hospitals made access easier whether they were living in the remote rural villages or relocated to the informal settlements located in the surrounding area of the Kiunga town. For such a wide geographical region of Western Province, the existing health service providers need government annual budgetary support. There is a government grant for church health service providers which seems to not be protected as the amount allocated fluctuates or is not forthcoming from the national government. The Fly River government needs to allocate additional funds to support existing and expanded church health services and open the closed government aid posts.

4.7.1 Logistical requirements and use by health service providers

The health care providers used available logistical means to continue their health and educational services within these remote communities. Mission Aviation Fellowship (MAF) conducts flights for health and education in these remote communities. The MAF is an equivalent of the Royal Flying Doctor Service of Australia that ensures those in remote areas can be transported to where the required health care is located. Without MAF, critically ill patients will be unable to reach the urgent medical care available at the hospital. The existing service of MAF also need support from the provincial government so it can operate to serve these remote communities.

The Ok Tedi Mining Ltd responds to emergency medical calls by allowing its fixed-wing flights or helicopters to airlift emergency cases. Without these mercy flights, those that experience medical emergencies are unlikely to receive the urgent medical attention they require to survive. It is within this type of environment that this study must endure to research sago poisoning. There is a need for logistic support to reach these remote communities which was enabled by Ok Tedi Mine Ltd and Talisman Energy Niugini Ltd.

Recently, Adventist Church aviation was operating out of Kiunga to serve the Adventists communities logistic needs. Charter flights are operating but doing so on commercial hire.

These commercial flights are restricted to landing on designated town or city airstrips and do not land on village airstrips at all. Therefore, remote communities are confined to their localities. They can alternatively travel out on foot or by paddling their traditional canoes. Most travellers would need to use a combination of foot and river transport travel and would take days to weeks or even months to reach the closest town.

According to Bishop Cote, the Monforte Catholic mission had a priest who was a pilot, and they were essentially the transport system that connected their remote church stations, health facilities, and schools and also served their outreach programs. Since the plane crash at Membok airport, the pilot lost his life and the bishop received severe burns from which he recovered. The Catholic Mission therefore lost their air transport, and their extensive airstrips within the local communities were idle. The Catholic Mission now uses river transport instead.

The ECPNG church partners with Mission Aviation Fellowship (MAF) to access their remote communities over the extensive area of land. The well-maintained rural airstrips are managed and paid for by the ECPNG church, as confirmed by Dr. Adeline Sitther of Rumginai hospital. The influence of the ECPNG church on the communities was further reflected by the community's maintenance of a clean environment in the village along with well-constructed pit latrines and general cleanliness of the villagers.

The MAF also responds to urgent medical calls for transporting medevac emergency cases to hospital. Had this comparison been made between communities without health care availability, it would not have been helpful. Self-reported access to inpatient hospital care was different but not statistically significant. Regardless of that, access to hospitals needs to be secured to transfer medical emergency cases from remote communities to hospitals for essential life-saving treatment. There has been a lack of visibility regarding government services in these remote communities. In place of these services, the church health services, particularly the ECPNG have held a strong presence through their aid posts operating among the remote communities which are supported by the hospitals. Similarly, Catholic Church health services operated aid posts within the Fly River communities and westward remote communities towards the Papua New Guinea and Indonesia border. Catholic health service does not have a hospital, therefore refers patients that needed doctor-based care to the Kiunga government hospital. Their outpatient services showed that the access and use are the same as that provided by the Kiunga government hospital's outpatient services. To obtain such results,

all village aid posts need to be operating. But the government aid posts remained closed as observed during the fieldwork. The logistical transport link was provided by the Mission aviation fellowship (MAF) by working in close collaboration with health and education providers to these remote communities.

There was greater reliance on Church health services by remote communities as they were the major health care providers in Western Province; whilst weakened government health care machinery was supported by OTML and AusAID in strengthening hospital services. Support was not necessarily provided for reopening their closed village aid posts or health centres to improve access to health care by remote communities.

The government must consider the use of fixed-wing flights on a regular basis to provide health care to rural villagers. The use of fixed-wing flights was essential for medical retrievals in addition to the delivery of government supplies as well as health and education personnel to remote communities. There is a lack of government visibility in these remote communities. Mission Aviation Fellowship operate flights to these remote communities and have been conducting medical retrieval of critically ill cases for many years.

4.8 Recommendations

4.8.1 Budgetary support to Mission Aviation Fellowship

Logistics is a necessity for any organization and therefore government charter flights need to be secured to deliver government services to remote communities. This is important to improve access to health care and ensure medical emergency retrieval of critically ill cases to hospitals. This can be achieved through budgetary support to assist the Mission Aviation Fellowship in continuing their aid to the people of Western Province. Rural airstrips also need to be maintained to allow planes to land. This will also allow the transfer of sick people to the nearest airport to be airlifted to the hospital.

The provincial government could consider a fleet of sea ambulances as there are extensive river systems which the people can use for travel using modern means. This will allow patients to be brought to the nearest airport to be airlifted by fixed-wing flights. Other patients can be brought in powered dinghy direct to the wharf where the hospital ambulance can transport them.

4.8.2 Budgetary support needed to open closed government health facilities

Disadvantaged communities with closed government aid posts needed to be rescued by reopening those aid posts. The Fly River Provincial government had not approached the church health services to manage these remotely located aid posts. The church health service managers were concerned as the government aid posts were permanently closed and were eager to negotiate with the Fly River Provincial government to be allocated the resources to reopen and manage them. The people needed health services, and the churches were effectively operating similar aid posts throughout the region. This would be more efficient as current operators have an existing health network with logistical support into these remote communities and just require the government budget to take on extra aid posts. Collegial communication between the principal investigator and Dr. Adeline Sitther of ECPNG Church health services highlighted the dire need to open the closed government aid posts, but this requires staff and budget resources. These were the basic requirements to operate facilities in these remote communities.

Whilst the church health services continue effectively operating extensive aid posts and hospitals, the government healthcare delivery outward ceased and its hospital in Kiunga was operated by nurses without doctors. Patients requiring doctor-level care were rapidly transported by ambulance to the church hospital. Data collected on sago poisoning cases reflected their referral to Rumginae and Balimo Hospitals. It was the juxtaposition of a weakened government system burdening the church health services that had extensive health outreach program. Dr Sitther of Rumginai ECPNG church hospital informed the principal investigator that when hospital workload increases, she was no longer able to go to their remote aid posts for their regular doctor supervision. Both Sr Lois and Dr Sitther reported their support to government hospital workload directly reduced their own health outreach programs into the communities which was unacceptable to them. A permanent solution was needed to restrengthen the weakened government health system. Whilst the government remained silent and lacked visibility in the communities, Ok Tedi Mining Ltd took a proactive step by placing their doctor (the principal investigator) in Kiunga Hospital. This reduced the burden of patients seeking doctor consultation at the Rumginai and Tabuil mine hospitals. This further resulted in the engagement of international health non-government organisations as an intervention to alleviate lack of doctor-based service. However, a permanent solution still evades this problem. The budget and staffing of the government health system needed to be transferred to current church health service providers. Whilst this appears an obvious

solution, it is not fostered by the Fly River Provincial Government. The culture of government employees getting paid without necessarily working rostered hours is an accepted as normal operation. It seems to be beyond repair from the weakened government delivery system, but the church health services continue to improve access to health by their doorstep in most remote communities. This is common knowledge among the communities and other service providers but is not effectively managed by the government of Papua New Guinea.

There were three different health care providers located in Kiunga and a fourth hospital was reachable by road operated and maintained by the Ok Tedi Mine Ltd. Each health service had their own extensive aid post locations throughout their area of coverage. These provide health care needed by remote communities which remain isolated due to the lack of government developed logistics for efficient and safe travel. The health care providers support remote communities by delivering supplies and supervisory visits to maintain aid post operation. Indirectly, access to an operating aid post by remote communities amplified the beneficial effect on the control of endemic diseases like malaria and filariasis; aid posts became the distribution points for bed nets as well as providing rapid access to treatment for malaria.

4.8.3 Financial support to international health non-government organization

This study recommends that church organizational health services are supported by government and other funding sources to enable them as existing health care providers and reach more remote communities. The data on improved health contained in this study was the effect of sustained long-term operators such as the public health services provided by the Ok Tedi Mining Ltd. International health non-government organisations cannot transform the wellbeing of rural communities without real investment and outreach programs. International non-government organizations that embed within government services needed to be evaluated in terms of their output and the sustainability of their activities. Assessment is required regarding their health intervention activities and impact on the governments set of priorities.

5 Chapter 5 Health assessment of rural remote villagers

5.1 Introduction

5.1.1 Aim

A cross-sectional study (also known as a prevalence study) was used to assess the baseline health status of the population living in rural remote communities of North and Middle Fly districts of Western Province where Sago haemolytic disease was endemic. Clinicians practicing in lowland communities in Papua New Guinea have no prior knowledge on the premorbid health profile of SHD cases and their source populations. It was difficult to ascertain the severity and effects of SHD from that of other pre-existing conditions. Identifying proxy health indicators of SHD endemic communities sheds light on the severity and complications caused by SHD and differentiates them from that of pre-existing medical conditions. Sago haemolytic disease was shown to be a medical emergency condition. In this study, the baseline health of sago eating communities was measured. This will inform the clinicians of the premorbid health status of the population when they present to the hospital with any illness, but particularly sago poisoning. The baseline health of the remote communities was recorded by measuring demographic details, body mass index, blood pressure, full blood examination, and biochemistry. These parameters were used as proxy measures for nutritional, renal, and liver functions in addition to testing for urinary abnormalities (by use of multistix) as well as the burden of malaria and microfilaria. Results of malaria and microfilaria data are not discussed in this chapter.

5.2 Study sites

5.2.1 Fly River and Inland villages of North Fly District

Eight remote communities in three regions were evaluated in the North and South Fly Districts: the highland villages of Ok Tarim, Tengkim, and Tarakbits are located northwest of Kiunga township towards the Papua New Guinea and Indonesia border; the inland villages of Ningerum Tamaro, Menumgrupe, T'moknai are located on the Ningerum plateau and reaching into the mountains northward of Kiunga Township; and the Fly River villages of Membok and Kukuzaba located south of the Kiunga wharf. A comprehensive clinical, haematological, and biochemical assessment was undertaken to reflect the health profile of these communities.

5.2.2 Permission for access into communities

Permission to access communities was secured through the community relation officers of Talisman and Energy Niugini Ltd. Accommodation arrangements and village support were secured with meal preparation duties delegated to the group selected by the village leaders and elders.

5.3 Logistics required by the health team

Health team visits to communities were organized by Community Relation Officers of Talisman Energy Niugini Ltd through consultation with village leaders and elders. Through the arrangement, each community approved the use of accommodation and selected a team of helpers from the communities to cook meals for the health team. The health team and their medical supplies were transported to each village by helicopter, except for the village for Ningerum Tamare community located on the Kiunga Tabubil road where road transport was used.

5.4 Selection of study subjects

Study subjects were restricted to adults who attended the adult medicine clinic. The study only recruited adults that verbally consented to fully participate by allowing collection of their demographic details, responses of self-reported symptoms and clinical signs. In addition, they provided 10 ml of blood for haematological and biochemistry as well as urine samples for field tests.

5.5 Sample size calculation

The sample size calculation was based on the worst-case scenario of 50% of the population being burdened by ill health. The precision of the estimated sample size will use a 95% confidence limit to detect the burden of illness to with a 5% margin of error and a required sample size of 385 people. The sample size consisted of 429 adults, 226 males and 203 females who were drawn from 8 villages. The adult study subjects were examined by the principal investigator during the village clinics.

5.5.1 Sampling Frame

The 2000 census population of each village that received health programs is presented in Appendix 1. The population of the 8 villages during the 2000 census was 1,743, split into 857 males and 886 females. Since then, there had been major rural-urban migration leaving a lower population in these remote villages. The population count has not been updated since, despite the recent census for the population of Ok Tarim, Tengkim, Tarakbits, Ningerum Tamaro, Menumgrupe, T'moknai, Membok and Kukuzaba villages.

5.5.2 Requirements for sample size calculation:

Confidence interval=95%, Standard deviation=0.5, Margin of error or confidence interval =5 %

Calculation of sample size= $(1.96)^2$*0.5(0.5)/ $(0.05)^2$

= 3.8346*0.25/0.0025

= 0.9604/0.0025

=384.16

=385 study subjects were required.

The study selected 708 adult study subjects to account for population with and without access to health care to capture differences in proxy health indicators measured between the two groups.

5.5.3 Selection of study subjects

A convenient sample of 708 adult study subjects was recruited by the study to evaluate clinical symptoms and determine proxy health markers between those populations with and without access to health care. Access to health care was defined as the village health facility was operational.

The remote communities' access to health care is shown by whether their village aid post was operating (Figure 5.1). Their health assessments were compared using their access or lack of access to an operating aid post. The Government and Catholic health service offer health service in the area depicted on the map. Government aid posts were not operational..

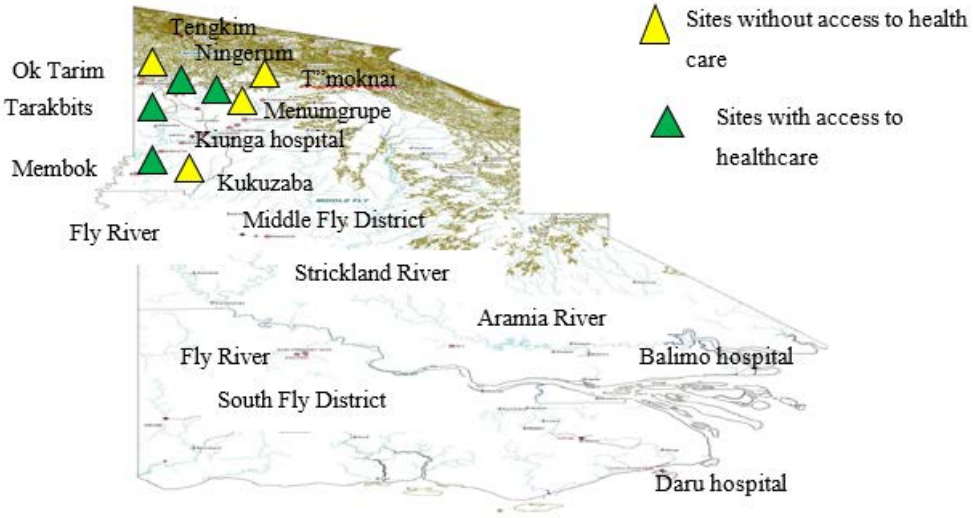


Figure 8 Operational status of village aid posts. Figure prepared by Miila Gena.

The health assessment conducted on the communities that live in th highlands region of Ningerum, the lowlands communitiesliving along the Kiunga Tabubil road as well as the Fly River communities. The results are compared between populations according to the operational status of their village aid post to ascertain their health profile.

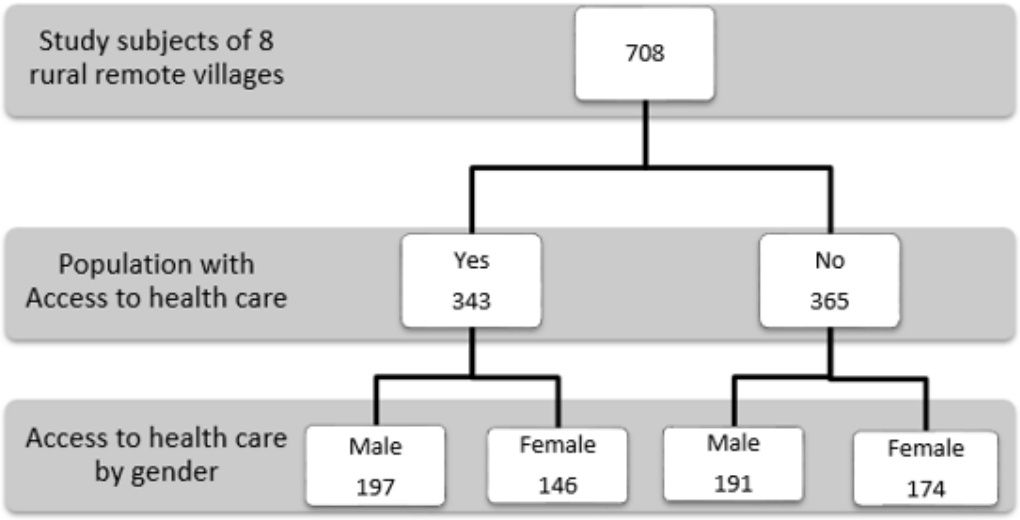


Figure 5.2 Health assessment study subjects' selection by gender. Figure prepared by Miila Gena.

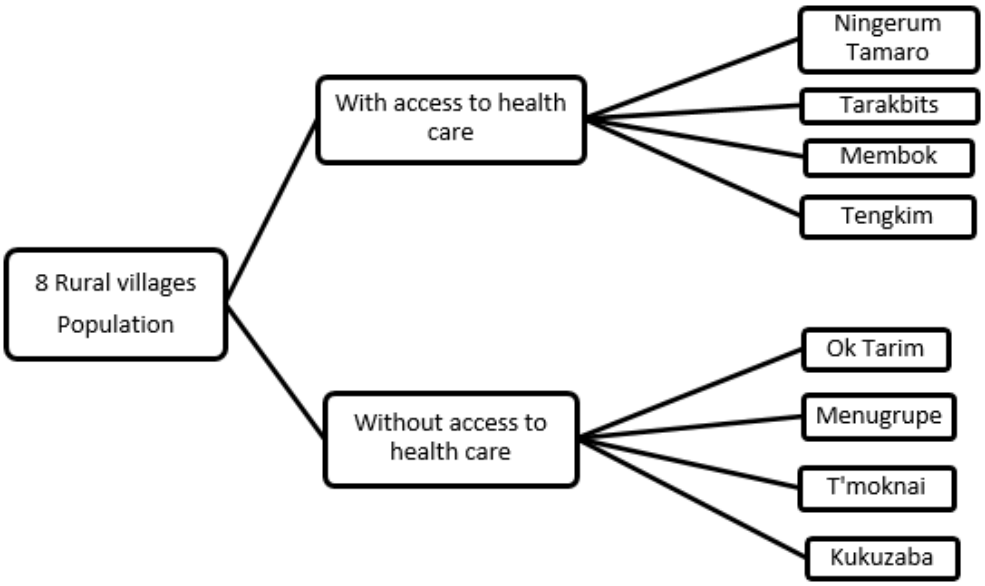


Figure 9.3 Access to health care by village. Figure prepared by Miila Gena.

5.5.4 Selection of study subjects by villages by gender for the study

Table 5.1 Total number of adults evaluated by gender

Access to health care	Male	Female	Total
Yes	197	146	343
No	191	174	365
Total	388	320	**708**

Table 5.2 Village population with and without access to operating health facility

Villages with access to health care					**Villages without health care access**				
No.	**Village**	**Female**	**Male**	**Total**	**No.**	**Name**	**Male**	**Female**	**Total**
1	Tengkim	35	21	**56**	**1**	Ok Tarim	57	52	**109**
2	Tarakbits	49	43	**92**	**2**	T'moknai	74	59	**133**
3	Ningerum Tamaro	62	39	**101**	**3**	Menumgrupe	11	22	**33**
4	Membok	51	43	**94**	**4**	Kukuzaba	49	41	**90**
Total		**197**	**146**	**343**	**Total**		**191**	**174**	**365**
Grand total	**708 interviewees (study subjects) from the highland and lowland and Fly River villages in North Fly District**								

A total of 708 study subjects were chosen out of the total population of 1,743 in the 8 villages. At the time of the health program, there had been a marked reduction in the population at those remote villages due to rural-urban migration.

Due to the availability of transport, all samples of blood were transported to Kiunga laboratory where haematological analysis was undertaken, and this facilitated storage of sera for biochemistry and future testing. Field tests were conducted on urine samples.

5.5.5 Inclusion and exclusion criteria

The inclusion of study subjects was restricted to ethnic groups that resided in the village thereby excludes visitors who were allowed to receive health care from the clinic. An equal number of males and females were not possible to be recruited in some remote villages as women were instructed by their husbands to stay away. Blood samples were drawn only from the study subjects who gave their verbal consent to participate in the study. Individuals were excluded if they were unable to consent. The participation was sought in an open and transparent way through the gathering during the health communication session with the presence of the community leaders and elders.

5.6 Selection of proxy health indicators

Proxy health markers were determined by the proportion of the population that registered low or overweight body mass index, a haemoglobin level <10gms/L (designated as anaemia), and abnormal or elevated levels of blood urea, nitrogen, creatinine, and/or uric acid. Other proxy health indicators were low levels of total protein and serum albumin and elevated levels of bilirubin, cholesterol, triglyceride, and HDL (high-density lipoprotein). The albumin and globulin ratio was also determined to assess adequacy for mounting an immune response. Due to the availability of daily transport between Kiunga and these villages, blood samples were able to be transported daily to Kiunga hospital where a full blood examination was conducted, and the remaining blood was stored for biochemical analysis.

5.6.1 Collection and handling of samples

Venepuncture was carried out by a pathology technician, who collected 15 ml of blood from each consenting adult study subject. Of this 15ml, 5ml were collected in an EDTA bottle for haematology and a further 10ml was collected in a plain bottle as clotted blood for separation and storage. A single blood film was prepared for each study subject to be used in microscopic examination for malaria parasites and micro-filarial worms. Field tests were conducted on urine samples by use of a multi-stick to detect the presence of protein, sugar, blood, and haemoglobin. Log sheets were used to record details of study subjects and results of urine tested in the field. Kiunga hospital laboratory technicians used a coulter counter analyser for haematological examination on samples on the same day of collection. Blood films were stained, and microscopic examinations were conducted throughout the study to

identify malaria parasites type and microfilariae. The results of the malaria and filariasis examination are part of the impact study on bed net distribution and results are presented in Chapter 4 to assess health care access and impact of this public health intervention.

5.6.2 Data collection – data entry forms

A data collection form was created listing the specific variables to be recorded for each study subject. Height, weight, blood pressure, as well as symptoms and signs were to be recorded. During the evaluation, the attributes were recorded or where required a yes or no response was entered to responses for specific variable questions. Data entry was done using Microsoft Excel. The use of a detailed questionnaire was difficult where work needed to be processed rapidly and accurately as it required at least 20 minutes per study subject.

5.6.3 Self-reported symptoms and medication

The adult population that attended the medical clinic were the study subjects. They were interviewed to report if they had been ill in the last 2 weeks. What were the symptoms affected them? Had they sought medical attention from a health worker? Did they receive inpatient care at any hospital in the last 6 months? Questions on symptoms were on the presence of cough and its duration, shortness of breath, swelling of the feet and ankles, presence of diarrhea, vomiting, and abdominal pain. These symptoms would indicate the presence of respiratory, cardiovascular, and/or gastrointestinal illness. Furthermore, a question on the possession and taking of prescription drugs were also asked of each study subject.

5.6.4 Physical evaluation, measurements, and treatment

The physical evaluation included measurements of height measured in centimetres using a height meter, weight measured in kilograms on a bathroom scale and blood pressure checks with a mercury sphygmomanometer after 10-15 minutes whilst the study subject sat in a chair during the interview. The presence of pallor and splenomegaly were recorded. Any further physical examination was directed by the subject's history and presence of other abnormal clinical features. Each study subject's clinical details, diagnosis, and prescribed treatments were recorded in their personal medical record book. This is the property of the study subject and is used to obtain care at the treatment station.

5.7 Data Collection from personal medical record books

Clinical findings, height, weight, blood pressure and responses obtained were recorded into the study subjects' medical record book as evidence of the clinical evaluation undertaken. This provides a permanent medical record that informs clinicians and other health workers of their past medical history which they present to access health care or as an outpatient. The Papua New Guinea government advocates for all children ≤ 5 years old to have a baby book to record immunizations, illness, diagnoses, and treatment received by the child that provides a continuum of records that is kept by the parents, usually the mother. Similarly, adults were also encouraged to buy personal medical record books (or any book) to take to the health facility at the time of medical consultation to allow health workers to keep records. This record remains with the patient and is produced at each attendance as an outpatient. Furthermore, a discharge summary on care received as an inpatient is attached to the personal medical record book. Where there is no supply of paper, the inpatient diagnosis, treatment, and laboratory results are written in the personal medical record book. One thousand personal medical record books for babies, adults, and women's health were distributed to participants during the study. When reviewing cases, it is recommended to ask for ownership of the record as other family members may use the same book for their health needs, particularly if they do not own a book. Due to the lack of stationery at health facilities, health workers ask all attendants to bring their books to allow documenting clinical notes, treatment, and follow up.

5.7.1 Issuance of treated bed nets to communities

The study provided 1,000 insecticide-treated bed nets of varying sizes for a single person up to a family net that would allow several persons such as mother and several children. The provision of bed nets was highly appreciated by community leaders and those that received them. The communities stated that while they will get sick again, they now have the bed nets and can sleep under them for a long time to remain well for longer periods. Giving bed nets to the participants increased the scope of treatment to these individuals by allowing their use as a public health intervention. This was in addition to the treatment of medical conditions detected during the clinical evaluation. The members of these communities appreciated both the clinics and the bed nets. Their full participation allowed data collection from remote communities which usually are not available.

5.7.2 Treatment station

The nursing officer and community health worker operated one treatment station where treatment was dispensed to cases. This was done according to the treatment plan recorded in their personal medical record book. Each participant was also given a bed net to use in their homes.

5.8 Community engagement programs

To create an open dialogue between the health team and community, the principal investigator first met with the village elders and members of the health committee to introduce members of the health team. The principal investigator then introduced members of the health team to the community. Each member gave a short account of their professional history to their current status as part of the health team that demonstrated the wealth of professional experience present. This built the profile of cumulative experience of the health team who were engaged to conduct health clinics for the community. Additionally, it was requested for members of the health team to meet with the community to deliver public health messages. Questions from the community were responded to by members of the health team. This strategy was adopted for delivering health programs to each remote village to impart important public health messages, but also to increase interaction between villagers and health teams. This was done with the aim of enhancing individual and community understanding of health.

The church supported communities were cleaner, had regular scheduled clean up days, operating aid posts, schools, and an operating airstrip. The airstrips were maintained and paid for by the church. Communities that received government services were not as organized; these were communities that had relocated to a new site such as a migrating population near a resource developer site for oil and gas exploration or mining. Collective activities that can be undertaken by the communities to promote their health were evident but required organization and schedules. Church supported communities were able to achieve means to better health outcomes compared to communities without church supported services. Public health messages on improving understanding around access to clean and safe drinking water was emphasised at each village health meeting, for example, drinking water sources must be fenced in to prevent human and animal waste entering the water as rain can wash faeces deposited on the ground, causing it to enter the water source. Communities were instructed to build pit latrines away from drinking water sources. Images of drinking water sources

contained in the thesis show the lack of access to clean water (Chapter 3). Discussions were interesting as well as entertaining and provided a direct benefit to communities as they could interact with doctors and senior health workers in a community setting. This was a rare occurrence but very much needed to enhance greater understanding as well as facilitate and sustain health improvements at the village level. The community leaders recalled such meeting during the colonial era where the government officers met with people in their villages. Since independence, remote communities were not visited by government patrols. It is important for villagers to see their government and its services reaching them where they areow the lack of access to clean water. Discussions were interesting as well as entertaining and provided a direct benefit to communities as they could interact with doctors and senior health workers in a community setting. This was a rare occurrence but very much needed to enhance greater understanding as well as facilitate and sustain health improvements at the village level. The community leaders recalled such meeting during the colonial era where the government officers met with people in their villages. Since independence, remote communities were not visited by government patrols. It is important for villagers to see their government and its services reaching them where they are.

5.8.1 Need for interpreters

The village elders identified interpreters to translate the health talks. Health workers who spoke local dialect would also interpret during the health program. At the end of the health talks, questions were invited from the audience and responses were provided by the appropriate health professional who delivered the relevant health topic. Due to prior arrangements, communities were able to eagerly gather to hear health talks delivered by members of the health team. Some villages visited had 5 different languages spoken but the elders chose 3 interpreters based on the language spoken by most of the population.

5.8.2 Health education talks

The emphasis of these health talks consisted of two parts. The first part focused on promoting community health by specific group activities described in community engagement program. The second part focused on the health needs of specific segments of the population in the communities such as the health needs of women and men during their reproductive years, health needs of children 5 years and under, health needs of adolescents, and health needs of the older population.

The advice provided touched on good nutrition and frequent feeds for children. The paediatrician stressed the importance of completing the immunization plan for each child to protect against specific illnesses such as polio, whooping cough, diphtheria, tetanus, measles, and hepatitis B.

In order to promote women's reproductive health, the talks had to openly advocate for it. Reproduction and associated parturition were considered culturally taboo subjects. The strategy to break a cultural taboo was to have a male obstetrician gynaecologist to give the talk. This strategy allowed the naming of anatomical parts of female and describing of the birthing process to be done by the male obstetrician rather than any of the three women doctors on the health team. This strategy forced men to listen to another man whose profession focused on pregnant women and that ensured they delivered their baby safely. For the first time, men expressedin the community meeting that they know the hardships faced by pregnant women but were bound by their customs and cultures so when their wives died, due to pregnancy they took on new wives. Now they could start to take steps suggested to protect their wives like spacing children with use of contraceptives. Their wives must deliver in hospitals but when the hospitals are too far, they could call for help early for medical retrieval. The men were told to not allow the sun to set when a woman is in labour. The baby must be born as any delay will result in two deaths, the mother and the unborn child stuck in the birth canal. This was how men could contribute to improving and protecting women health.

The health team felt safe and welcomed when health messages were received as well as they were intended to. The adults opened up to inform the health team about the frequent teenage pregnancies experienced by the communities. Their daughters were not going to high schools because of pregnancies. The boys were also not completing their secondary education. The community was divided into groups of men, women, adolescent males, and adolescent females. Each doctor was able to talk to the groups to answer questions. The leaders reported that they have learnt from the health talks because of the time spent interacting with them in question-and-answer sessions. Most of the communities agreed that there needs to be more communication and interactions like this to help them progress their community health.

5.8.3 Clinics for each segment of the population

Five different clinics were conducted concurrently for each village to ensure that all segments of the community received a medical evaluation. Paediatricians conducted clinics for children, obstetrician gynaecologists conducted clinics for women, a physician conducted a clinic for

adults, and school children and adolescent health clinics were evaluated by the senior general practitioner. Eye and dental clinics were also delivered by the ophthalmologist and dental technician from the government health service of Daru hospital.

5.9 Results

5.9.1 Analysis and hypothesis testing

Descriptive statistics were used to describe the data. A single proportion test was conducted for the proportion of study samples that had normal body mass index and anaemia to compare to the results of the past study. Additionally, a t-test was used to test for differences in mean levels of biochemical proxy health indicators of total protein, serum albumin, blood urea nitrogen, creatinine, cholesterol, triglyceride, and high-density lipoprotein between communities with and without access to health care.

Two hypotheses were tested to assess overall health improvement by testing a single proportion found to have anaemia, haemoglobin <10gm/L and a registered normal body mass index of 18.5-25kg/m^2 in this study compared to results of the previous study by Flew- OTML in 1998 (Flew 1998).

5.9.2 Mean age distribution by village

In the North Fly District, the villagers either live in the highlands or at the lowlands or by the river side of the Fly River. The highland villages are Ok Tarim, Tengkim, Tarakbits and T'moknai whereas the lowland villages are Ningerum and Menumgrupe. The villages along the Fly River are Ereckta, Moian, Membok and Kukuzaba.

Table 5.3 Descriptive statistics of ages of the adult population of 8 villages of the North Fly District.

Remote Villages	N=707	Mean Age in years	Median	Standard Deviation	Minimum	Maximum
Ok Tarim	Male	45.05	41	13.59	18	78
	Female	45.44	42	12.69	18	70
Tengkim	Male	30.77	24	15.53	18	68
	Female	35.86	38	12.43	18	56
Tarakbits	Male	37.88	38	16.99	16	78
	Female	38.09	38	16.27	16	78
T'moknai	Male	40.22	41	10.7	20	69
	Female	41.16	42	10.86	20	69
Ningerum	Male	40.34	41	10.96	20	69
	Female	40.56	41	11.11	20	69
Membok	Male	36.78	36	16.42	16	75
	Female	37.37	36	16.53	16	75
Kukuzaba	Male	35.14	30	16.08	15	76
	Female	32.93	30	14.34	15	70
Menumgrupe	Male	43.55	46	17.26	18	70
	Female	42.41	45.5	14.44	17	70

This table shows the summary statistics by age for the 8 villages that had a comprehensive health assessment. Due to the low literacy rate reported in Papua New Guinea, age recall is an estimate provided by the investigator. The study participant will recall their probable age at a time of a major or significant event then count the number of years from that event to the current year to obtain their age. As such the estimated age is not accurate. The church records may verify ages for some individuals.

The age distribution of these villages individually is shown in Figures 5.4-5.10.

Ok Tarim (Figure 5.4) was the most remote village and was located near Papua New Guinea and Indonesia's border. Many young families had migrated to other towns after the teacher abandoned his post at the school. Predominantly older men and women remained in the village. The resident health worker had left the village for a long time, so the aid post was closed. Travel to Kiunga town takes three weeks of walking and canoe ride.

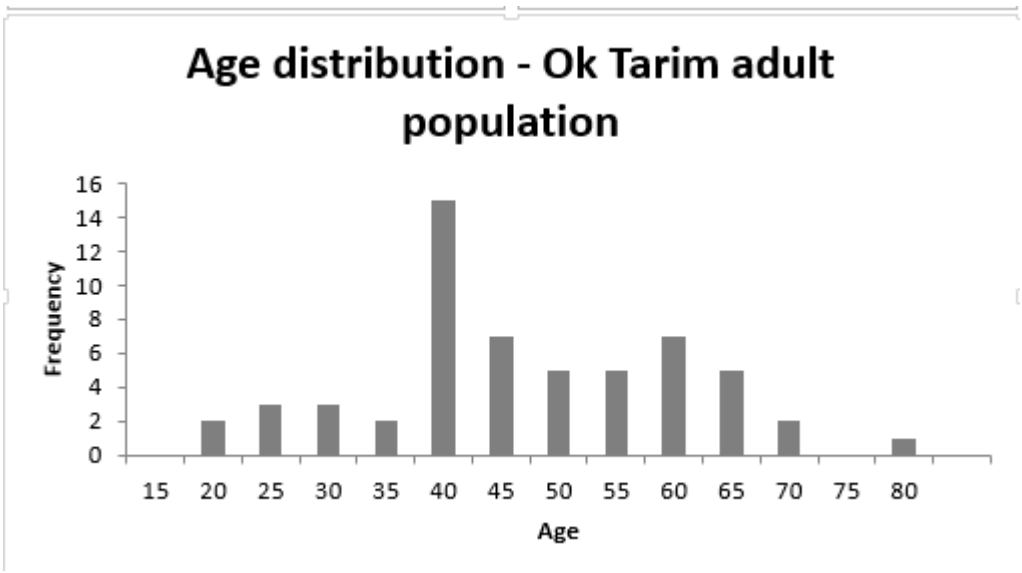


Figure 5.4 Age distribution of Ok Tarim population.

The majority of the Tengkim population (Figure 5.5) had moved to resettle near towns and the government station at Ningerum to allow their children to go to school, this was despite a local school being established in their village. There were many young adults in the population. Physically fit individuals were able to travel to and from Ningerum government station in a day. Onward travel to Kiunga takes 2 hours by motor vehicle, or a whole day of travel downstream on the Ok Tedi River with further travel upstream on the Fly River to reach Kiunga by night when the health facility was operational.

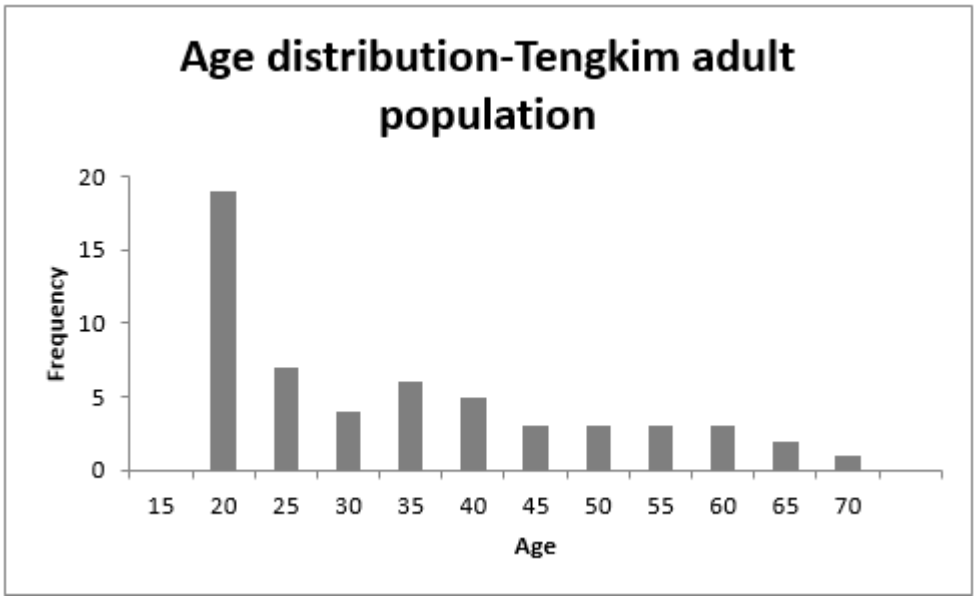


Figure 5.5 Age distribution of Tengkim population.

The population of Tarakbits (Figure 5.6) consisted of young adults and an older population. The Catholic Church operated the high school and a large health facility that had nursing officers, who provided health care.

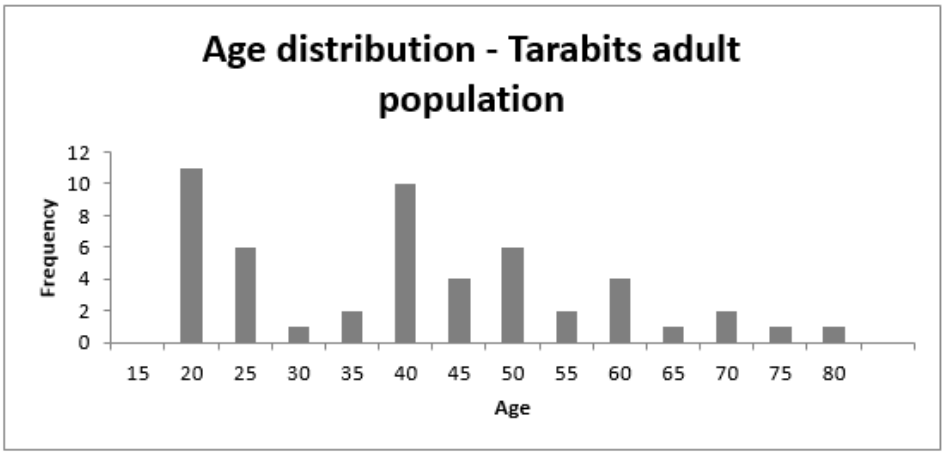


Figure 5.6 Age distribution of Tarakbits population

Many families with children from Menumgrupe (Figure 5.7) moved northward to Sonai's main village to enable their children to attend school. The remaining population was older

people as well as young parents, whose children leave home for school each week and return on the weekends and holidays.

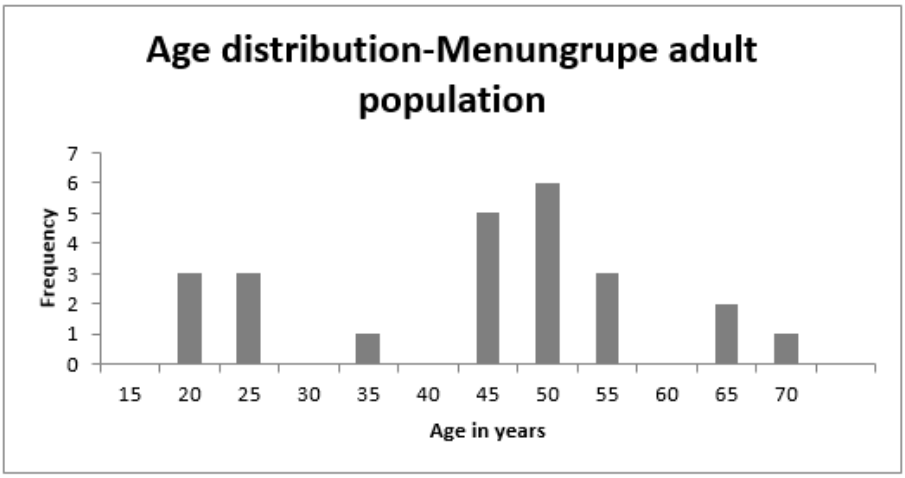


Figure 5.7 Age distribution of Menumgrupe population.

The young population from Ningerum (Figure 5.8) moved to the main town for employment as well as education for children. Older adults remained in their village and participate in engagement with resource developers, particularly the mine.

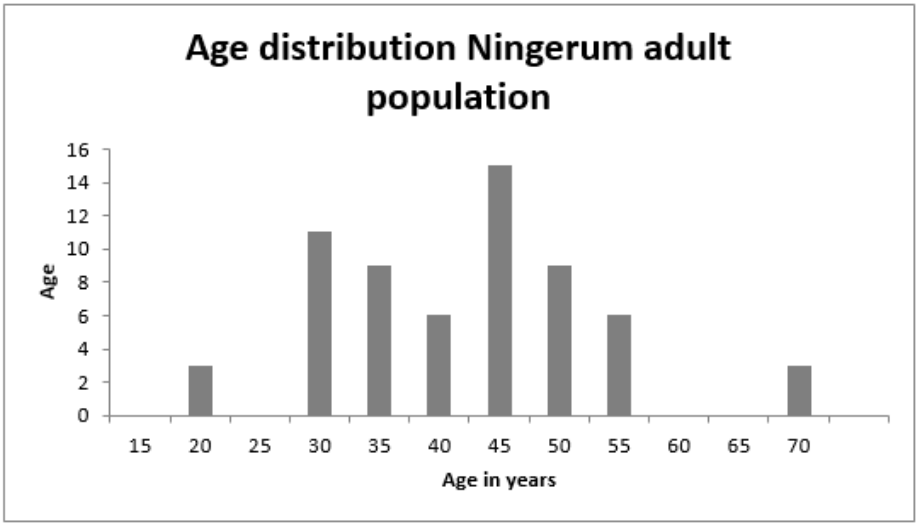


Figure 10 Age distribution of Ningerum Tamaro population

The Catholic Church operates a school and health facility in Membok that serves several villages in Kukuzaba and Karemgo. There were young, old, and refugee populations here (Figure 5.9).

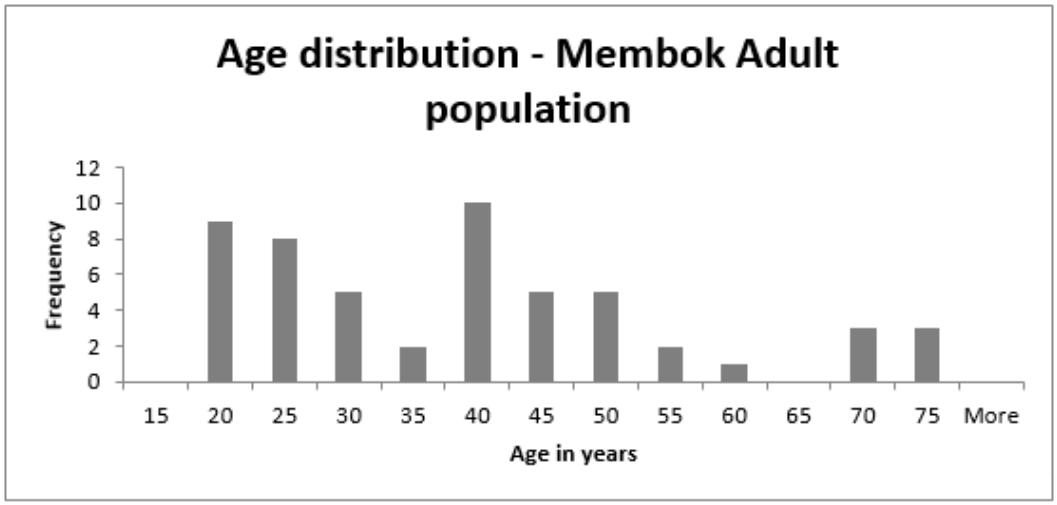


Figure 5.9 Age distribution of Membok population

Kukuzaba (Figure 5.10) was the furthest village visited. It had a young and old population as well as a refugee population. Its school and health facilities were closed for a lengthy period. It was the only village that managed to connect a large water tank to collect rainwater. Men instructed women not to attend health programs.

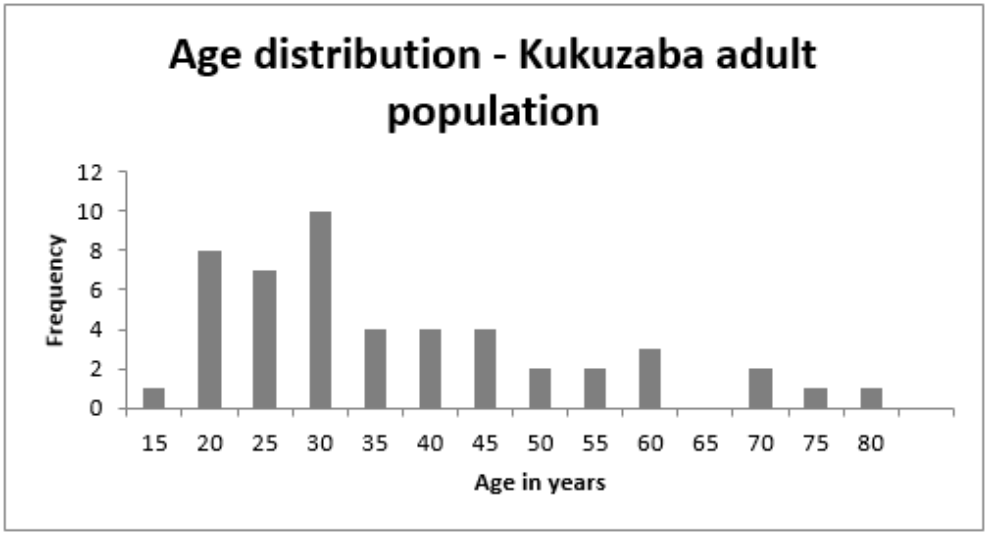


Figure 5.10 Kukuzaba population

5.9.3 Self-reported illness

This study attempted to assess the burden of self-reported illness of fever, body aches, and joint pains in the last 2 weeks by three villages of Takarakbits, Membok and Kukuzaba (Table 5.4). In males this was 8-24% compared to women with 6-22%. This was for the villages of Tarakbits in Ningerum highland as well as the Membok and Kukuzaba villages of the Fly River.

Table 5.4 Self-reported illness by gender by village

		Self-reported illness last two weeks		
Region	**Village**	**Total**	**No**	**%**
Ningerum	Tarakbits	67	5	7.46
Fly River	Membok	46	5	10.86
Fly River	Kukuzaba	54	9	16.67

The health survey showed 7.46%-16.67 % of the remote villagers had self-reported acute illness of fever, body aches and joint pain over the previous 2 weeks. This was related to access to an operating health facility. The highest level (16.67%) was reported by Kukuzaba village which does not have an operating health facility.

5.9.3.1 Impact of operational aid post on self reported illness

The research question addressed here was: Was there a relationship between the burden of self reported illness by rural populations and the operational status of the village aid post? (as described in Chapter 1.

A chi-square test of independence was used to test for any differences in the self reported burden of illness. Chi - square analysis was used to test for difference in the self reported illness with 1 degree of freedom; the test statistic critical critical value was 2.22, which was <3.841 for an alpha value of 0.05 indicated that an operating aid post had no statistiscally significant impact on the burden of self reported illness. The completed steps taken for the Chi square analysis was attached to the Appendix.

> The Null hypothesis: Self reported illness burden was similar for rural populations irrespective of operational status of the village health facility.
> The alternalte hypothesis: Self reported illness burden was different between the 2 rural populations dependent on the operational status of health facility.

5.9.3.2 The burden of self-reported illness in adults by gender

Tables 5.5 and 5.6 show self-reported illness in different villages.

Table 5.5 Tarakbits community self-reported illness by gender

Ningerum Highland illness last 2 weeks	Tarakbits Illness	No illness	Total pop
Male	5	28	33
Female	2	15	17
	7	43	50

Tarakbits self-reported illness was 5/33=0.15 in males and 2/17 = 0.12 in females.

Table 5.6 Kukuzaba adults self-reported illness by gender

Fly River village Gender	Kukuzaba Illness	Not ill	Total pop
Male	5	35	40
Female	2	7	9
	7	42	49

Kukuzaba self-reported illness was 5/40 = 0.13 in males and 2/9 = 0.22 in females.

5.9.3.3 Smoking status of remote communities

Self-reported current smoker status for males was 67-88% and for women this was 29-35% (Table 5.7). They smoked locally grown tobacco and leaves. Villagers preferred to smoke cigarettes but were unable to buy any in their villages as there was no operating trade store.

Table 5.7 Self- reported as smokers by gender by village

Region	Smoker Village	Total	M	%	F	%
Star Mountain	Tarakbits	67	23	34.32	14	20.89
Fly River	Membok	46	14	30.43	11	23.91
Fly River	Kukuzaba	54	35	64.81	2	3.7

More males reported that they smoked 30-65% compared to 3.7-21 % of women. Membok women reported the least number of smokers at 4% compared to 20-23% of women from other villages. Similarly, fewer Membok men self-reported as smokers at 14% compared to

23-35% by men of other villages. Tobacco used for smoking was grown and villagers used other leaves to roll their smoke. Cigarette smoking was preferred but not used due to the lack of general lack of access to manufactured goods in remote communities. Needless to say that exposure to smoke generated from a wood fires in homes was common, and is a norm in remote communities. It is a way to keep their roofs dry for longevity and is used for preserving food items in Papua New Guinea.

5.9.4 Physcial findings

5.9.4.1 Mean age and blood pressure by gender

The age of adults was estimated in remote communities due to the inability to recall birthdays accurately. Younger adults were able to recall a birth date or view baby books that had birthdays recorded by health workers. It is not unusual to have adults recorded as an estimated age (Table 5.8, Table 5.9 and Figures 5.11-5.13).

Table 5.8 Men mean age and mean blood pressure by village

Remote village	Men Mean age in years	mean systolic BP mmHg	Mean diastolic BP mmHg
Tengkim	31.48	120.9	75.26
Kukuzaba	34.51	121.47	82.83
Ningerum	35.55	120.39	81.52
Membok	36.62	119.32	80.32
Tarakbits	37.74	121.81	77.9
T'moknai	40.17	120.9	75.26
Menumgrupe	42.6	119	75
Ok Tarim	45.6	120	72.63

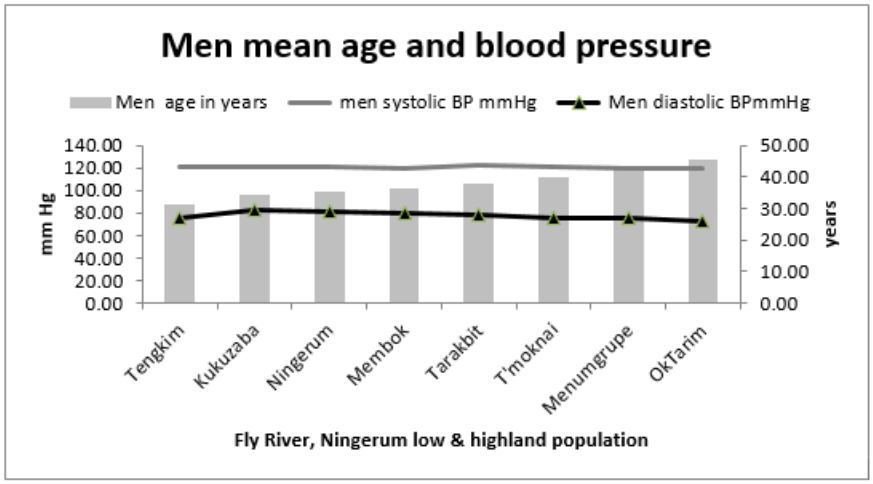


Figure 5.11 Men mean age, systolic and diastolic blood pressure by village

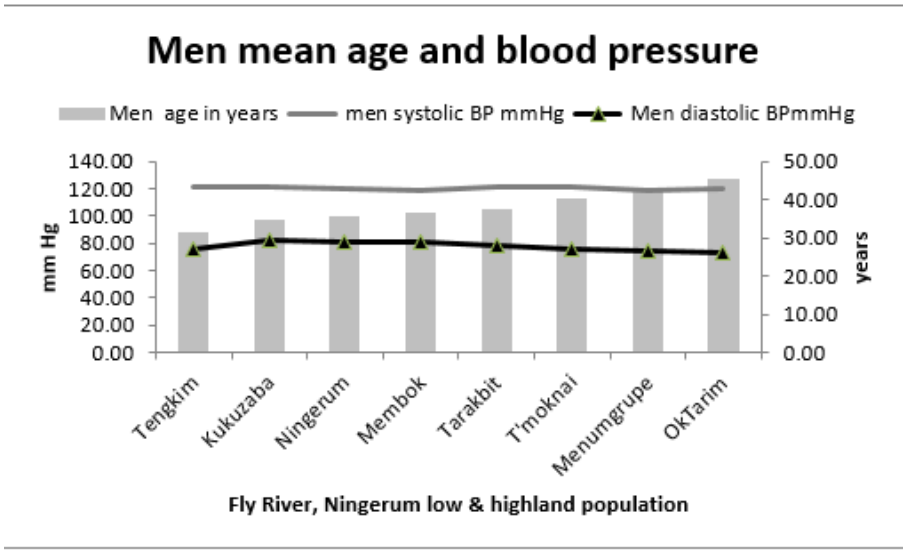


Figure 5.12 Men mean age and blood pressure by village

Table 5.9 Women mean systolic and diastolic blood pressure by village

Remote Village	Women Mean age in years	Mean systolic mmHg	Mean diastolic BP mmHg
Tengkim	32.26	119.99	75.37
Kukuzaba	33.02	120.93	83.02
Ningerum	34.94	120.14	81.67
Membok	36.85	119.34	80.31
Tarakbits	38.41	119.48	77.67
T'moknai	40.28	119.99	75.37
Menumgrupe	42.14	119	75
Ok Tarim	46.6	120.51	73.08

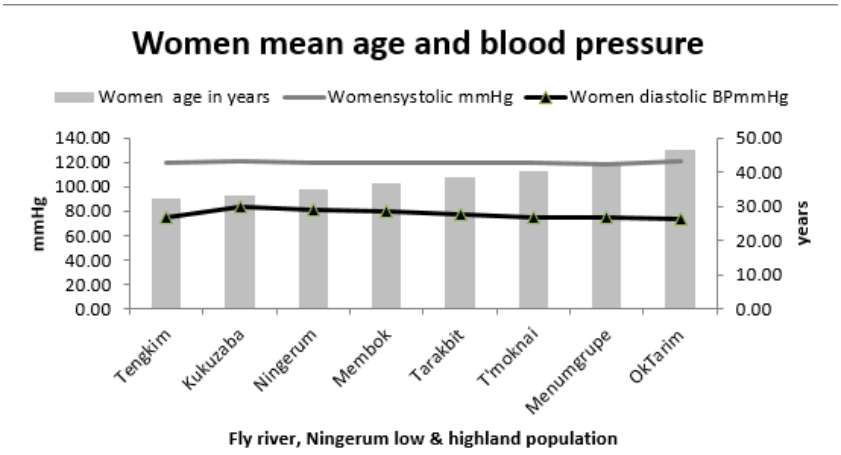


Figure 5.13 Women mean age, systolic and diastolic blood pressure by village.

5.9.4.2 Body mass index assessment

Physical measurements of height in centimetres and weight in kilograms were used to calculate body mass index (weight/height^2). Its distributions are tabulated and also illustrated as a bar graph by village by gender.

Table 5.10 shows body mass indexes of 305 adults from 6 villages of rural Ningerum and Fly River. Sixty-nine adults (22.6%) registered abnormal body mass index, 15.1 % (46/305) were underweight, 4.9 % (15/305) were overweight and 2.6 % (8/305) were emaciated. As rural

dwellers they lived without access to mechanized transport and access to refined starch, fats, and overall excess calories. Furthermore, 77.4 % (236/305) of subjects had normal body mass index. This is graphically demonstrated in the figure below.

Table 5.10 Categories of body mass index by village

Health care Yes/No	Villages	<16kg/m^2 Emaciated	16-18.5kg/m^2 Under weight	18.5-25kg/m^2 Normal	25-30kg/m^2 Overweight	Total
No	T'moknai	1	7	34	0	42
No	Ok Tarim	2	13	30	3	48
No	Kukuzaba	1	2	25	5	33
Yes	Tarakbits	3	10	42	1	56
Yes	Membok	0	4	51	5	60
Yes	Tengkim	1	10	54	1	66
Total	6	8(2.6%)	46 (15.1%)	236(77.4%)	15(4.9%)	305(100%)

5.9.4.3 Distribution of body mass indices by category.

Bmody mass indices for rural villages are shown on Figure 5.14.

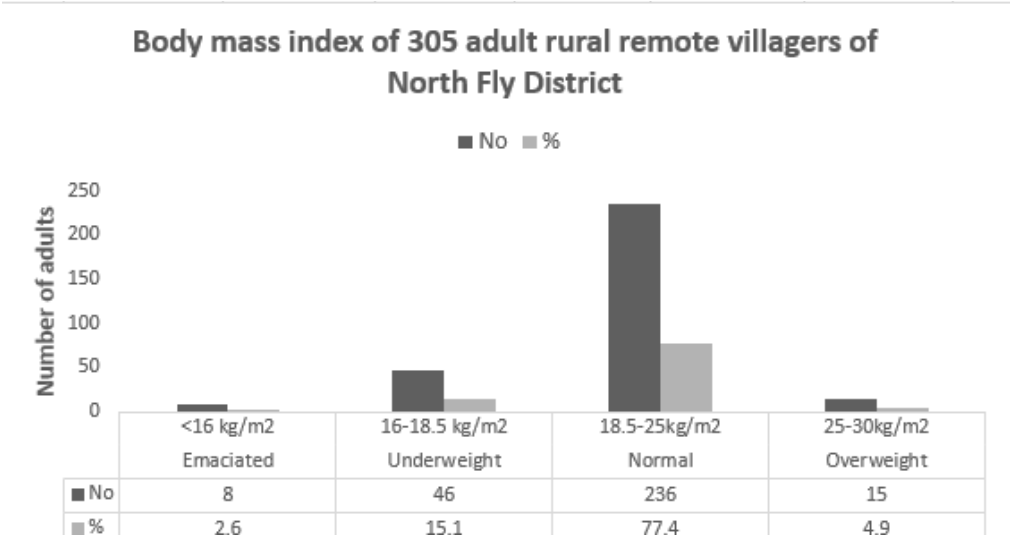


Figure 5.14 Body mass indices of rural villagers.

Hypotheses testing was done for changes in proportion of normal body mass index and anaemia. The 1998 Flew-OTML study of 322 study subjects along the Fly River revealed 83% had a normal body mass index and 11% had anaemia. These statistics were tested against this study proportion's results on the body mass index and anaemia. The conditions of normality were met for both tests as the study used simple random sampling and the samples were independent. The sample size calculated for n (p) and n (q) >10 was greater than 10 for both hypotheses.

Normal body mass index	Anaemia
1 H_O P = 0. 83	2.HO: P=0.11
H_A P ≠ 0.83	$H_{A:}$ P≠ 0.11
Phat= 0.774	Phat = 0.17
q = 0.23	q= 0.83

The conditions for normality were met as a random independent sample, and sample sizes of N*P and N*Q were greater than 5 for both and alpha was 0.05.

This allows hypothesis testing between the 77.4 % of 305 and 83% of 322 study subjects of 1998 study by Flew-OTML. The null hypothesis states no statistically significant difference in the proportions of normal body mass index of the previous and this study. The alternate hypothesis states that there was a statistically significant difference between the two proportions of normal body mass index.

The following parameters were used in analyses to test for any significant difference in body mass index. A significance level of 95% was used with a margin of error of 0.05, N=305, p = 0.83, q= 0.17, p hat = 0.774. There was no statistically significant difference in the proportion of adults registering a normal body mass index between 1998 and this study. This is because the Z score of 0.02157 was less than the critical value of 3.178 accompanied by a p-value of 0.982 which is not statistically significant. The null hypothesis cannot be rejected as there was no statistically significant difference in the proportion of adults with normal body mass index between the two studies. This meant that these remote communities had little to no significant change in their diet or access to mechanised transport to increase their body mass index and therefore remained the same.

Despite the lack of any statistically significant difference in proportion of normal body mass index, new proportions for abnormal body mass index were established for future comparisons. These indicated being emaciated 2.6%, underweight 15.1%, or overweight 4.9%. Moreover, the emergence of noncommunicable disease was confirmed by 4.9% of body mass measurements being indicated as overweight.

5.9.5 Haematology results

5.9.5.1 Anaemia

When designating haemoglobin levels to anaemia, a number of traits are to be considered such as a population's diet, endemic diseases, and genetic traits for different erythrocyte responses to the environment. Anaemia in Papua New Guinea was determined as haemoglobin < 100gms/L as stipulated in the standard treatment handbook for Papua New Guinea. This is the equivalent of a hospital treatment handbook provided to resident medical officers to use in hospitals in a developed country. This study detected anaemia in 52 (or 17%) of 310 blood samples (table 5.11).

Table 5.11 Summary of haemoglobin level among 310 males and females

Level of Haemoglobin gm/L	Male	%	Female	%	Total	%
≥ 120	0		0		0	0
<120	86	27.74	172	55.48	258	83.23
<100	11	3.55	40	12.90	51	16.45
≤50	1	0.32	0		1	0.32
Total	98	31.61	212	68.39	310	100.00

The haemoglobin levels in lowland and highland communities of the North Fly District showed that 83.2 % (258/310) had haemoglobin between 100-120gm/L. Only 16.8% (52/310) had haemoglobin (<100gms/L) low enough to be considered to have anaemia. Reproduction and associated parturition were considered culturally taboo subjects. This affected 12.9 % (40/310) of women compared to men with 3.9 % (12/310), a single male recorded anaemia with haemoglobin of ≤50gm/L.

The burden of anaemia was reported by the Flew study in 1998 as 11% in a sample of 322. This study detected 16.8 % of 310 study subjects had anaemia. The null hypothesis of no difference in the proportion of anaemia between the two samples was tested. The alternate

hypothesis there was a statistically significant difference between the two proportions of subjects with anaemia.

The following parameters were used in analyses. A significance level of 95% was used with a margin of error of 0.05, N=310, p = 0.11, q= 0.89, p hat = 0.168. The Z score of 3.26376 was greater than the critical value of 3.178 and its corresponding p-value of 0.0011 meant that both were statistically significant. The null hypothesis of no difference in the proportion of adult population with anaemia was rejected and the alternate hypothesis was accepted as had a statistically significant difference in the 2 reported proportion of anaemia. The rural remote population had reduced anaemia levels compared to 1998 with the use of minimal interventions such as access to the treatment of malaria, and public health measures such as the use of bed nets against endemic infections like malaria and filariasis.

5.9.5.2 Haemoglobin and indices distribution by village

A box plot distribution of haemoglobin identified the burden of anaemia among study subjects of inland lowland villages of Ningerum, Timoknai, and Menumgrupe (Figure 5.15). These communities live on the foothills of Ningerum but spend prolonged periods in the lowlands to gather food and harvest sago, which exposes them to mosquito bites. Past studies have shown these populations to have the highest burden of malaria and micro-filariasis with enlarged liver and spleen. This improved with treatment for filariasis instituted by OTML public health intervention (Lourie et al. 1986; Schuurkamp et al. 1992).

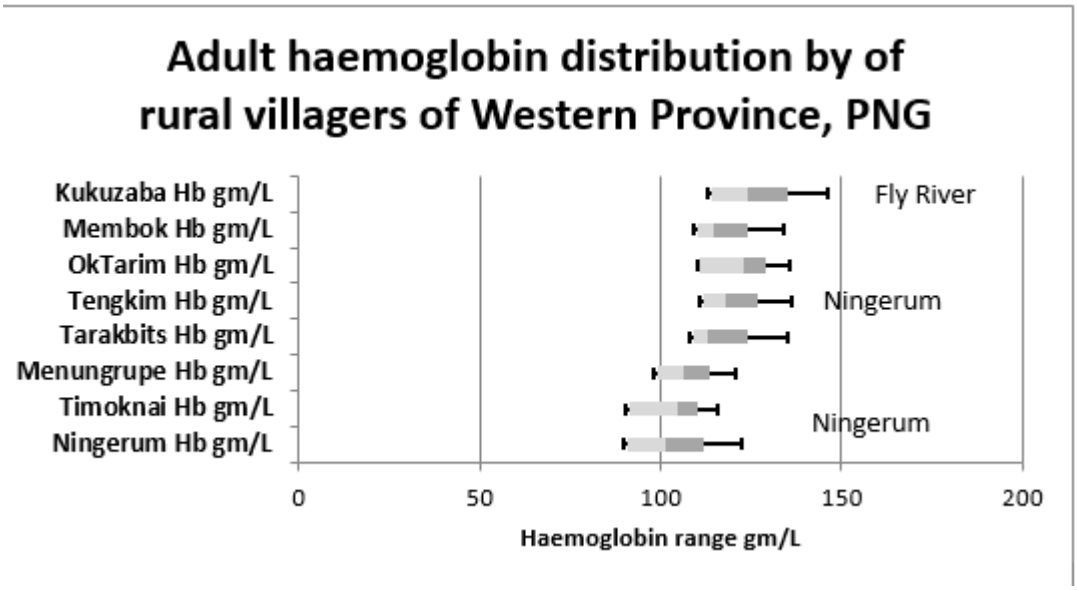


Figure 5.15 Box and whisker plot of haemoglobin by villages

Box and whisker plot of haemoglobin distributions by village illustrate the three villages of Ningerum, T'moknai, and Menumgrupe to have lower haemoglobin (Figure 5.15). They are located in foothills of Ningerum compared to the other 5 villages of Tarakbits, Tengkim, Ok Tarim (which were in the highlands) and the Fly River villagers of Kukuzaba and Membok. Schuurkamp studied the prevalence of malaria among the communities of North Fly District as part of the Ok Tedi Mining Ltd public health investigation of endemic disease surrounding the mine operation in the late 1980s. The inland lowland villages of Ningerum, and surrounding villages in the mine lease area (40km radius from the mine) were reported to have a high burden of malaria and filariasis and accompanied by an enlarged liver and spleen. In order to secure the health of miners, OTML public health specifically targeted treatment of malaria and filariasis by the use of antimalarial drug therapy and mass drug therapy for microfilaria. The distribution of treated bed nets and use of a case detection registry for all Tabubil outpatient and inpatient attendees with a febrile illness was performed. This allowed data collection on the burden of malaria and microfilaria and surveillance on the response to treatment and the community use of the treated bed nets. These interventions were initiated by Ok Tedi public health team during mass drug-administration for filariasis in the late 1980s (Schuurkamp et al. 1990; Schuurkamp et al. 1992).

The distribution of haematocrit levels by the population of each village was in the lower range of normal values, except for Kukuzaba village (Figure 5.16). This village had large water tanks used for drinking.

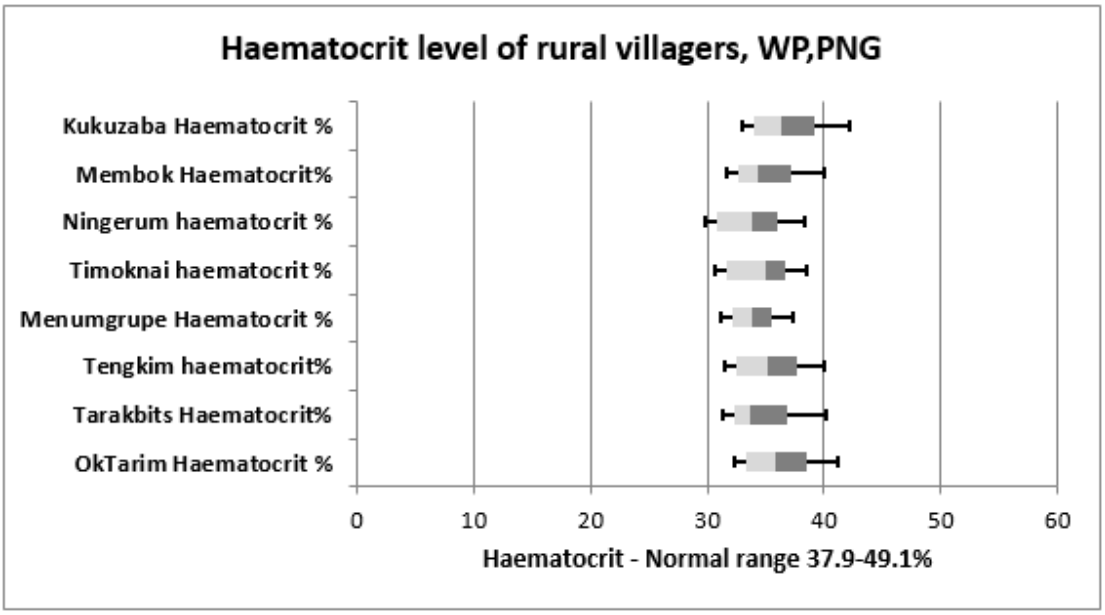


Figure 5.16 Box and whisker plot of haematocrit by village

Results of red cell mean cell volume red are shown in Figire 5.17. The mean cell volume was reduced except for in Membok and Tarakbits villagers.

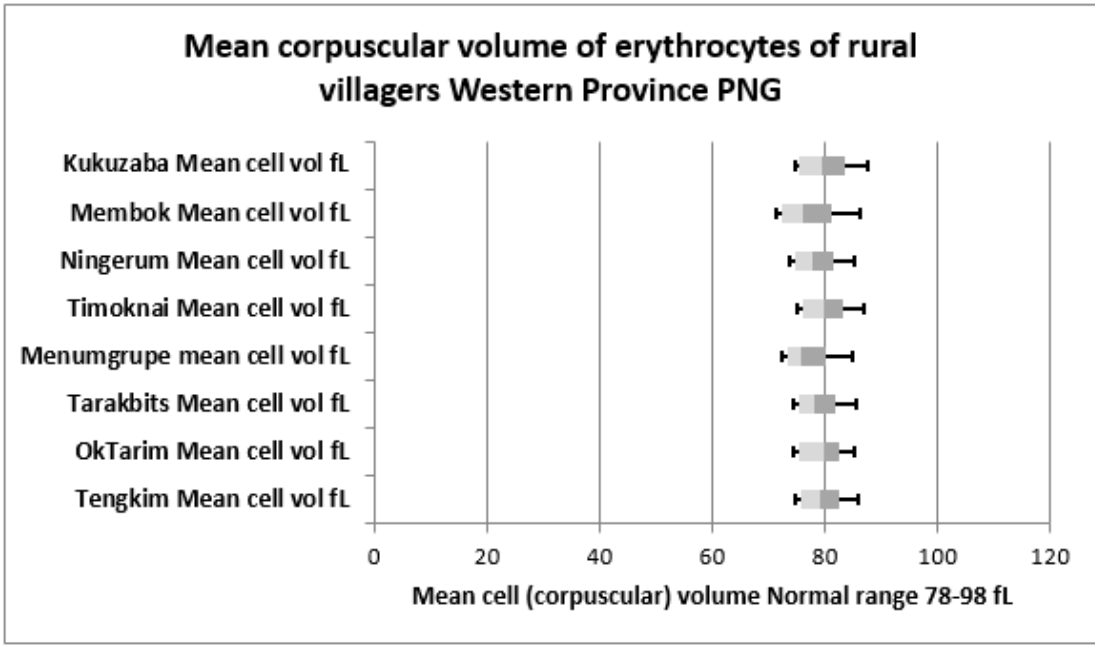


Figure 5.17 Distribution of red cell mean cell volume.

Mean cell haemoglobin is shown in Figure 5.18 (pg) and 5.19 (g/L).

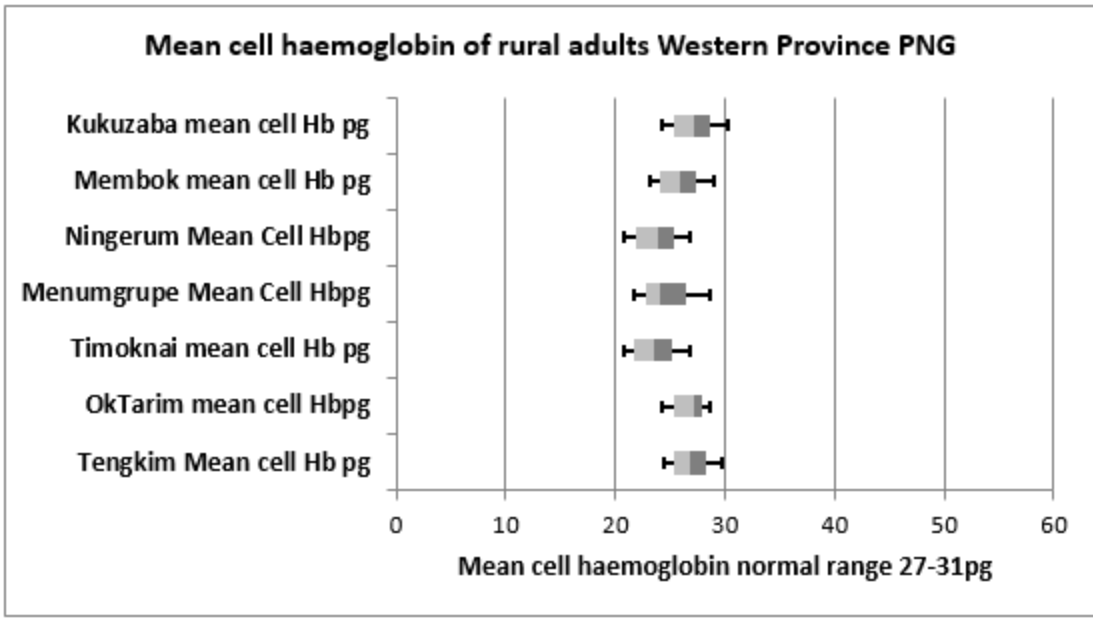


Figure 5.18 Boxplot distribution of red cell mean cell haemoglobin for 5 villages.

The mean cell haemoglobin was also reduced for most of the villages.

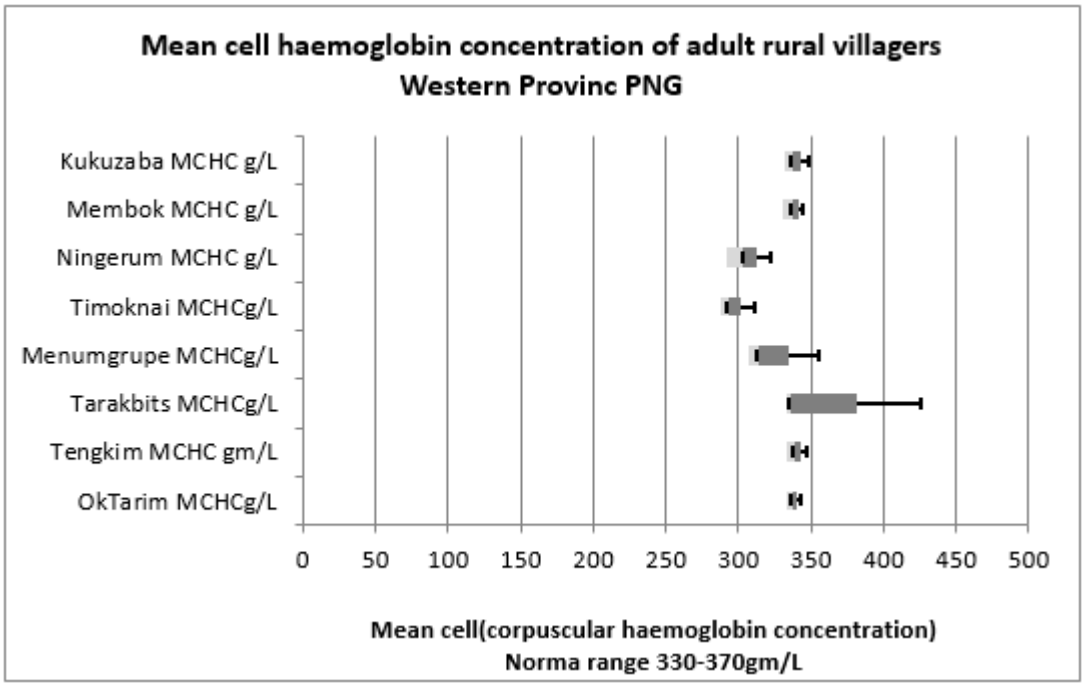


Figure 5.19 Boxplot distribution of mean cell haemoglobin concentration.

Box and whiskers plots were used to graphically illustrate the difference in haemoglobin distribution between villages. Whilst lowland inland villages have the greatest burden of anaemia, the different haemoglobin indices of MCV, MCH, and MCHC were generally reduced. This was not the case in Tarakbits as this was the only village with normal MCHC. Tarakbits village has a long-standing Catholic Church school, and a health facility operated by nursing officers as well as a village airstrip.

5.9.6 Biochemical health profile of villagers

Results of biochemistry analysis including total protein and albumin levels were presented as summary statistics in order to establish baseline data for the remote communities. They can be used to identify biomarkers for liver and kidney diseases, as well as to establish objective evidence of the nutritional status of remote communities and provide a baseline lipid profile to monitor risk factors for noncommunicable disease (Benjamin 2001; Benjamin 2007).

Furthermore, there seems to be distinct group of people accessing health care, those that have an operational village aid post compared to those that the lacked access; either by closure of the aid post or having no such infrastructure. The statistical analyses were conducted separately for men and women.

The null hypotheses for each of the biochemical health biochemical profile of albumin, total protein, urea, creatitine, uric acid, cholesterol, triglyceride, and high density lipoprotein and iron level were equal between the men or women in the groups irrespective of the operational status of their village adidpost. The alternate hypotheses were that the biochemical health parameters were different.

Biochemical parameters were analysed and tabulated as summarydata including mean, median, standard deviation of the individual biochemical variables (Tables 5.12-21 and Figures 5.20-5.29). A two-sample independent t test was used to test for the anticipated difference. Results of all analyses are summarised in Table 5.18 and 5.19 for men and women respectively. Results based on village are summarised in Table 5.20 and 5.21.

5.9.6.1 Albumin levels by gender by village

Descriptive statistics of albumin levels are shown in Table 5.12.

Table 5.12 Summary of albumin level by gender (normal level 35- 55gms/l) Western standard

Remote Village	Gender	Mean Albumin	Median	Standard Deviation
Ok Tarim	Male	41.15	37.8	36.4
	Female	41.83	38.25	38.06
Tengkim	Male	39.14	40.7	7.38
	Female	40.78	40.2	11.25
Tarakbits	Male	37.81	39.3	7.22
	Female	36.44	38.2	5.96
T'moknai	Male	30.13	30.95	10.65
	Female	30.96	31.65	10.58
Ningerum	Male	32.21	36.2	12.09
	Female	32.63	36.1	12.28
Membok	Male	40.75	41.2	6.08
	Female	40.96	41.4	6.49
Kukuzaba	Male	39.8	40.6	5.34
	Female	40.01	41.2	5.33
Menumgrupe	Male	24.38	24	10.48
	Female	25.39	27.1	9.69

5.9.6.2 Total protein levels

Descriptive statistics of total protein levels are shown in Table 5.13.

Table 5.13 Summary of total protein (55-80gm/l) of remote communities

Total Protein	Count	Mean	Median	Standard Deviation	Minimum	Maximum
Ok Tarim	57	73.79	80.8	26.63	0.2	128.8
Tengkim	54	80.81	85.2	18.67	14.6	118.2
Tarakbits	51	73.49	75.8	18.11	6.7	100.4
T'moknai	79	76.11	74.7	50.64	2.3	488.9
Ningerum	52	73.84	80.75	19.79	20.4	97.7
Membok	52	80.44	85	20.65	0.3	99.1
Kukuzaba	47	81.93	86.1	19.20	6.5	119.3
Menumgrupe	24	58.54	57.4	14.65	28.5	81.9

5.9.6.3 Ratio of blood urea and serum creatinine

Descriptive statistics of urea and serum creatinine are shown in Table 5.14.

Table 5.14 Ratio of blood urea and serum creatinine

Blood urea nitrogen and Creatinine ratio		
Normal ratio BUN to Serum creatinine Normal 10, range 6-20	**No**	**%**
Sample ratio values 6 to 8	5	1.26
Less 6	390	98.73
	395	99.99

The normal ratio between the blood urea and nitrogen is 6 with a range of 6-20. All 395 urea levels were well below a ratio of 8. A known case of renal failure with toxaemia during a subject's pregnancy. She was evaluated during her postpartum period and had normal urea and creatinine levels. Uric acid levels were significantly lower than the normal range at 202-416 mmol/L.

5.9.6.4 Triglyceride and high-density lipoprotein levels of remote communities

Triglyceride and HDL levels are shown in Tables 5.15-5.16.

Table 5.15 Triglyceride level of rural remote communities

		Triglyceride			
N		**>2.26**	**%**	**>4.52**	**%**
222	Men	34	8.25	1	0.45
190	Women	30	7.28	0	0
412		64	15.53	1	0.45

Due to insufficiency of the content of samples only 65 were tested. Only one male out of 412 had a triglyceride level of >4.5mmoles (considered in the borderline high range), with 64 acceptable levels of >2.3 but also <4.5mmoles.

Table 5.16 Rural villagers HDL levels by gender

N=346	**Male**	**%**	**Female**	**%**	**Total**	**%**
<1.04mmol/L	173	50	155	47.50	328	94.8
>1.56 mmol/L	1	0.289	1	0.289	2	0.58

Three hundred and thirty samples were tested. Only 2 of the villagers (one male and a female) had HDL levels of >1.56 which is the desirable level. The other 94.8% (328) of the villagers had a less than desirable level of HDL.

5.9.6.5 Blood sugar level of remote communities

Capillary blood was obtained by a finger prick and was evaluated for blood sugar (measured in mmol). A handheld glucometer was used to perform the test in the field. Blood samples were obtained 2 hours postprandial. There were no cases of symptomatic diabetes mellitus among the 185 adult study subjects. There were higher levels of blood glucose obtained from Erekta village, nearest to Kiunga township where they had elevated mean and median blood sugar levels compared to the other villages (Table 5.17).

Some members of the communities were growing rubber trees as a source of income, but the trees were often not tapped. These communities had the potential of disposal income from the sale of rubber to the North Fly Rubber, a company set up specifically to be the buyer in the

Western province, assisted by OTML. The villagers have minimal access to processed food. Trade stores were seen without goods and remained closed.

5.9.6.6 Blood sugar level of rural villagers

Results of field tests from random blood sugar checked by a handheld glucometer

Table 5.17 Summary of random blood sugar of Fly River communities (mmol/L)

Remote villages	N=185	Count	Mean	Median	Standard Deviation	Range	Maximum
Erekta	Male	35	6.64	6.28	1.6	6.11	10.61
	Female	38	6.71	6.39	1.63	6.11	10.61
Karemgo	Male	33	5.6	5.3	1.8	8.9	9.7
	Female	28	5.7	5.4	1.9	8.9	9.7
Moian	Male	25	5.5	5.3	1.4	6.4	10
	Female	26	5.3	5.2	1.1	3.8	7.4

5.9.7 Proxy health indicators

5.9.7.1 Renal function proxy measures

Blood urea nitrogen was elevated for all remote communities tested. This was not accompanied by any marked increase in either serum creatinine or uric acid to signify the presence of renal disease. Reduced renal function almost always results in significant elevation of blood urea nitrogen, serum creatinine, and uric acid. This was not the case in this study. The raised blood urea nitrogen was not accompanied by a similar increase in creatinine which was low to normal at 55-86 µmmol/L. The normal level for serum creatinine is 70-120 µmmol/L for males and 50-90µmol/L for females. The ratio of blood urea to serum creatinine also remained within normal limits of 6-20. Elevated ratios occur during reduced glomerular filtration, therefore, this is an indicator of acute renal failure (Dossetor 1966). A known case of renal failure associated with toxaemia during a subject's pregnancy was evaluated. During her postpartum period, she had a normal creatinine level. Arguably, the elevated mean blood urea nitrogen evident in lowland communities of Menumgrupe, Ningerum, and Kukuzaba (from 12-51mmol/L compared to the normal level of 2.5-8mmol/L) was indicative of widespread dehydration affecting the population.

These levels indicated reduced fluid intake along with a high level of physical activity daily in an environment where the temperatures are 28–32 ^{0} C daily all year. During the study, villagers were observed not to carry a bottle of water to stay hydrated. This state of dehydration poses a significant risk for developing hypotension and acute renal failure; should a person encounter acute febrile illness or diarrhea and vomiting where a sudden loss of body fluids occurs. Uric acid levels of 0.1-0.21 µmmol/L were well below the accepted level of 180-420 µmmol/L among the rural remote communities whose livelihood was plagued by food scarcity.

5.9.7.2 Hepatic function proxy measures

Serum albumin, total protein, and total bilirubin were measured as a proxy for liver functions. The measured levels for serum albumin, total protein, and total bilirubin were in the lower range of normal. The normal ranges of levels were 35-50gm/L serum albumin, 60-83gm/L total protein and a 3.4-17mmol/L total bilirubin level. Dehydration can increase the levels as measured therefore the true levels may be even lower.

Table 5.18 Summary of results of men biochemistry proxy health indicators

Biochemistry results of men from rural remote communities								
	Men with access to health care			Men without access to health care				
Men	N	Mean	Standard Deviation	N	Mean	Standard Deviation	test	two tails
Age	120	36.65	15.95	109	39.66	15.42		
Albumin	120	37.26	9.44	109	34.47	11.30	-2.035	0.04
Total protein	115	78.43	15.75	107	73.55	21.87	-1.920	0.06
Total bilirubin	119	4.24	7.62	108	7.05	14.66	1.838	0.07
Urea	110	16.38	19.18	100	24.78	22.61	2.912	0.00
Creatinine	118	82.37	31.56	107	69.91	50.40	-2.245	0.03
Uric acid	108	0.99	8.56	100	0.14	0.13	1.980	0.30
Cholesterol	119	4.36	1.28	108	4.25	1.51	-0.622	0.53
Triglyceride	113	1.37	1.05	107	0.97	0.90	-2.850	0.00
HDL	108	2.41	19.06	69	0.19	1.49	1.980	0.23
Iron	116	41.16	47.53	107	43.34	64.33	0.288	0.77

Two tail tests analysis showed statistically significant differences in the serum albumin, urea, creatinine, and triglyceride between men with and without access to health care. Total protein, total bilirubin, cholesterol, high-density lipoprotein, and serum iron did not have a statistically significant difference.

Table 5.19 Summary of results of women biochemistry proxy health indicators

Biochemistry results of women from rural remote communities								
	Women with access to health care			Women without access to health care				
Female	N	Mean	Standard Deviation	N	Mean	Standard Deviation	t-test	Two tail
Age	102	37.82	13.43	101	42.00	11.94		
Albumin	102	37.58	9.85	101	32.94	9.82	3.362	0.0009
Total protein	94	75.69	23.29	100	76.05	47.09	-0.067	0.95
Total bilirubin	102	4.54	6.21	101	9.68	12.57	-15.203	3.35E-35
Urea	85	19.72	27.13	97	27.95	26.92	-2.052	0.046
Creatinine	101	80.98	43.00	99	57.36	34.59	4.274	2.98E-05
Uric acid	92	0.14	0.13	100	0.31	1.42	-1.152	0.25
Cholesterol	101	4.57	1.85	99	3.87	1.36	3.048	0.0026
Triglyceride	93	1.38	1.02	99	0.91	1.01	3.234	0.0014
HDL	78	0.55	0.34	91	0.39	0.34	2.798	0.0058
Iron	94	44.66	61.13	99	67.55	176.65	-1.191	0.24

Differences between the mean values of biochemical variables were analysed using a two-tailed t-test that showed statistically significant differences in total protein, serum albumin, blood urea nitrogen, cholesterol, triglyceride, and high-density lipoprotein between women with and without access to health care. There was no statistically significant difference in serum total bilirubin, iron, uric acid, and serum creatinine.

Urea levels were indicative of a state of dehydration in all groups. Notably, that was not accompanied by concomitant increases in creatinine level, and this confirmed insufficient fluid intake by the population, who were therefore in a dehydrated state. Rural remote communities were physically active in order to acquire sufficient food to eat each day. This occurs whilst living in a hot environment where the daily temperature is usually 29-32 degrees Celsius. Poor hydration increases the level of protein and serum albumin. Therefore, the levels measured by this study may be lower than stated. A state of dehydration poses a great danger as it can pre-empt rapid reduction in blood pressure when confronted with an acute febrile illness or episodes of diarrhea and vomiting, a common illness in Papua New Guinea. Reduced blood pressure or hypotension decreases pre-renal perfusion pressure, and this can precipitate the onset of acute renal failure. Hence, this may account for the presumed

anecdotal reports of kidney failure noted by clinicians working in these lowland communities. Any form of kidney disease among this population would have a reduced survival when challenged by a state of dehydration, and therefore would not be detected in surveys such as this study.

The key differences with and without access to health care are shown in Table 5.20

Table 5.20 Differences in mean biochemistry by the status of health care access

Variable	Men with access	Men without access	Women with access	Women without access
Age in years	36.65	39.66	37.82	42.00
Albumin 35-50gm/L	37.26	34.7	37.58	32.94
Total protein 60-83gm/L	78.43	73.55	75.69	76.05
Urea 7.1-8 mmol/L	16.38	24.78	19.72	27.95
Creatinine <106mmol/L	82.37	69.91	80.98	57.36
Uric acid 202-416mmol/L	0.99	0.14	0.14	0.31
Cholesterol <5.2mmol/L	4.36	4.25	4.57	3.87
Triglyceride <2mmol/L	1.37	0.97	1.38	0.91
HDL 1.1-1.4mmol/L	2.41	0.19	0.55	0.39
Iron M 11-31mmo/L F 8-30mmol/L	41.16	43.34	44.66	67.55

5.9.8 Normal range for biochemistry tests

Laboratories adopt standards from developed countries, therefore the comparability of normal levels from tests conducted on rural remote communities must be considered. The normal albumin level is accepted at 35-50gm/l, the median levels recorded among the remote communities were below normal and more towards the lower limit of normal from 27 - 40.6gm/L. This level may indicate low hypoalbuminemia. Mean total bilirubin also shows lower than normal levels of 4-15µmol/L compared to the normal <27µmol/L. An elevated level of unconjugated bilirubin was related to handling from collection to storage.

Liver enzymes

Raised level of lactate dehydrogenase was related to handling and storage of blood samples. Mean levels for gamma-glutamyl transferase, aspartate aminotransferase, and alkaline transferase were in the normal range.

Cholesterol

Cholesterol levels among rural remote communities were low. With median levels of 3.8-4.5mmol/L these communities were well below what is considered a cardiovascular risk. These communities have minimal-to-no access to processed food and fats in their normal diet. Despite this, the communities have elevated median triglyceride levels of 3.8-4.5mmol/L, compared to normal <2.2mmol/L. Elevated triglycerides are considered to be a mild to moderate increase and are the only risk factor for cardiovascular disease that may have a genetic basis. Xanthoma and acute pancreatitis are recognized complications of elevated triglycerides, but both were not evident in clinic consultation and physical evaluation during the period of the study. Median high-density lipoprotein (HDL) levels were markedly low at 0.13-0.61mmol/L, compared to a normal level of <1.0mmol/L.

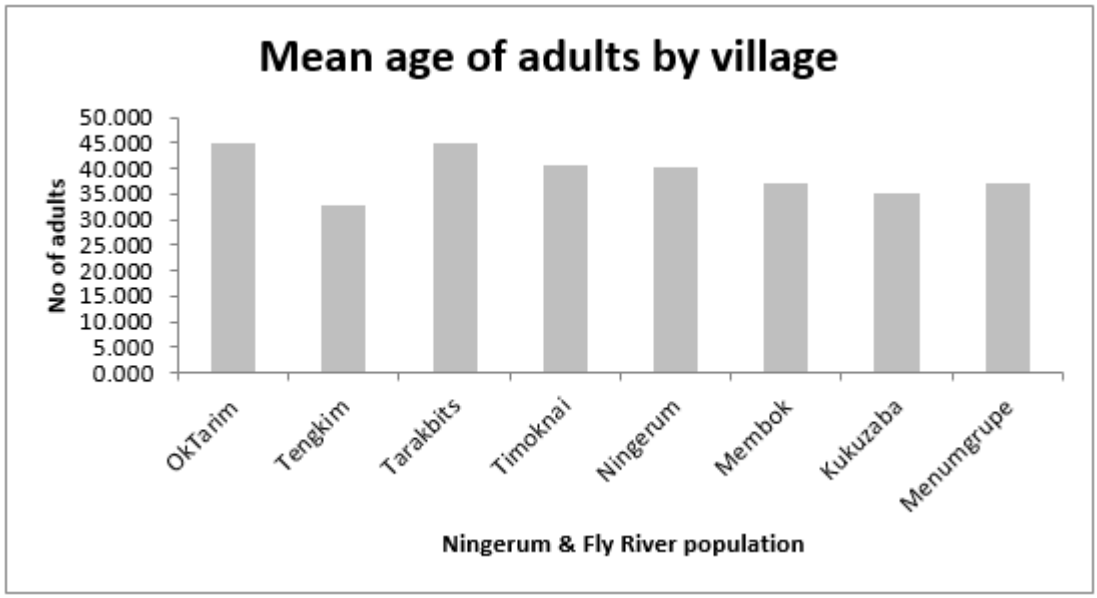


Figure 11 Mean age distribution of adults by village

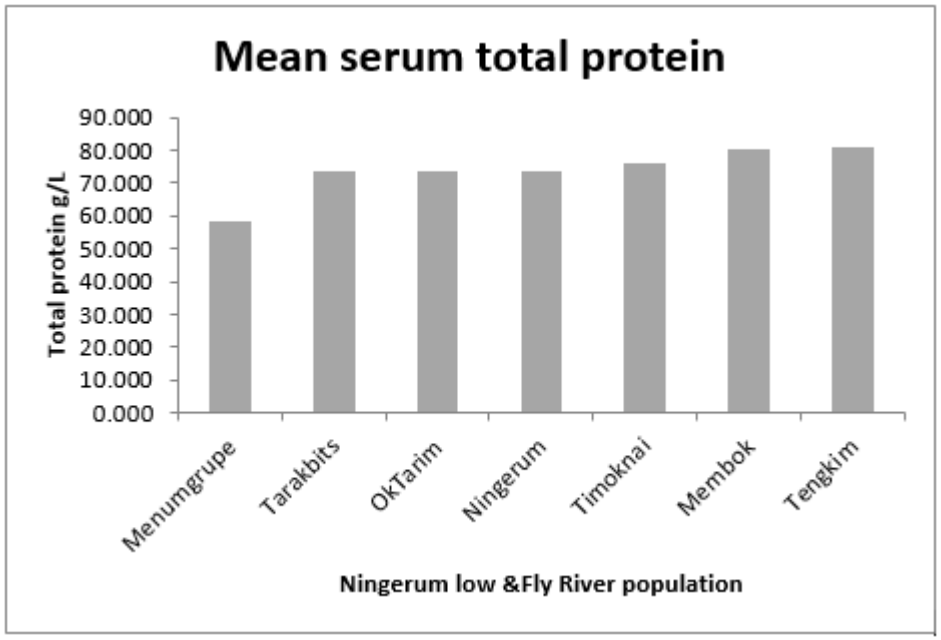


Figure 12 The lowest mean total protein recorded in the adult population of the lowland village of Menunprupe. Who were also burdened with higher malaria and microfilaria loads.

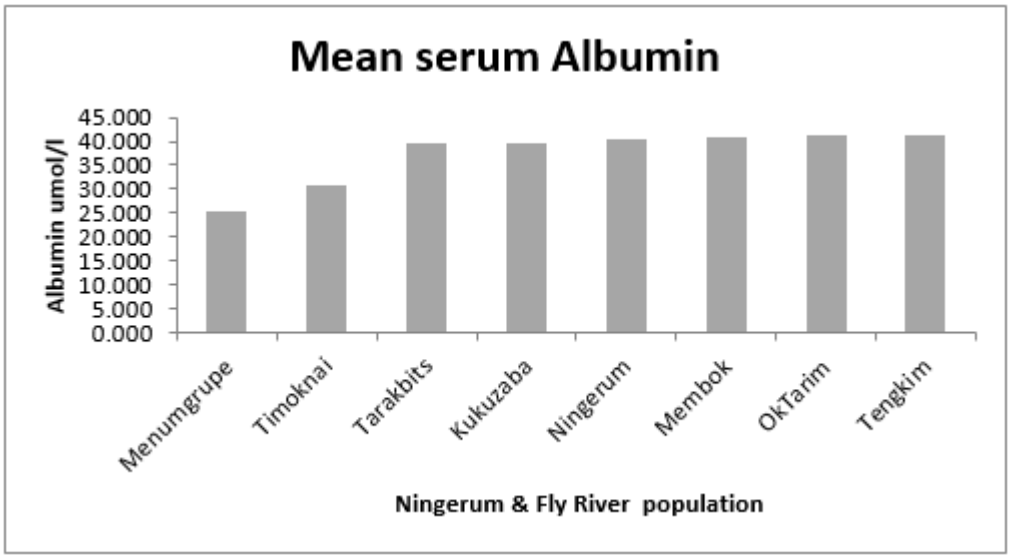


Figure 13 Menumgrupe and T'moknai adults have low mean levels of albumin.

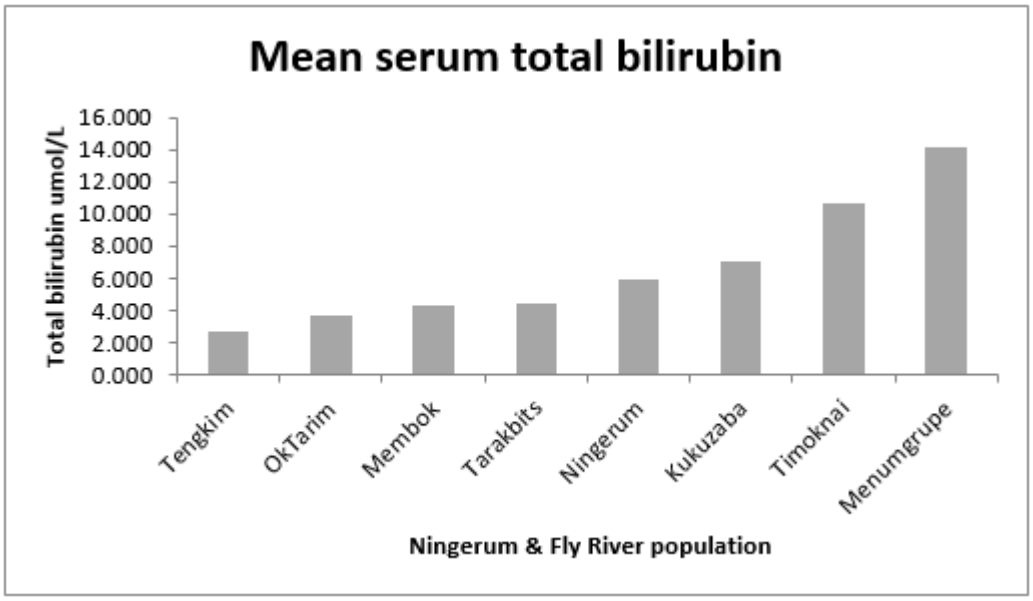


Figure 14 T'moknai and Menumgrupe adults had elevated total bilirubin levels.

The villagers have admitted that many of the families have migrated and relocated to peri-urban informal settlements at government stations and towns. They are also the villages with a high burden of malaria and microfilaria.

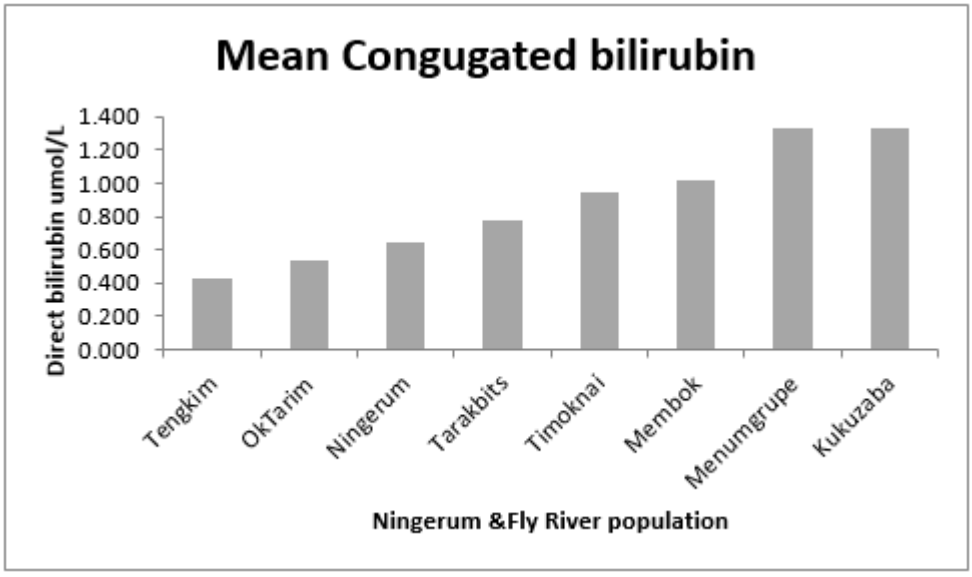


Figure 15 Mean conjugated bilirubin level of adults by villages

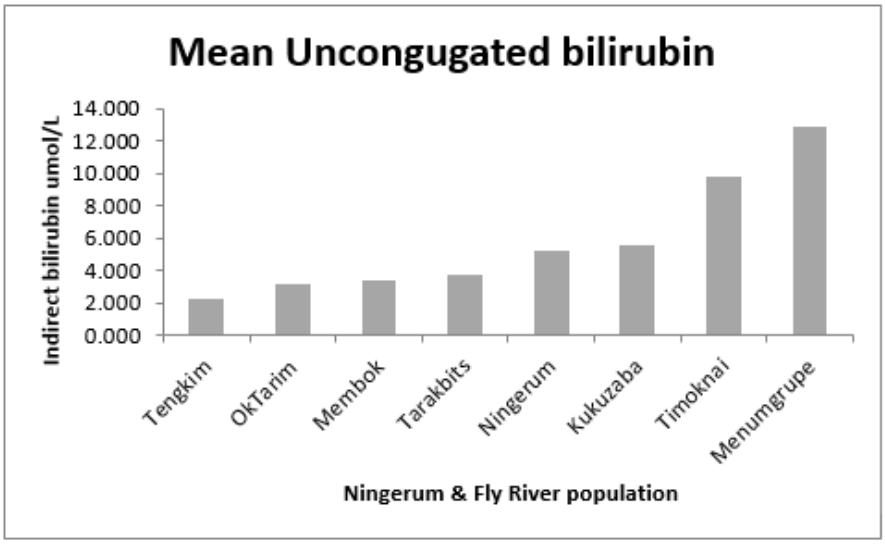


Figure 16 Mean unconjugated bilirubin of adults

Note the increase in the unconjugated bilirubin in the villages' population that has high burden of malaria, though storage time may account for this.

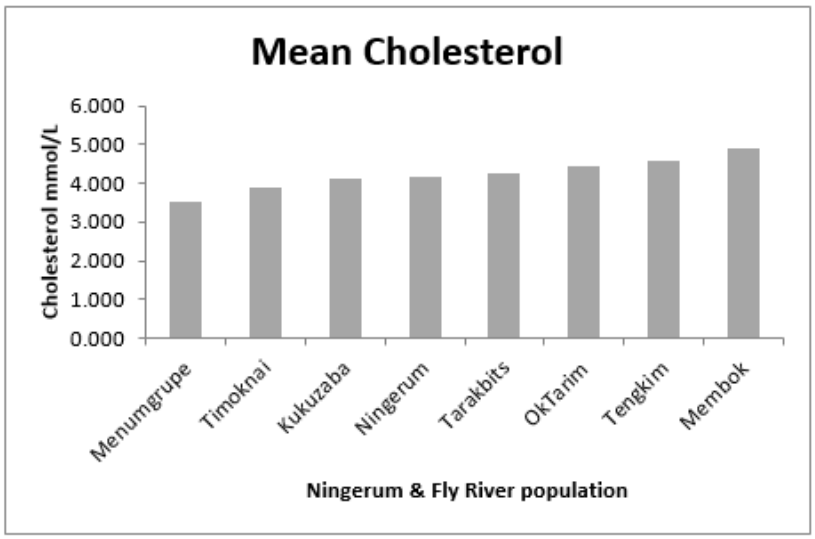


Figure 17 Mean level of cholesterol of adults by village

Villages that have economic activity such as planting rubber trees and tapping are undertaken by villages in the NFD, highlands, inland communities, and the Fly River Villagers.

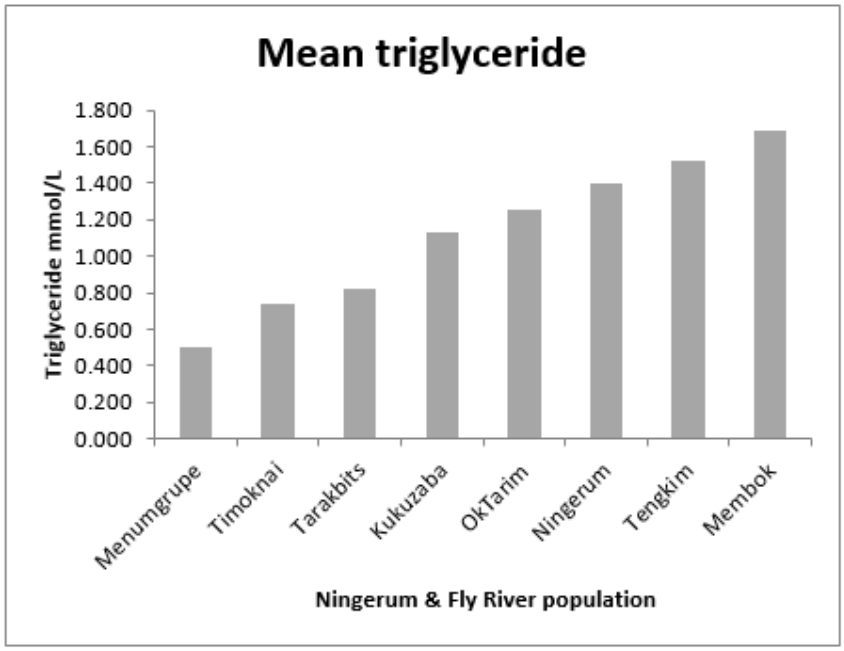


Figure 18 Mean triglyceride levels by village

Membok village had both long-term Catholic Mission School and health service support. There is a village airstrip, but it has ceased operation since the priest pilot had a plane accident there. The Catholic Health Services continue using outboard motor-powered dinghies for transport.

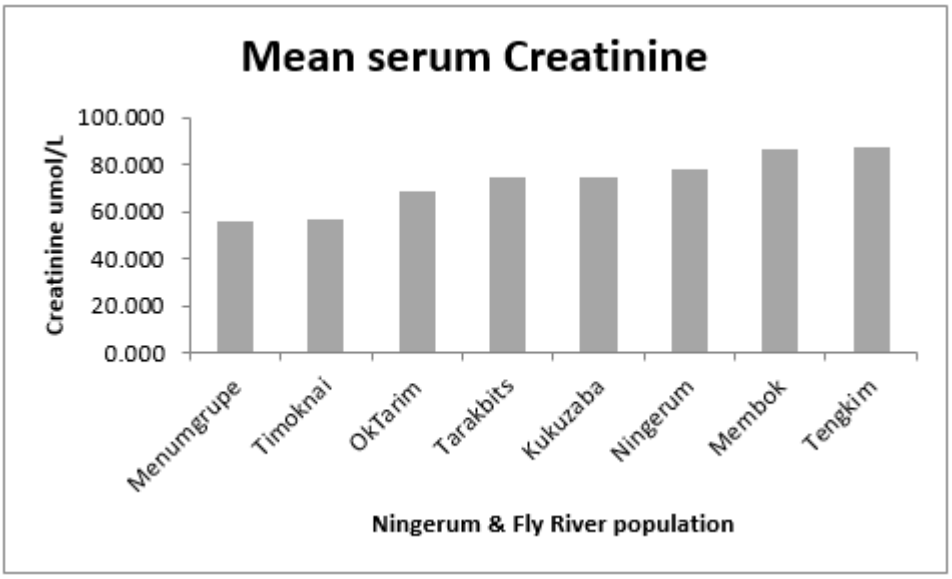


Figure 5.28 Mean levels of serum creatinine of adults by village

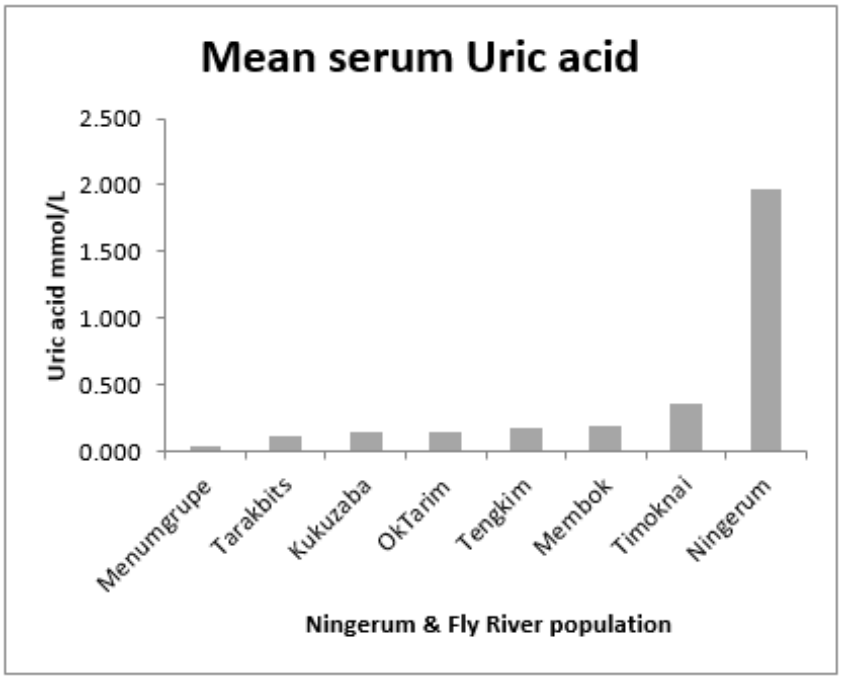


Figure 5.29 Mean level of uric acid of adults by village

5.9.8.1 Urinary abnormalities

The 376 urine samples were tested for urinary abnormalities. The proportions were 30% with proteinuria, 10% with haematuria, and 10% with glycosuria respectively (Table 5.21).

Table 5.21 Table Urine abnormalities detected among the rural population

Village	Total Number of urine samples	Proteinuria	%	Haematuria	%	Glycosuria	%
Ningerum	58	27	0.5	20	0.3	16	0.3
Kukuzaba	53	0	0.0	0	0.0	0	0.0
Tengkim	58	8	0.1	0	0.0	1	0.0
Tarakbits	71	14	0.2	0	0.0	11	0.2
Ok Tarim	45	9	0.2	0	0.0	0	0.0
T'moknai	91	46	0.5	1	0.0	3	0.0
Total	376	104	0.3	21	0.1	31	0.1

The prevalence of urinary abnormalities was calculated for the North Fly District population of 62,850 in the 2011 census using the following formula.

$$\text{Prevalence} = \frac{\text{persons with a given health indicator during a specified period}}{\text{the population during the same time}} \times 100$$

The prevalence of proteinuria, haematuria and glycosuria for North Fly District was 17%, 3.3% and 4.9% respectively.

5.9.9 Inspection of village drinking water sources, and sanitation

5.9.9.1 Access to clean drinking water

There was a lack of access to clean drinking water evident in all rural remote villages visited during this study. Only 3 rainwater tanks were observed, which was no different to other parts of Papua New Guinea. Two of the water tanks identified were at health facilities and the other was a disused tank at a remote village built as part of a community project. Wells, streams, and rivers were the main sources of drinking water. No significant attempt was made by the village people to collect rainwater, although water tanks, roofing irons, and other building materials were received under the community development project by the Ok Tedi Mine Ltd. See Appendix for data on the source of drinking water by villages. The following photographs are of superficial wells used by communities in the Nomad area.

Figure 19 Tamivi community drinking water sources.

The most common source of water was wells followed by creeks and rivers. The Ok Women and children fetch water using various water collection vessels like plastic bottles, pots, and buckets but these were scarce items. The use of bamboo for water collections was not evident. The communities did not report any practice of home purification of water by sedimentation of water to discard solid particles in the water. Water containing vessels were not exposed to sunlight to allow some sterilization of water even though bottles were used to store water.

5.9.9.2 Sanitation

Clean village environments were observed in villages supported by churches. The ECPNG and Catholic supported communities had regular scheduled cleaning activities such as cutting grass around the village, school, and church. The villages supported by government health service were the least clean and had overgrown grass, community halls were dilapidated, and their health facilities were closed without a health worker. There was a large dog population in remote villages that assisted in hunting wild animals for the owners, but the dogs were grossly underfed and malnourished.

5.10 Discussion

The first evidence for improved indicator for the health of remote communities was the burden of anaemia which was significantly reduced from 11% in 1998 to 3.2% in 2010. Persisting anaemia was prevalent among inland lowland communities of Ningerum Tamaro, Menumgrupe, and T'moknai but was mild and much improved due to public health interventions like wide-scale drug treatment of microfilariasis undertaken in the late 1980s (Lourie et al. 1986; Schuurkamp et al. 1990; Schuurkamp et al. 1992). Following prior wide-scale drug treatment of microfilaria as well as the 2009 mass distribution of bed nets to communities of Western Province, the burden of anaemia was reduced to levels similar to other regions in Papua New Guinea (Hii et al. 1997; Hii et al. 2001). The burden of anaemia will continue to affect the inland lowland communities due to the flood plain environment that supports mosquito breeding as well as the people exposed through their food gathering practices. They spend considerable long periods from days to weeks in the lowland to harvest sago as part of their staple diet. Sago harvest is labour intensive and it required living in a temporary shelter for prolonged periods. This exposes them to mosquito bites that transmit malaria, microfilaria and other arthropod-borne viruses that cause disease that sustained the cycle. The situation is unlikely to change and required villagers to use personal protection whilst harvesting sago, unlikely to adopt and adapt due to the high costs of such equipment.

The proportion of participants with a normal body mass index was not significantly different to that of the Flew-OTML study 12 years ago. However, the emergence of risk factors for non-communicable diseases were detected in 4.9 % of the study sample had an overweight body mass index, elevated mean blood glucose recordings, and 4.9% had glycosuria. These levels were recorded in 2 villages that were more proximal to the Kiunga town (Flew 1998).

The prevalence of proteinuria was 17% which correlated to the prevalence reported for the Lake Murray population (Hongo et al. 1994) who had significantly higher levels compared to the rural population of the Solomon Islands (Nakazawa et al. 2002).

There were also other indicators for significant health gains. These were measured by biochemical proxy health indicators between communities with and without access to health care. This study defined access to health care as having an operating village aid post compared to villages that have no posts or non-operating aid posts. The total serum protein albumin was higher among communities with access to health, as was the creatinine level. This indicated larger muscle mass in communities with access to health care, but generally reflected the poor nutritional status of the communities. Low total protein and serum albumin are described as indicators of high morbidity and mortality, and therefore poor survival in critical illness. This strongly suggests that ability of these communities to combat acute infections was likely to be greatly reduced when confronted with an acute illness such as SHD (Rich et al. 1989; Herrmann et al. 1992; Horwich et al. 2008) (Kyle et al. 2004). Moreover, serum albumin was important to binding drugs and harmful toxins in the body and may even change their effects. Therefore, low levels of albumin in poorly nourished communities meant they were likely to suffer more severe effects of SHD compared to a population with good nutrition (Sjoholm et al. 1979; Fasano et al. 2005).

An interesting finding was the discovery of elevated blood urea nitrogen levels in all communities. There was no concomitant increase in serum creatinine or uric acid, which signified the high blood urea nitrogen, was due to the presence of dehydration among the rural communities. Dehydration could be explained by the increased daily physical activities undertaken as daily chores by the community members where the temperatures were normally between 28-32^{o}C. This can contribute to loss of body fluid by excessive sweating resulting in dehydration. Rural villagers were not observed carrying bottles or containers of water to stay hydrated during these physical activities. There have been anecdotal reports by clinicians working in the area (Tabubil and Rumginai hospitals) of acute renal failure among the young population in the region without an obvious cause; this was also experienced by the principal investigator. A pre-existing state of dehydration can precipitate acute renal failure during febrile illness or diarrhea and vomiting. These conditions contribute to acute fluid loss and that may lead to hypotension resulting in the onset of acute renal failure. (Feest et al. 1993; Needham 2005). The presence of dehydration can falsely elevate biochemical markers such as protein and serum albumin which meant the levels measured in this study could well be lower,

such as those seen in marathon runners (Kratz et al. 2002). Low levels of total protein and albumin were known indicators for higher mortality and morbidity risk. These risks can be mitigated by improving food production amongst these remote communities remained a high priority. These communities depend heavily on sago, the labour-intensive nature of harvesting practices and had a poor nutritional value compounds their low nutritional status as indicated by the body mass index and serum albumin (Townsend 1974; Townsend & Tan 1977).

Blood pressure recordings obtained were within normal limits for lean and physically active communities. Despite the existence of the Ok Tedi mine in the North Fly District for three decades, its effect on the communities in this study was minimal. Their lifestyle and diet have remained unchanged. The past study confirmed low blood pressure in remote communities in Papua New Guinea where it was observed that there was a significant absence of known risk factors for non-communicable diseases such as obesity and high blood pressure among the rural remote communities. Moreover, some had an even lower level of biomarkers known to be risk factors for cardiovascular diseases like diabetes mellitus, hypercholesterolaemia, and hyperuricaemia among Papua New Guineans (Sinnett & Whyte 1973; Carvalho et al. 1989; Maddocks & Rovin 2005).

Health gains were noted from a reduced burden of anaemia and healthier biochemical proxy health indicators including protein, albumin, creatinine, and lipid profile. This was due to the reduction in endemic diseases such as mosquito-borne malaria which was achieved by the use of bed nets to prevent mosquito bites. Mass distribution of bed nets was undertaken in 2009 where operating village health facilities became the distribution points that provided families bed nets. Their usage accounted for significant health gains by the population also supported by rapid access to health care (Charlwood & Graves 1987). Unfortunately, those without operating aid posts were not able to access bed nets and have been shown in this study to have poorer proxy health indicators. The diminished health status of rural communities without access to health care in Papua New Guinea has been widely reported (Kolehmainen-Aitken 1992; Duke 1999; Feeny 2003; Gibson & Rozelle 2003).

Social corporate responsibility by resource developers has become fashionable, with varying effects on remote communities receiving community health programs where they operate. Whilst new operators embraced corporate social responsibility to mitigate some of these poor health indicators, others remain oblivious to the health needs of local communities. Public health interventions directed at food production and access to clean water would have

improved and sustained their effects. Moreover, assisting local communities' business groups by providing various forms of transport would enhance the referral of cases to hospital and facilitate school travel. Logistics and funding for this study were provided by resource developers to not only investigate SHD, but also conduct mobile clinics and assess the health status of remote communities. Partnering with resource developers in meaningful ways can improve not only health care but facilitate other developments. In a provinces with weakened government machinery, resource developers became a significant contributor (Imbun 2007) and support logistics for government outreach programs and church health hospital function. They augment or kick start a weakened government machinery into delivering health care to Papua New Guinea such termed as private public partnerships (Connell 1997; Feeny 2003)

At an organizational level, health care delivery remained challenging due to the logistics required to deliver health care to remote communities. A weakened government delivery system reduces its ability to provide basic health care to inhabitants of the Western Province. Allowing church health services to reopen closed government aid posts would improve access to health care for the most remote communities. The Church health services were willing to do so but required the government to provide an operating budget for each facility so that necessary resources could be acquired to reopen and operate government aid posts in the North Fly District. Avenues were provided for such discussions during the Ok Tedi Mine closure meetings with all health providers in North Fly District 200-2004. This was considered a lost opportunity to recognise and support churches operated health and education services in the remote villages, a case of out of sight and out of mind to the government. Government driven equipment support did not reach church operated hospitals in the Western Province. Dr Sitther and the principal investigator informed the health minister of this at the 2014 medical symposium.

Attrition of health workers from remote rural postings was problematic. There have been various reasons for the closure of aid posts that included abandoning posts due to isolation, low wages, lack of supervision, and lack of professional development and progression (Razee et al. 2012). The challenge of retaining of health workers in remote villages has been studied in Papua New Guinea and other Pacific countries (Henderson & Tulloch 2008), and was unlikely to be resolved without government support. Health workers employed in remote health facilities remained the first contact point for patients and was critical to sustain access to health care. Community health worker clinical skills were assessed and observed to be poor (Beracochea et al. 1995), they required supervision and retraining if they were to work

effectively. Retention of health workers in remote areas through various interventions such as professional development was promoted by WHO and fostered by various governments globally (Ashwell & Freeman 1995; Ashwell & Barclay 2010). Sustaining such services also depended on continued support from the health service providers operating in the area. The Church health services in Western Province had benefitted from infrastructure development and energy supply from OTML. This also extended to sponsoring annual eye surgery, managed by Callan Service as part of Catholic health service. Whilst its core function was to provide support and training to people living with disabilities at two operating centres at Kiunga and Daru, it also provided ear and primary eye care services for the community. They therefore organised annual eye surgery for people with cataracts at Kiunga Hospital sponsored by OTML. Adopting early consultation, capacity building, and partnering with resource developers was an opportunity to maximize community benefit under social equity (Veiga 2005). This study also benefitted from such collaboration between the different health providers, with funding provided by OTML and logistics to access most remote communities provided by Talisman Energy Niugini Ltd.

The Church health service operations preceded the arrival of resource developers and were more likely to continue when these resource developers cease their operations. Resource developers responded to the villagers' calls for help required the government health provider that operates in the area to ensure any assistance provided will be sustained through budgetary support.

The logistical requirements of communication and air travel to remote communities remains as the main challenge to overcome. Mobile phones were introduced in 2010 but there was poor network coverage in most remote villages that were visited during this study, therefore VHF radios operated using solar energy continues to be used by operators. Transportation to remote communities provided by Mission Aviation Fellowship through its alliance with Evangelical Church of Papua New Guinea needed acknowledgement, praise and admiration. Their fixed-wing flights ensured the delivery of health and education services to most remote communities and allowed medical retrievals in the Western Province. Regular users of village airstrips maintenance cost to the church as villagers were paid to clean and maintain runways. Resource developers also paid a landing fee to the landowner group. There was a blatant lack of government involvement in transport for health service delivery. The national government mandated the Dept. of Civil Aviation to monitor the redevelopment of village airstrips to enhance the development of rural communities in a March 2013 forum. This led to the

development of the Rural Airstrip Agency to oversee the reopening of the old airstrips in remote areas in PNG. Communication with the organisation directed its website www.ruralairstrip.com.

A single and significant public health intervention led to the use of bed nets to prevent mosquito bites at night. This caused a reduction in malaria burden in communities that used treated and untreated bed nets (Burkot et al. 1990; Hii et al. 1997; Hii et al. 2001). They also have improved proxy health indicators as measured in this study. Such gains need to be sustained.

Food security has been an issue in these remote communities. Contributing factors include poor nutritional values of their main staple food along with an environment that does not support other food crops or had no impact on a hunter-gather lifestyle, the inadequate nutritional status of these communities was evident in their low protein and albumin levels (Gibson & Rozelle 2003; Allen et al. 2005).

In the Western Province, the Church Health and Education service made a significant contribution to health and education services to remote communities that existed at the fringe of or beyond government services. The Church Health and Education Services reached out to remote communities that practiced their faith in different geographical locations within Western Province. Non-government organisations and churches delivered health and education services needed to be formally recognised and to receive government budgetary support, particularly in areas where there's absence of government presence. Formalizing non-government organisation's delivery of health and education through contractual arrangements with both churches and the Mission Aviation Fellowship would greatly enhance and extend existing services out to most remote communities and the hard-to-reach villages where 87% of the PNG populations live. Such a strategy would overcome the lack of government visibility in rural remote communities that continues to deprive them of their right to basic health care.

Regular fixed-wing flights to remote communities were essential to sustain existing health and education services. Such an understanding exists between the Mission Aviation Fellowship (MAF) and the ECPNG Church. MAF supported the ECPNG Church health services to rural remote areas and provided medical retrieval from rural remote communities to the hospitals. Regular assistance provided by resource developers such as Ok Tedi Mine and Talisman Energy Niugini Ltd as they responded to calls by the government and the Catholic health

service for surgical, obstetric, and medical emergencies such as SHD highlighted the actual needs of these inaccessible populations.

5.11 Conclusion

The health status of remote communities with and without access to health care was significantly different. Improved health indicators were noted among communities with health access due to the effectiveness of bed net use and access to treatment. A similar effort was required to plan and deliver public health interventions such as access to food, clean water, and improved sanitation to achieve an even higher level of health than was currently observed in addition to ensuring greater access to health care by remote communities.

Poor nutrition was prevalent as indicated by body mass index as well as low serum protein and albumin measures. This was the case even though communities with access to health care had healthier levels of serum total protein, albumin, and creatinine over communities without access to health care.

Therapeutic food interventions could be considered as part of inpatient care treatment for underlying illness in patients from the Western Province. Meals for patients admitted to the hospital were non-existent, or it was left to relatives to organize their feeding program as was witnessed by the principal investigator (Gatchell et al. 2006; Gera 2010). Adopting innovative methods to improve access to food sources was needed to combat poor nutrition as this contributed to the high morbidity and mortality of SHD and other prevalent diseases in the Western Province such as tuberculosis (Warner et al. 2007; Gilpin et al. 2008; Simpson et al. 2011).

The possibility to improve access to clean water exists in rural communities that have iron roofs on churches, classrooms, and health facilities. These buildings only required additional plumbing to connect tanks that captured the rain. This can be achieved by supporting current church health providers who have achieved this for the church stations. The Church health services have also fostered improved sanitation and living standards among rural communitiesvisited during the study.

The Western Province administration could boldly consider budgetary support to church health services operating rural health and education services. This was an clear need to reopen

all government aid posts that have closed in rural remote areas. The government health workers left their employment leaving an unmanned aidposts depriving health care to villagers. The situation was confirmed by the principal investigator's personal communication with assistant director of rural health services.

Government budgetary support for flight operations by Mission Aviation Fellowship was necessary for continued medical retrieval of emergencies from remote communities who are in dire need of urgent access to life-saving treatment at hospitals.

The Western Province administration can assure greater health improvements in most of its population by funding more public health interventions, supporting church health services to improve access to health care, and ensuring that the Mission Aviation Fellowship continues to transport health and education services to the most remote communities.

6 Chapter 6 Retrospective study of sago poisoning cases

6.1 Introduction

Sago haemolytic disease (SHD) is an enigmatic haemolytic syndrome with high mortality affecting lowland rural Papua New Guineans. Although the disease was reported in the 1970s, its aetiology and epidemiology were unknown (Taufa 1974; Donovan et al. 1977; Greenhill 2006). As there was no structured and ongoing disease outbreak surveillance in rural PNG, evidence surrounding the incidence and significance of the disease remained anecdotal only. Poor health resources in these communities may exacerbate misdiagnosis and under-reporting.

Sago starch is central to lowland Papua New Guinean lifestyle, not only as a food source, but also through its cultural significance (Connell & Hamnett 1978; Greenhill 2006) Early reports of causation presumed a link to consumption of stale sago (Taufa 1974; Donovan et al. 1976), and speculated that microbes or microbial toxins present in stale sago starch were the cause of the disease (Donovan et al. 1977). Studies by Greenhill and co-workers conducted on sago samples destined for household consumption (non-SHD implicated samples) revealed high levels of fungal and bacterial contamination including potentially pathogenic and toxigenic genera. However, definitive links are yet to be made between microbial agents and SHD (Greenhill et al. 2007a; Greenhill et al. 2007b; Greenhill et al. 2009; Greenhill et al. 2010b).

Despite the lack of definitive evidence regarding the aetiology of SHD, improved health outcomes are possible for SHD patients. In reviewing medical records retrospectively, a greater understanding can be gained of the clinical presentation and management of the disease. It may be possible to identify other factors that contribute to poor clinical outcomes such as access to health care, need for transport, and the underlying risk factors of individual cases and gender differences.

A retrospective review will lead to the development of an interim case definition, which when communicated to health workers throughout the endemic region will increase awareness of the disease. This could potentially result in an improved diagnosis and, through more directed management, improve patient outcomes. Additionally, an interim case definition may enable the identification of more cases through early reporting and transfer of cases to receive hospital-based treatment, thus facilitating further study into the aetiology of SHD.

6.2 Material and Methods

6.2.1 Retrieval and review of hospital records

A 12-year (1998-2009) review of the medical records of SHD cases was conducted at four rural hospitals of Tabubil, Kiunga, Rumginai and Balimo in the Western province during November to December 2007 (Figure 6.1). Extraction of relevant demographic details, clinical observations, and laboratory results was conducted following approval from each hospital's administration. Due to the incompleteness of hospital records and failure to retrieve some medical records, clinical staff at the point of care in the village aid posts and hospitals where the patients first presented were interviewed to verify or provide additional information.

The medical records records for sago poisoning cases were reviewed at Tabubil, Kiunga, Rumginai hospital and Balimo hospitals. The principal investigator with the Tabubil cases and their medical records in addition to the Suki family records of 5 patients at the Kiunga hospital as well as the accompanying daughter and 2 and half year old brother. The experience of being the clinician who was incharge of carrying for the cases in Tabubil and Kiunga hospitals provided the foundational knowledge to progress the clinical epidemiology study of sago poisoning. Figure 6.1 showed the different hospitals where medical records were reviewed.

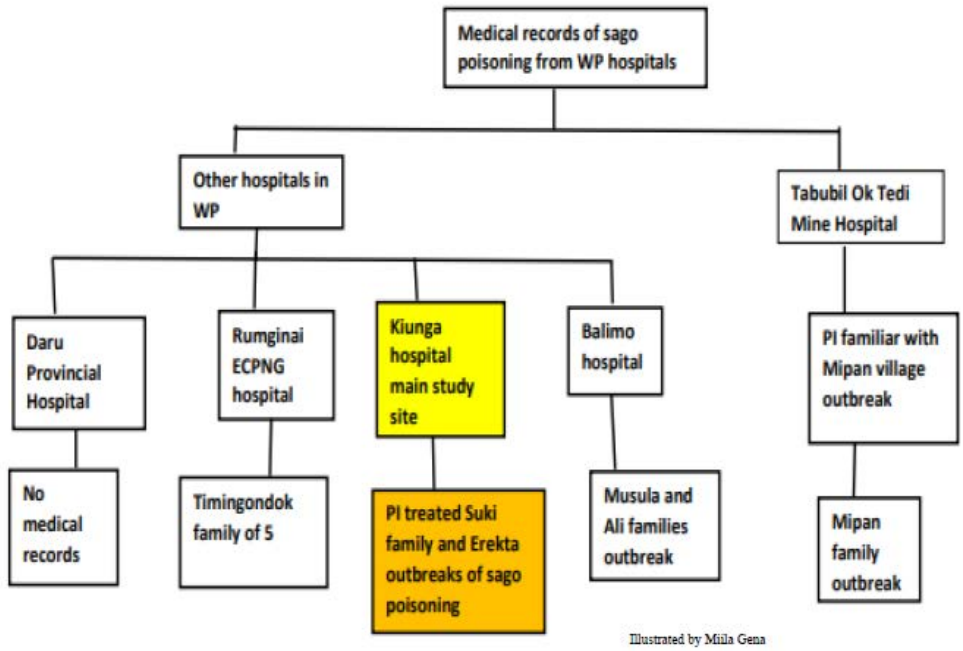


Figure 20 Review of medical records of the 4 hospitals

6.2.2 Retrieval and review of epidemiological evidence

6.2.2.1 Interview of SHD survivors for exposure status

SHD survivors who gave informed consent were interviewed to gain further insight into the disease and interrogate patients reported exposures in addition to determine if there were any long-term effects from SHD or recurrence of illness in the patient. Importantly, the interview sought to exclude exposure to other known causes of acute intravascular haemolysis such as prior ingestion of the antimalarial primaquine in glucose-6-phosphate-dehydrogenase deficient individuals (Winkelmann et al. 1982; Winkelmann et al. 1986; Beutler 1991; Baird & Surjadjaja 2011; Kim et al. 2011), consumption of *Amanita* mushrooms (Meunier et al. 1995; Chen et al. 2014), or exposure to snake and spider venoms (Forrester et al. 1978; Williams et al. 1995; Lalloo et al. 1996; Gibly et al. 1998). Reviewing such exposures was relevant as potential causes of intravascular haemolysis. Obtaining a negative history of these exposures was sufficient to exclude them as probable cause for SHD. Furthermore, the interview also enabled the principal investigator to validate information provided in the hospital records regarding patient history, clinical outcomes, and ascertained some perspective of the time from exposure to illness. The interview guide was provided in Chapter 3 .

6.2.2.2 Management of sago haemolytic disease cases

Information garnered from hospital records and survivor interviews was used to review the management of SHD patients. Pre-hospitalisation variables such as time from onset to hospitalisation as well as transportation used were recorded and analysed. Clinical considerations such as recorded symptoms, laboratory results, medical interventions and clinical outcomes were recorded and analysed too.

6.2.2.3 Seasonal effect on SHD outbreak

Data on the date of outbreaks was sourced from the medical records and this was correlated with meteorological records to ascertain the seasons of the outbreaks. Temperature and rainfall records were sourced from the Papua New Guinea Meteorological Service and analysed to obtain mean temperature and rainfall for the previous 9 years against which SHD outbreaks in those corresponding years were plotted to determine the seasonal effect.

6.2.3 Case definition of sago haemolytic disease

A case definition for SHD was formulated based on the review of data extracted from hospital records and supplemented with the interviews of survivors and health workers.

6.2.4 Data analysis

Graphpad and Excel data analysis toolpak were used to support the statistical analysis. Basic descriptive statistics were conducted to obtain summary statistics on quartile distribution of age, the prevalence of symptoms and signs, as well as haematological and biochemical results of SHD cases by gender. A timeline from exposure to the development of the first symptom was obtained to capture the incubation period and confirm the food item responsible for SHD, thereby identifying the risk factors for the first time. Furthermore, logistic regression was used to ascertain the dose-response effect by correlating the level of exposure to the severity of the disease. The odds ratio was calculated by use of 2 x 2 tables to measure the magnitude of risks and effects of treatment on clinical outcomes of SHD cases.

6.3 Results

6.3.1 Overview of data obtained in the retrospective review

Over the 12 years for which the retrospective review was conducted, 40 cases of SHD were recorded in the ward admission books. However, the records for only 16 of the 40 cases could be retrieved from the four hospitals included in the study (Tabubil, Kiunga, Rumginai and Balimo). Of the 40 cases documented in hospital records between 1998 and 2009, 20 patients were male and 20 were female. Of those 16 patients for which hospital records could be retrieved, 6 were male and 10 were female. The age ranged from 2 to 50 years. The mean age for men was 20.5 years with a median of 15 years; compared to women with a mean age of 18.5 years and a median of 14 years. There was no systematic storage of medical records in Kiunga hospital which reduced the successful retrieval of records. Kiunga was the main referral hospital that received most emergency referrals from outer-lying villages and therefore registered 26 cases, but only 9 medical records were retrieved. Of these, 3 were admitted to Tabubil Hospital (3 records retrieved), 4 were admitted to Rumginai Hospital (4 records retrieved), and 6 were admitted to Balimo Hospital (6 records were retrieved).

6.3.2 Distance between SHD outbreak villages and hospital

The SHD outbreak villages identified from the medical records are provided in Table 6.1. These show the type of transport used and the time taken to reach hospitals. Medical emergencies occurring in remote communities without the availability of efficient transport (such as fixed-wing aircraft or helicopters) led to delayed arrivals at the hospital and even death of cases in the villages. The map of the Western province (Figure 6.2) shows the

location of hospitals, communities, and village airstrips that allowed fixed-wing aircraft to land and transport cases to the hospital.

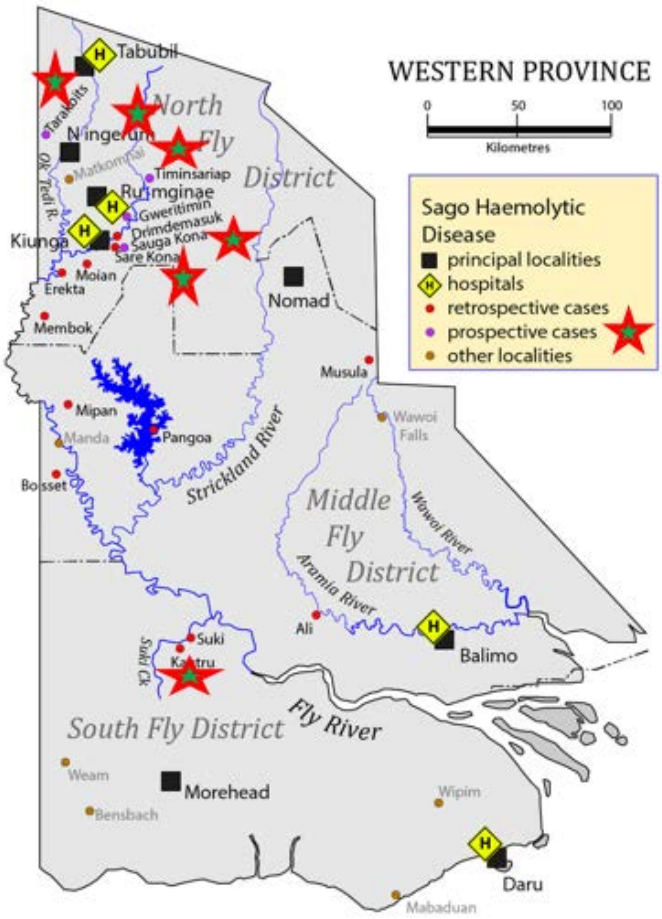


Figure 21 Western Province SHD outbreak sites. Image prepared by Miila Gena and John Burton

The above figure depicts a map of Western Province with the four hospital locations and the SHD outbreak sites marked. The outbreak sites were confined to the NFD, the Lake Murray and Nomad region of the MFD, and in the Suki region and Aramia River regions of the SFD. The trend of past and new outbreaks follows the same pattern of mostly occurring in the NFD.

6.3.3 Verbal histories of SHD outbreaks

There have been many anecdotal reports of sudden deaths among children and adults in remote communities as Bishop Giles Cote noted on many of his pastoral visits to remote communities. These visits included two outbreaks in refugee camps resulting in deaths. The

principal investigator interviewed Kelua, a Fuma village counsellor who reported death of several families in one household after they ate sago cooked with mareta fruit. This is a conedium fruit found in Papua New Guinea. The surviving daughter reported that her mother became ill after eating a sago meal. Her mother told her daughter that she was too sick to harvest sago and needed to be taken to the aid post. The daughter ran back to the village and returned with her father and other men to carry her mother to the village aid post.

The principal investigator interviewed 6 survivors of SHD from the past 5 SHD outbreaks that occurred in 1990, 1992, 1998, 2005, 2007, and 2009 from the following villages of Gweritimin, Membok, Suki, Timingondok, and Sauga Kona a peri-urban settlement in the vicinity of Kiunga town. They consumed stale sago, became ill, and were admitted to the hospital for treatment. There was 1 male survivor and 5 female survivors from villages in the North, Middle, and South Fly Districts of Western Province. The survivors were from Membok, Suki Timingondok, and Gweritimin villages. With peri-urban settlement Sauga Kona located in the vicinity of Kiunga town. The outbreaks occurred during the months of March, April, May, and the late months of October and November in the years reported above from the reported villages as well as within the vicinity of Kiunga Township urban settlements. The years of the outbreaks for each village were Membok (1998), Suki (2005& 2007), Timingondok (2009), Gweritimin (1990& 1992), and Sauga Kona in Kiunga (2009). The survivors age range was 18 to 40 years. A total of 4 deaths were reported, 2 male and 2 female, and it was also reported that 3 of these deaths occurred in hospitalised cases who had not received treatment with a blood transfusion.

6.3.4 Gender determined age difference in mortality

Figure 6.3 showed age differences in the tolerance of acute anaemic hypoxia induced by the sago poisoning between male and female children. Due to early deaths of the male children, Figure 6.3 illustrates this by the lack of data on male children who were unable to withstand the effects of acute hypoxia, died in the village but revealed the younger age of female children who were able to tolerate the effects of sago poisoning and reached the hospital. Figure 6.3 not only confirmed this but also showed a wider variability in the mean age difference between the males and females.

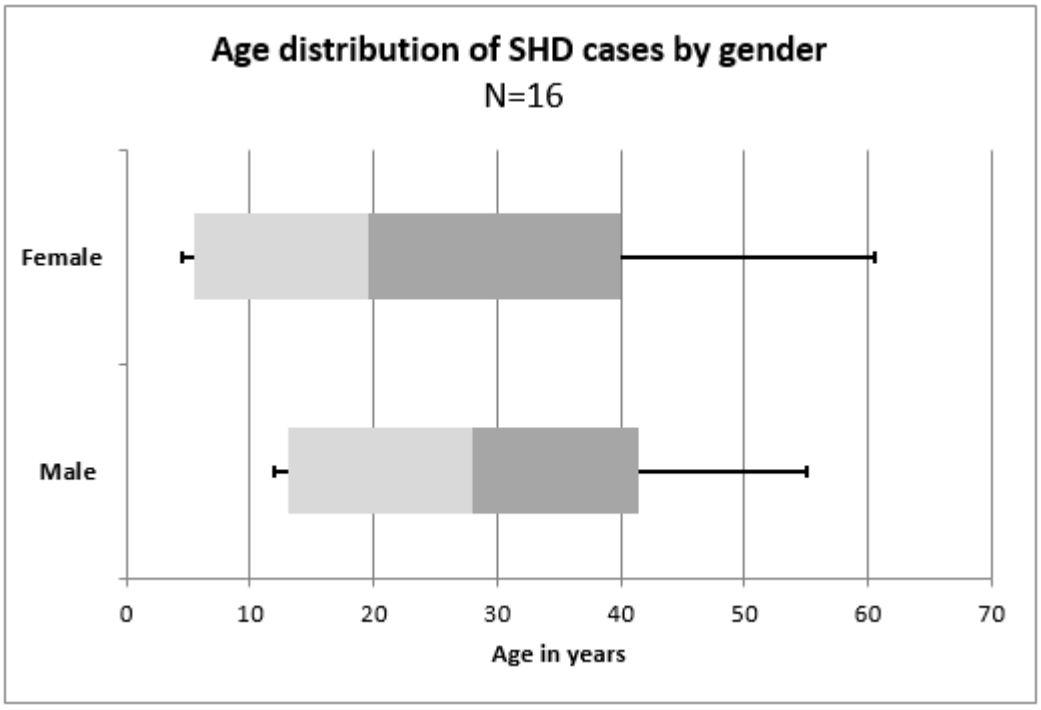


Figure 22 Median age difference in gender of SHD cases.

6.3.5 Incidence and case fatality rate of SHD

All 40 reported cases were used to determine the incidence rate of SHD for the Western Province, with population estimates derived from the 2010 PNG national census. The 12-year incidence rate was calculated to be 26.5 per 100,000, with an annual incidence rate of 1.3 - 5.8 per 100,000.

The case fatality rate was 35% (14/40). Men were more likely to die than women (11 of 14 deaths in men); the odds ratio was 6.8 (95% confidence interval of 1.4-32.8, Z test 2.83, P 0 .0168). Most reported deaths were early deaths that occurred in villages before cases were transferred to the hospital. These deaths occurred predominantly in male children and young men. For the 16 patients for which medical records were retrieved, 3 of the 4 deaths occurred in a hospital in cases that did not receive blood transfusion due to lack of recognition of SHD by health workers. The death of one case in the village occurred on day 3 of illness as a plane arrived to transport seven members of the family to the hospital for treatment.

6.3.6 Gender determined mortality difference

Figure 6.23 shows male deaths exceeded that of females. Women and girls tolerate acute anaemic hypoxic effect of sago poisoning compared to men and boys. Being a male increased

the risk for early death. It seems to suggest that they may have genetic susceptibility inherent in the erythrocytes. That would have to be another study that documents the risks of intravascular amongst SHD endemic community. Figure 6.3 showed the evidence of no male child with sago poisoning. This is to the contrary as male child succumbs to early deaths and therefore rarely brought to the hospital.

Figure 24 SHD mortality by sex.

This data appeared interesting and not described before showed male deaths exceeded that of women as more women survived the sago poisoning contrary to men. Being a male was a risk for early death during SHD outbreaks.

6.3.7 Types of transport used to transport SHD cases

Table 6.1 captures the location and month of sago poisoning outbreaks and the types of transportation they used to arrive at the hospital. The case fatality of 35 % was generated from this data. Due to the remoteness, the possibility of not knowing of deaths associated with sago poisoning remained high; not all communities have radio communications as they exit out of reach of service providers such as the government, church and resource developers. Unless the transportation system is improved into remote communities, such condition as sago poisoning would be a daily risk for lowland communities who consumes sago daily as the only food that that available in abdundance in their environment.

Table 6.1 Details of outbreak and types of transport used

Year of SHD outbreak	Village	No of cases	No. Dead	No Subclinical	Time of Arrival at the hospital	Transport used
Mar-90	Gweritimin	3	1	0	24 hours	Canoe
Apr-09	Kiunga Sare Kona	1	1	0	< 1 hour	Foot & road ambulance
Apr-98	Ali	7	4	0	7 days	Canoe
Mar-98	Musula	6	2	1	48 hours	Plane
Mar-99	Mipan	5	2	0	2 weeks	Canoe & plane
Mar-04	Moian	1	1	0	24 hours	Canoe
Nov-05	Erekta	1	0	0	48 hours	Canoe
Oct-98	Membok	2	1	0	5 days	Canoe
Apr-05	Suki	8	1	2	48 hours	Canoe & plane
Mar-09	Timingondok	4	0	0	48 hours	Canoe
Apr-09	Kiunga Sauga Kona	2	1	0	30 minutes	Road ambulance
	Total	40	14	3		

Traditional canoes were the most common mode of transport used to transport cases to the nearest village airstrips. Fixed-wing flights were considered essential to transfer SHD cases to hospitals. Due to the limited road networks, ambulances were only used to transfer cases from the airport, waterfront docks, and local communities surrounding the hospitals. Fixed-wing flights remain the most important way to rapidly transport cases as they provide the most immediate transfer to receive life-saving treatment at a hospital. Rapid access to urgent

treatment with a blood transfusion was required for SHD and other cases that require a higher level of medical attention to stabilize deteriorating their health. Hospital-based care remains vital to preventing deaths amongst rural-remote inhabitants.

6.3.8 Seasonal association of SHD outbreaks

There are two main seasons prevailed in PNG; the wet and dry seasons. The wet season begins in October through to May followed by the dry season from June to September. SHD outbreaks were more common during the wet season begins in October and ends in April before the beginning of the dry season. Data on seasonal variations pattern of temperature and rainfall was requested and obtainedfrom the PNG Meteorological service to compare with the time of SHD outbreaks. The temperature and rainfall data obtained for 1997-2005 (Table 6.2). The mean temperature and rainfall were calculated for the 9 years then compared with the known plot the number of SHD cases to the respective month of outbreak. The graph below showed that SHD outbreaks occurred during both wet and dry seasons, but more often during the wet season. This was also new information not previousy knowm. During the dry season, old sago was consumed leftover from past sago harvest found in temporary shelters compared to wet season outbreaks where 2 weeks old sago starch post harvest were consumed prior to sago poisoning illness. The illness occurred with old sago consumption was known previously but illness developed after consuming recently harvested sago was new informaiton.

The annual temperature and rainfall for 2005 were graphed and compared with the occurrence of the SHD outbreaks in mid-May of the same year. The minimum and maximum temperature remained constant, whilst the only change noted in the rainfall. The temperature remained constant at 29℃-30°C throughout the year, whereas rainfall changed from high during the September to May wet season, to low between May and August. Rainfall was the only variable that changed and was therefore most likely to affect the moisture content of stored sago. Implicated sago starch was stored for long periods that exceeded 1 month; in one outbreak up to 4-6 months. Rice bags were used to store sago starch which was left standing on the earthen kitchen floor or timber flooring of the house.

Table 6.2 Rainfall and temperature data for Western Province during the SHD outbreaks.

Rainfall (mm) Max Temp (°C) Min Temp (°C)

Year	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	Annual
1990	229.2	108	335.8	90	653	369	160	29.4	42.4	5	59	55.8	2137
	31.1	31.8	30.9	30.8	30	29	28.5	28	28.3	30	31	32.8	30.1
	24.3	24.4	24.3	24.6	25	24	24.4	23.4	23.6	25	24.3	24.6	24.3
1998	214	269	261.4	129	276	134	15.8	44.8	20.2	75	350	276	2066
	33.4	31.6	31.2	31	30	29	29.1	29	30.7	31	31.1	31.1	30.7
	25	24.9	24.8	25.5	25	25	24	24.2	24.2	25	24.2	24.4	24.7
2004	276.2	315	389	190	268	60	41.6	12	26.2	8.4	10.6	61.2	1657
	31.7	31.4	31.4	30.5	30	29	28	28.1	28.9	30	31.5	32.2	30.2
	24.6	24.5	24.5	24.9	25	23	23	22.3	23.6	24	25.5	25.3	24.2
2005	399	192	328.4	472	36	41	38.2	22.2	10.8	12	128	202	1881
	31.3	31.9	31.5	29.8	29	29	28.9	28.9	29.1	31	31.5	31.8	30.3
	24.3	24.5	24.6	24.2	24	24	23.4	23.3	23.9	24	25.3	24.8	24.3

This data was provided by the Papua New Guinea Weather Bureau. Data for 2009 was not available for the Western Province.

SHD outbreaks occur both during the wet and dry seasons but appear to be more common during the wet season months (September to May) The amount of rainfall and therefore the moisture content is the only changing feature of the weather pattern whilst the temperature is held constantly high.

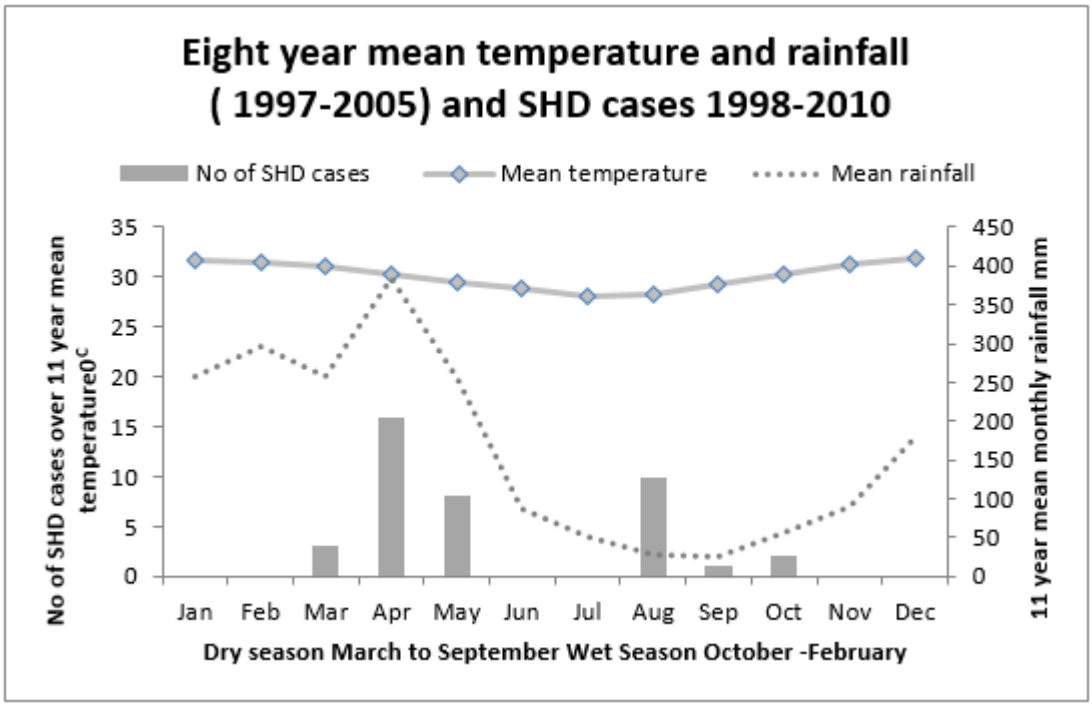


Figure 25 Mean temperature and rainfall from 1997-2005 and SHD cases from 1998-2010

Rainfall differs dramatically from the north to southern region of the province. In the North Fly District received the highest (200mm of rain all year) compared to the drier Middle and driest South Fly District according to the Papua New Guinea Meteological Service (Figure 6.5). There were 5 different zones of differing rainfall levels overall. The important zones were those that had higher rainfall like the dark blue zone of North Fly District which had the most SHD outbreaks compared to the red zone that received 100-200mm of rainfall annually (see figure 6.6). SHD outbreaks were also more prevalent in the light blue zone of the Lake Murray region and the light pink zone of the Suki region. Lake Murray and Suki belong to the MFD and SFD respectively; these areas have the least rainfall compared to the NFD. The temperatures remained constantly high throughout the year at 29-30°C. In figure 6.5, SHD outbreaks are shown to occur annually during the early wet season and later dry season months of the year. Water is essential to dissolves the sago starch contained in macerated pith of a sago palm so the process of sedimentation produces the blocks of sago starch. This explains the outbreaks occurring in areas of high rainful and less to no reports from the driest regions in the south of Western Province.

6.3.9 Rainfall map and spatial distribution of SHD outbreaks

The number of SHD outbreaks listed against the legend. The dark blue zone had the highest outbreaks in the NFD. The Nomad region in the MFD also has high rainfall similar to the NFD. The appreciation of the extensive river system marked as greenlines on the map.

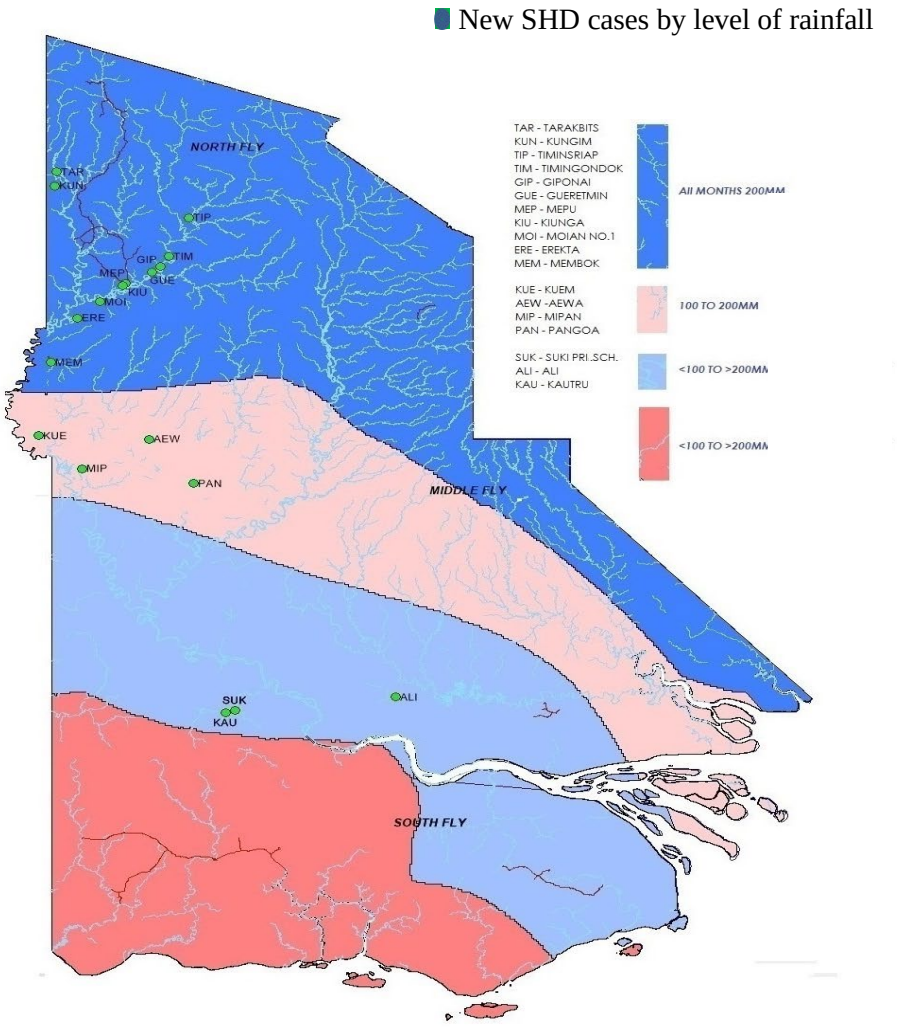


Figure 26 Western Province rainfall and spatial distribution of SHD cases

The number of outbreaks lessens from the MFD to the SFD. Special regions for SHD outbreaks are in the Lake Murray and Nomad areas of the MFD, and the Suki and Aramia River regions of the SFD.

6.3.10 Clinical Observations

Sago haemolytic disease presented as a systemic illness with a rapid onset, the most notable symptoms are severe anaemia with hypoxia. The most frequently observed clinical signs recorded in 16 patients' medical records were retrieved and are provided in Table 6.1. These records showed severely ill cases were described to be unconscious, with tachypnoea and tachycardia observed in all patients, approximately two-thirds of patients exhibited pallor and sallow complexion, while hypotension was present in approximately one-third of patients. Emesis was reported for most patients (13/16; 81.25%) but localized symptoms and signs of gastrointestinal illness were lacking in all 16 cases. There was no documented evidence of clinicals signs of septic shock or coagulopathy in addition to reported as absent in 9 patients examined and managed by the principal investigator.

SHD is to some extent characterized by pertinent negative findings. First, there seems to be a lack of sustained fever; only 31% of the cases were febrile on admission but this subsided within 24 to 48 hours, though patients all reported having fever at some stage of the illness. Secondly, there was the absence of bleeding tendencies, namely petechiae and purpura as signs of coagulopathy that are usually evident in sepsis or septic shock. In addition to the absence of these clinical signs and symptoms, there was a paucity of both haematological and biochemical markers that could be drawn upon. Though this was largely because tests that may be of diagnostic value were not conducted due to poorly resourced rural hospital laboratories.

6.3.10.1 Record of clinical signs

Table 6.3 Proportion (%) of SHD cases with clinical signs during hospitalization.

Frequency of signs (N=16)	%
Altered conscious state	100
Unresponsive to painful stimuli	100
Muscle power Grade 3-recumbent	100
Pulse rate 80-110	100
Respiratory rate in >18/min	100
Pallor	68.75
Sallow complexion	43.75
Febrile (≥38°C)	31.25
Blood pressure <90 mmHg systolic	31.25
Tenderness of right hypochondrium	6.25

6.3.11 Temporal traits associated with mortality and hospitalization

SHD cases required immediate hospitalization for treatment to prevent the early deaths that constituted 71.4% or 10/14 deaths that occurred in the first 12 hours of illness (Figure 6.7). A prolonged delay between the onset of symptoms and arrival in the hospital was common, duration varied between 2 hours and 6-10 days. Kiunga government hospital received the majority of cases from the Fly River villagers as well as those from the surrounding informal peri-urban settlements. A clear timeline from eating a meal to becoming ill was not obtained from the medical records and substantiated by both the health workers and surviving relatives

of cases from the informal peri-urban settlements. Medical records showed that cases from the 2009 outbreak in Kiunga arrived in hospital within 1 hour of illness. The cases from remote villages that had no operating airstrips such as Ali, Mipan, Membok, Timingondok, Gweritimin took 7-14 days to arrive at the hospital. The Mipan outbreak affected 5 members of one family that resulted in 2 deaths in the village, a male child, and the young male father of the dead child. Another 3 adults, one male grandfather, the grandmother, and mother of the dead child was transferred by air to Tabubil Hospital 2 weeks after the illness with debilitating effects of anaemia that prevented them from ambulating. Their conditions improved dramatically following a blood transfusion and they were repatriated by fixed-wing flight. Without a formal medical retrieval service, SHD affected communities initiated travel by canoes to reach the nearest health facility where radio communication by the health workers to the respective health provider to organize medical retrieval. Immediate hospitalization of SHD cases was required to prevent early deaths. Prolonged travel time using traditional canoes during the Ali village outbreak increased the number of deaths to 4 out of the 7 cases. The early deaths of 2 male children occurred during the first 12 hours of illness. These were followed by a further 2 deaths, a male adult and his adult daughter who were at their 7^{th} day of illness upon arrival at the hospital. Deaths of sago haemolytic disease cases occurred in 2 peaks; the 8 deaths that occurred in the first 12 hours of disease onset were confined to males as demonstrated in the figure below. The second peak of 6 deaths occurred on day 3-4 of illness and this affected both males and females. The longest time from illness to death was 168 hours (day 7). This was associated with a long duration of travel time due to the use of non-motorized canoes for transport to hospital and lost more time when the patient overnighted at an aid post.

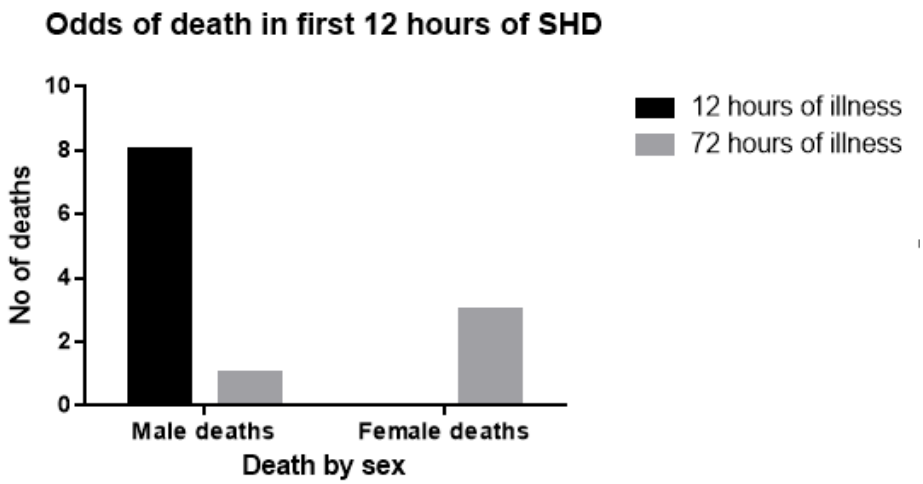


Figure 27 Early and late death by gender.

The 35% case fatality included the total number of deaths that occurred within and outside of hospital. The hospital deaths also occurred in those that did not receive blood transfusion due to lack of recognition and knowledge of sago poisoning. Those that received blood transfusion lived and were able to leave hospital without complications Almost all cases of sago poisoning require blood transfusion as shown in Figure 6.8.

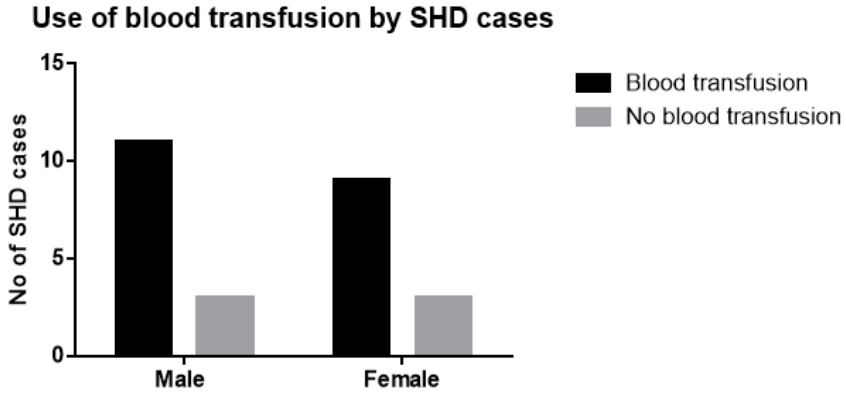


Figure 6.8. Use of blood transfusion by SHD cases.

Fatal outcomes were inevitable in those that did not receive blood transfusion for various reasons either through lack of recognition by health worker or lack of availability of blood due to increase number of cases or complacency of health worker not administrating blood transfusion in a timely way. More blood transfusion was required by males compared to females.

Table 6.4 illustrates when death occurred within the first 12 hours as early transportation to hospital that can easily diagnose and resuscitate the cases with rehydration while waiting for preparing to transfusion with blood as soon as possible. An additional problem relates hospitals inability to secure blood for patients when multiple cases were admitted that was so evident with through the study. Early intervention can prevent the late deaths on day three Adequate hydration and early blood transfusion; both interventions were time sensitive so earlier they are instituted will prevent the complications of acute renal failure. The very late deaths occur in those that took too long to arrive at the hospital. All remote villages need to be connected to the main town through radio or phone communication so that appropriate response to the need of rapid effective transportation can be organized.

Table 6.4 Duration of disease and time of death of SHD based clinical assessment.

Time of death and onset of disease		
Day of SHD illness	Time of death in hours	No of deaths
Day 1	12	8
Day 2	48	0
Day 3	72	3
Day 5	96	1
Day 6	120	0
Day 7	164	2
		14

Early fatal outcomes in males may indicate that they were less tolerant of acute prolonged hypoxia. Death on day 3 was most likely due to the onset of acute renal failure secondary to dehydration. Any deaths beyond day three showed that they would have survived had they arrived early for blood transfusion. The 2 patients' who died on day 7 revealed their body had reached the point of no return from the effects of prolonged period of acute hypoxia. The bone marrow response by day 7 may have been insufficient to sustain oxygen delivery.

6.3.12 The severity of SHD illness

Severity was associated with marked physical weakness demonstrated by the inability to maintain an upright posture and remained recumbent. Futhermore, severity also associated reduction in the level of consciousness from drowsiness to being unaware of surroundings and therefore unconscious and progressed to death in cases that did not receive a blood transfusion. Rarely mild cases would be unusual as those who consume a meal develop illness. Mild cases remained well and ambulated but complained of vomiting. Consuming a smaller quantity of sago equated with no adverse clinical effect but showed evidence of intravascular haemolysis by the presence of haemoglobinuria in the urine as subclinical cases described in the Suki outbreak of 2005.

6.3.13 Glasgow coma scale used to monitor SHD cases

Table 6.5 Levels of illness based on clinical symptoms.

Retrospective review of cases for the severity of SHD	No	%
Death	14	35
Severe illness (Glasgow Coma Scale 6-7 severe illness, altered conscious state, unresponsive to painful stimuli and recumbent)	21	52.5
Moderate illness(symptomatic but ambulant)	2	5
Mild Illness (symptomatic and ambulant)	1	2.5
Subclinical No clinical symptoms	1	2.5
No observable effect limit	1	2.5

Asymptomatic and mild cases of SHD were not common occurrences and presented when there was food scarcity or were reluctant to eat the implicated sago showed some characteristics like bitter taste on the first mouthful was chewed, tasted and discarded. These characteristics helped assess the dose-response effect described in detail in the chapter 6 clinical epidemiology retrospective study of sago poisoning. Severe SHD was prevalent in those that consumed regular portion sizes in a normal meal without exception so has a attack rate of 100%. The risk of disease was high upon consuming implicated meals of sago, and

young male children may have a higher risk of death. Sudden death among children was not investigated as these occurred in remote villages.

Post blood transfusion results in Table 6.6 showed a doubling of the mean haemoglobin in males and females that totally reverses the clinical effects of acute anaemic hypoxia as the patients became fully conscious and were able to ambulate without assistance. The benefit of blood transfusion improved the oxygenation of cells thereby reverses to aerobic cellular respiration that was clinically evident in patients waking up and becoming physically activity.

Table 6.6 Summary statistic of age and haemoglobin levels by gender.

Gender	Number	Mean age years range	Mean pre-transfusion haemoglobin gm/L	Mean post-transfusion haemoglobin gm/L
Male	6	28 (8 - 50)	49.3(36 - 68)	92.8 (70 - 113)
Female	10	21.9 (2.75 - 41)	43.1 (40 - 68)	89 (66 - 116)

Table 6.6 showed the response increase in haemoglobin levels post blood transfusion that equated to improved clinical conditions of the patients' as it restored their conscious level and they became ambulant without any neurological deficits.

6.3.14 Response to blood transfusion pre and post haemoglobin

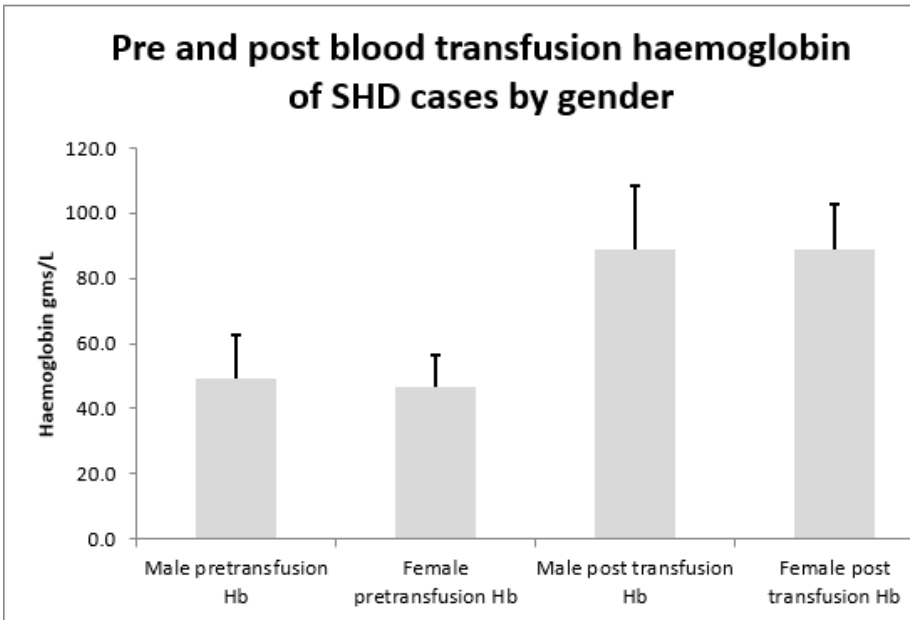


Figure 28 Pre and post blood transfusion haemoglobin

Whilst the mean pre-transfusion haemoglobin was not statistically significantly different in survivors that reached hospitals, the median haemoglobin was. Furthermore, male children < 8 years died soon after illness, and therefore did not reach hospital whereas female children less than 8 years old did reach the hospital and survived with treatment. Male children< 8 years old were likely to have the severe effects of SHD that led to an early death.

6.3.15 Haemoglobin levels and blood transfusions

Tables 5.2, 5.3 and Figure 5.4 provides an overview of haemoglobin levels for SHD patients and their clinical status. A normal portion size of a meal of sago led to the development of symptoms and signs consistent with severe acute anaemia, all these cases required blood transfusions. These transfusions are often given to patients, but a lack of awareness amongst health workers and prolonged delay in administering blood transfusion led to the death of case in the 2009 outbreak. It is uncommon to have the complete results of a full blood count, biochemistry, and urine sample.

Rural hospitals do not have blood transfusion service therefore the hospital announces it need for urgent blood donors through the use of loud haler. A list of known blood donors was the first contact point to call. The prevalence of blood groups was analysed, with type O being the most common at 81.25% which was predominant among males. Blood types A and B were

the least common and occurred among female cases. Hospitalized patients that received blood transfusions received at least one unit of blood, but in the 2005 outbreak 5 severe cases required multiple units of blood to raise their haemoglobin and improve their neurological status so they could become ambulant. These cases also had low nutrition levels; a family of 8 with predominantly young children lived on a diet of sago and tapioca (house in the village was visited on a follow up visit in 2005.

The mean age difference in males and females in Figure 6.10 was not statistically significantly different, but the minimum age of presentation in female children was 2.75 years compared to 8 years in male children. Younger male children less than 8 years as well as young men died in the villages during the first 12 hours of illness, even before transport arrangements were made for transfer to hospital.

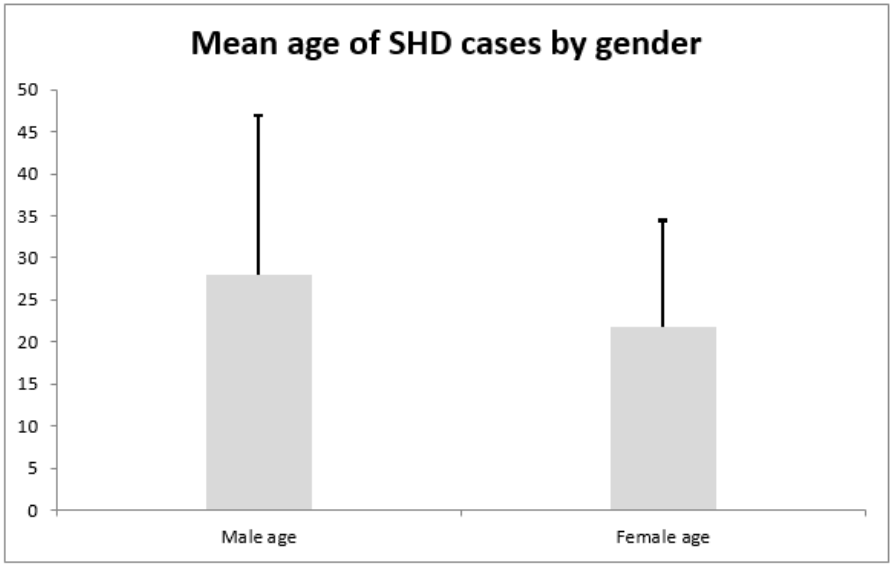


Figure 6.10 Mean age distribution of male and female cases with SHD

6.3.16 Blood transfusion and clinical outcome

Clinicians rationed the use of blood transfusions according to the severity of cases due to the scarcity of resources to obtain blood from donors and limited laboratory resources to conduct cross matches. A 16-year-old male with haemoglobin of 68gm/L did not receive a blood transfusion at the time when 3 other members of the family had to have it but denying blood transfusion can be fatal.

Older aged men survived which could be due to the possibility of eating less sago due to their poor state of dentition. Females were observed to be more tolerant of severe anaemia and hypoxia which were the main effects of SHD compared to male children of the same age who died within 6-12 hours of illness. Males encountered more deaths compared to females. The early death of males could indicate their increased susceptibility and less tolerance of the effects of acute severe anaemia and its hypoxic effects. They may have underlying genetic susceptibility in the traits of the constituents of their erythrocytes. This would require investigation in future study

Table 6.7 Blood transfusion and mortality by gender

	Survival in SHD	Death in SHD	Total
Male	10	8	18
Female	15	2	17
Total	25	10	35

Statistical analysis using Medical online software provides an odds ratio of 6 with a confidence limit that lies between the intervals of 1.049 – 34.3184 with a Z statistic of 2.014, and a p-value 0.0440. There was a statistically significant difference in the odds of death in males was 6 times more compared to female and had a significant 95% confidence interval.

6.3.16.1 Blood transfusion alleviates symptoms of debilitating anaemia

Blood transfusion alleviated the symptoms and signs of SHD. Severely affected SHD regained consciousness and were ambulate. Three cases that hadpersisting debilitated effects of severe anaemia and were bedridden for 2 weeks after the SHD outbreak were transferred by air to Tabubil hospital and improved with blood transfusion. The benefit of blood transfusion was

immediate. Cases were also prescribed iron and folate tablets for two weeks to facilitate erythropoiesis before they were repatriated home on fixed-wing flight.

6.3.17 Risk Factors

6.3.18 Consumption of sago starch

Interviews of five adult survivors (three from Suki, one from Kiunga and one from Membok) confirmed the consumption of sago pancakes made from old sago (stored in grass baskets or rice bags) definitely preceded the illness. The Membok survivor reported that the felled sago palm was stored by the riverside from which trunk fibres were harvested and washed intermittently over the months to obtain sago starch. The end of the trunk was reported to be mouldy. On the day that they fell ill, sago was the only food item they had consumed. Details of food history and the reported attack rate by food items was described in the outbreak investigation. All survivors denied eating any broad beans or mushrooms and were not taking any medications including antimalarials at the time of illness with SHD. They also denied being bitten by snakes or stung by spiders. They reported that they were well before consuming the implicated meal and linked their illness to it.

6.3.19 Laboratory results of 2001 and 2005 sago poisoning outbreak

Table 6.8 Full blood count investigation –Tabubil Hospital laboratory

Duration of acute anaemic hypoxia, pretransfusion haemoglobin, reticulocyte respo and white cell count							
Sex/Age	Place	Outbreak date	Hospital admission	Duration of illness-days	Haemoglobin gm/L	Retics %	WBC x10^6
F 30 yrs	Mipan	22.08.2001	29.8.2001	7	28	16	10.4
F 43 yrs	Mipan	22.08.2002	29.8.2001	7	43	22.4	7.7
M 50 yrs	Mipan	22.08.2003	29.8.2001	7	39	13.6	20.6
M 12 yrs	Erecta	28.09.2005	29.09.2005	1	36	13.2	40.2
M 43 yrs	Suki	29.05.2005	01.06.2005	4	61	5	25
F 40 yrs	Suki	29.05.2006	01.06.2005	4	50	7	11
F 9 yrs	Suki	29.05.2007	01.06.2005	4	58	5	26.7
F 7 yrs	Suki	29.05.2008	01.06.2005	4	59	10	19.8
F 5 yrs	Suki	29.05.2009	01.06.2005	4	36	8	39.8
F 16 yrs	Suki	29.05.2010	01.06.2005	4	89	6	11.9
M 3 yrs	Suki	29.05.2011	01.06.2005	4	121	3	7.1
M 14 yrs	Suki	day 3 dead	Aid post dead				
M 7 yrs	Mipan	12 hours dea	village-Dead				
M 30 yrs	Mipan	24 hours dea	village-Dead				

Arrival at hospital was delayed by 4-7 days. Those that presented on the day of illness at the hospital evaded diagnosis. A group of affected cases were easier to identify but single cases were missed in both children and adults. The number of deaths occurring overnight was troubling, this was examined by the principal investigator whilst working at Kiunga Hospital which in part led to this study. Inspecting the feet of sleeping patients for a sallow appearance was used by the principal investigator as a screening method. Children were able to receive blood transfusions when found to have SHD.

Table 6.9 Red cell morphology as reported by Tabubil Hospital

Red cell morphology									
Sex	Age - yrs	Hypochormasia	Polychromasia	Microcytosis	Macrocytes	Poikilocytes	Spherocytes	Anisocytosis	basophilic stippling
Male	43	present +++	present ++	present +++	not reported	present +++	present ++	not reported	not reported
Female	40	present +++	present ++	present ++	not reported	present ++	not reported	not reported	not reported
Female	9	present +++	present ++	present ++	not reported	present ++	not reported	not reported	not reported
Female	7	present ++	present +	present ++	present +	present +++	present ++++	present ++	not reported
Female	5	present ++	present +++	present ++	present ++	present ++	not reported	not reported	not reported
Female	16	present ++	present +	present ++	not reported	present ++	present ++++	not reported	not reported
Male	3	present +	not reported	present +	not reported	present ++	not reported	present +	present +
Male	12	present ++	present +++	present +++	not reported	present +	not reported	present +	not reported
Male	50	present +	present ++	present +	not reported	present +	not reported	present ++	not reported
Female	42	present ++	present ++	present ++	present +	present ++	not reported	present +++	present +
Female	30	present ++	present ++	present ++	not reported	present ++	not reported	present +++	present +

Table 6.10 Urine sample tests at Kiunga Hospital

Urine color changes during hospitalization and field visit on the 28th day later.							
Suki Family urinecolor monitoring indicator of intravascular haemolysis							
Sex	Age in yrs	Day 1	Day 2	Day 3	Day 4	Day 5	Day 28
Male	43	Dark Red	Dark Red	Yellow	Yellow	Yellow	Yellow
Female	40	Dark Red	Dark Red	Dark Red	Yellow	Yellow	Yellow
Female	9	Dark Red	Dark Red	Dark Red	light red	light red	Yellow
Female	7	Dark Red	Dark Red	Dark Red	Yellow	Yellow	Yellow
Female	5	Dark Red	Yellow	Yellow	Yellow	Yellow	Yellow
Female	16	Yellow	Yellow	Yellow	Yellow	Yellow	
Male	3	Yellow	Yellow	Yellow	Yellow	Yellow	

A notable phenomenon of urine colour was that it reflected the intensity of the intravascular haemolysis. Those patients who had worse symptoms would take longer for the dark red urine colour changes to become clear as normal urine colour. During blood transfusion, it was noted that the darkness of the red urine colour intensifies or gets darker before becoming lighter and returning to normal. It seemed that the transfused erythrocytes were haemolysed by possible excess preformed toxins in the blood stream. This was similar to snake bite cases, where the patient does not respond immediately to the antivenin and needs more to reverse the effects of venom fully in the blood circulation.

Table 6.11 Renal function test by Tabubil Hospital

Urea,Creatinine and electrolytes at hospital admission						
Sex	Age	Urea mmol/L 1.7 - 8.3 mmol,	Creatinine umol/L M:< 40 -97 , F	pH 7.36 -7.4	Sodium mmol(Na+)/L 136 - 148	Potassium mmol (K +)/L 3.6 - 5.0
Male	43	7.67	143	7.16	142	3.29
Female	40	44	597	7.97	132	3.12
Female	9	4.73	72.9	7.1	136.6	3.53
Female	7	3.97	49.2	7.26	132.7	3.81
Female	5	3.33	44.2	7.27	136.6	2.9
Female	16	9.11	44.4	7.19	137.8	3.78
Male	12	7.67	143	7.16	142.3	3.2
Female	30	>50	797	7.49	129.8	3.43
Female	40	10.8	84	7.42	136.1	3.5
Male	60	17.4	171	7.46	138.6	3.57

The Tabubil mine hospital has a well-resourced hospital laboratory with the capacity to conduct renal function, liver function, and enzyme analysis unlike other rural hospitals in the Western Province. The results of the tests greatly aided this study. Indicators of renal function showed elevated levels of blood urea and occasionally elevated serum creatinine. Potassium and bicarbonate remained normal. Note that a chloride level is not a routine test when electrolytes were ordered. Without chloride level, an anion gap calculation was not possible.

Table 6.12 Liver functions and enzymes of Suki, Erekta and Mipan cases

Village	Sex: Male/Female	Age-years	Total Bilirubin umol/L < 17	ALT umol/l M:< 40, F:< 33	AST umol/l M:< 41, F:< 22	Gamma GT umol/l M: 7-50, F:7-22	Alkaline phosphatase Umol/l M:< 270, F:< 240
Suki	Male	43	49.5	36.8	142	15.5	72.4
Suki	Female	40	184	34.6	241	5.5	104
Suki	Female	9	84.2	23.4	117	6.71	130
Suki	Female	7	63.4	16.4	81	7.94	163
Suki	Female	5	71.6	40.6	196	9.79	110
Suki	Female	16	78.5	458	1160	536	337
Erecta	Male	12	124	69.1	120	24.8	122
Mipan	Male	60	29.2	38.8	27.7	5.26	149
Mipan	Female	30	93.3	28.7	51.7	5.26	No result
Mipan	Female	40	65.5	25.1	58	No result	No result

Elevated total bilirubin levels were seen in SHD cases as reported in Table 6.12. It was not routine laboratory procedure to differentiate between conjugated and unconjugated bilirubin. A liver enzyme abnormality seen was elevated aspartate aminotransferase (AST) levels unaccompanied by a similar elevation in the alanine aminotransferase (ALT) and/or γ-

glutamyl transferase (GGT). By deduction, the high bilirubin could be explained by haemolysis or pre-hepatic destruction of erythrocytes as the other liver enzymes were within normal levels indicating the absence of hepatic cell injury.

Table 6.13 Salmonella Typhi serology tests for infection

		Salmonella Typhi antigen test		
Sex	Age	O	H	V
Female	30	Non reactive	Non reactive	Non reactive
Female	40	Non reactive	Non reactive	Non reactive
Female	60	Non reactive	Non reactive	Non reactive

Typhoid infection was suspected in the 2001 Mipan village cases. Therefore, the serology tests for typhoid was done at the Tabubil Hospital laboratory; Figure 6.13 showed negative results for known antigen of O, H and V.The mine hospital laboratory normally conducts regular tests on food handlers on a long-term surveillance.

Table 6.14 Suki and Erekta SHD cases heavy metal screen

Heavy metal blood screening in blood					
Sex	Age	Lead (<0.5umol/l)	Mercury (0.3 - 0.6umo/l)	Cadmium (<0.4umol/l)	Arsenic (<0.7umol/l)
Male	12	<0.56	<0.08	<0.01	<0.60
Male	43	<0.12	<0.05	<0.01	<0.60
Female	40	0.07	<0.08	<0.02	<0.60
Female	9	0.05	0.02	<0.02	<0.60
Female	5	<0.05	0.02	<0.02	<0.60
Female	16	<0.05	<0.02	0.01	<0.60
Female	7	No results			

The level of heavy metal in food and humans was of concern. These tests were conducted by the Brisbane laboratory provided these results for cases managed by the principal investigator as shown in table 6.14. The levels of lead, mecury and cadmium were below the the toxic level. The arsenic level was 0.1µmol/L.

Evidence to confirm intravascular haemolysis were sought from the 2005 Suki outbreak of sago poisoning; blood samples were sent to the Queensland Laboratory. A screen for erythrocyte abnormalities was conducted on the members of the family of the 2005 Suki

outbreak by the Queensland Pathology service. This was done to detect genetic abnormalities like erythrocyte membranopathy, enzymopathy and haemoglobinopathy. More importantly, the detection of haemoglobin scavengers such as the haptoglobin was indicated in the results (Table 6.14). For the first time, haptoglobin levels were reduced confirming the mechanism of haemolysis was intravascular. Furthermore, the presence of haemoglobinopathy as alpha thalassemia was also determined by the presence of occcasional haemoglobin H.

Table 6.14 Red cell and content investigations for the 2005 SHD outbreak

Screen for intravascular haemolysis, haemoglobinopathies and G6PD deficiency									
Sex	Age	Hb 135 -180 gms/L	Haptoglobin 0.35 - 2.20 g/L	G6PD Screen	HbEPP	HbA2 2.2 - 3.2%	Hb H	Unstable Hb	Hb F quantifie <1%
Male	43	128	1.2	Normal	Normal	3	Occassional	Not detected	0.4
Female	40	91	1.98	Equivocal	Normal	3	Detected	Not detected	0.4
Female	9	129	0.01	Normal	Normal	3.3	Occassional	Not detected	0.2
Female	5	116	0.02	Normal	Normal	2.3	Occassional	Not detected	0.1
Female	16	49 ?	1.32	Deficient	Normal	3.5	Detected	Not detected	0.8
Female	7	No result							

6.4 Case definition of SHD

An earlier case of SHD reported by relatives was defined as having an illness which makes the patient physically weak, sleepy, and unresponsive to external stimuli or unconscious. This is as well as observations of patients passing red-coloured urine following consuming a meal of sago. The patients remained recumbent throughout the time required to be transferred to the hospital. The time of meal to the time of onset of first symptom was not explicitly stated, but was reported as occurring after consuming the sago meal. Medical records did not contain time of meal and the subsequent onset of symptoms of illness therefore lacked epidemiological data required. The passage of red-coloured urine was observed by relatives in patients that were recumbent and drowsy or unconscious. The sudden onset of severe intravascular haemolysis was associated with sago consumption and clinched the clinical diagnosis. This study established and refined the case definition of sago-induced intense intravascular haemolysis accompanies the sudden onset of severe acute anaemic hypoxia with symptoms of dizziness and extreme muscular weakness that renders patients recumbent and unconscious. This is accompanied by intense haemoglobinuria identified by passage of red urine. Moverover, other improtant biochemical change of sago poisoning induced acute severe hypoxia triggered anaerobic cellular respiration will be explored in the prospective study. The appearance of the first symptom (vomiting) occurs within 10-15 minutes of consuming a contaminated sago pancake. The clinical effects were based on the sudden onset of severe acute and debilitating anaemia and its hypoxic effects on the musculoskeletal and neurological systems. The cases were reported to be drowsy or sleepy and became unconscious during the illness. Passing dark red urine was a universal feature that accompanied the illness and alarmed both patients and their relatives. Deaths occurred early during SHD among males which accounted for deaths that occurred in the villages before medical retrieval. Clinical features were described as extreme pallor that indicated the severity of anaemia, it was commonly seen in mucous membranes. However, the sallow complexion of skin most prominent in palms and soles of feet would be the diagnostic clue for SHD when compared to palms and soles of controls. Detecting haemoglobin in the urine by haematology or by use of multistix would strengthen the clinical diagnosis as haemoglobinuria provides the proof of the cause of anaemia. This haemoglobinuria is due to the massive or exponential haemolysis of red cells and the intensity of the intravascular haemolysis, which accounted for the severity of the anaemia that rendered cases unconscious. Sago-induced intravascular haemolysis was an unrecognised medical emergency where erythrocytes were depleted over short period of time

as a matter of minutes. The only intervention to save patient lifes was by the replacement of the erythrocytes through blood transfusion; a hospital-based treatment. These patients will need to be transported by air as it was the most efficient transport from their remote villages. These patients were flown by aircraft to the hospitals at Kiunga or Rumginai or Tabubi in North Fly District or to Balimo hospital in South Fly District.

There was a lack of detail in the clinical history of cases regarding exposure and timeline of events. These details would be needed to identify the exposure, incubation period, dose-response effect and establish the temporal relationship between exposure and disease. This reflected a lack of training of health workers being disease orientated and have blind spots to epidemiological knowledge. A prospective study on new SHD cases was described in Chapter 7 where the case definition was expanded to include the acute and extreme hypoxia induced anaerobic cellular respiration giving rise to lactic acid production induced acute metabolic acidosis.

Keeping time has been difficult for rural communities as time would be measured crudely as morning afternoon and night. The closest time that could be recognized as an incubation period was 2 hours in comparison to several hours, or even 24 hours as described in early reports (Taufa 1974; Donovan et al. 1976)

6.5 Discussion

Analysis presented here showed that a lack of awareness around SHD by health workers contributed to the case fatality rate of 35%. Dissatisfied family members of cases that died in hospital reacted by confronting and physically assaulting health workers and doctors, they also damaged hospital buildings. The histories were obtained from health workers and matrons of Kiunga Hospital and were confirmed by survivor interviews. Frequent assaults on doctors contributed to them leaving their posts, resulting in a lack of doctors at Kiunga hospital for many years.

Kiunga hospital was plagued by poor medical supplies and weak clinical care delivery to patients. Only a few dedicated health workers worked prolonged shifts and did so without regular pay. As a result, there was no stationary available to write clinical notes for inpatient cases. Health workers weren't able to keep records for patients. The majority of SHD cases were airlifted from remote villages landed at Kiunga airport followed by a short ambulance transfer to the hospital. The hospital lacked proper storage of medical records therefore

records of cases described by survivors could not be found. Management of SHD from 2000 to 2006 was known and recorded by the principal investigator who was employed by Ok Tedi Mine Ltd and worked in Kiunga hospital from 2000-2006 to provide doctor-based support to health workers and patients. Dedicated health workers that were not previously being paid were paid by Ok Tedi for 6 months, this was approved by the MD Keith Faulkner to assist the principal investigators' efforts to revamp the level of clinical care at Kiunga hospital.

Establishing a case definition for SHD in this study was an important step forward to educate both health workers and communities. This was not only to improve surveillance for the prospective study of SHD, but also to improve survival for cases. This was done through prompt evaluation and crossmatching to allow blood transfusion for patients without delay. For far too long health workers were not familiar with the symptoms of acute anaemic hypoxia, patients were unconscious and did not appear distressed on arrival at the hospitals. Educating health workers and the communities on the case definition improved their understanding of SHD symptoms and signs and helped them accept blood transfusion as the replacement treatment for erythrocytes. Dehydration was to be prevented by intravenously rehydration in such patients. This education will facilitate communities rapidly communicating outbreaks to their local health workers, OTML trustees, or church representatives at their village so they can contact health service providers for transport of cases to their nearest hospital.

Although the early case records were not found, the florid histories recounted by the survivors indicated that illness began soon after the sago meal was completed. One Membok survivor stated that her mother reported illness at the end of a meal of sago pancake and smoked small fish. She was too ill to do the physical pounding required in harvesting sago. The daughter had to get help from the village adults to physically carry her mother to the Membok aid post. Similarly, the daughter became ill after eating her sago and fish in the evening and was also admitted to the aid post with her mother. Both were referred to Kiunga hospital on day 5 of illness where her mother died, the daughter was transferred to Rumginae hospital for blood transfusion and survived.

The most dramatic events in an SHD outbreak occurred in Kiunga. A high school student came home for lunch, ate a single sago pancake, and then became ill. They were taken to hospital within an hour but went without a blood transfusion and died the same evening. The mother bought the sago from the Kiunga town market. The grieving father confronted and

physically assaulted health workers over the death. This story was recounted to the principal investigator by the Matron Pok of Kiunga Hospital and community health worker Siapan Sagi. The same family experienced another outbreak several years later which resulted in the death of a second son. Personal communication with Pastor Bonai, former hospital secretary to Rumginai hospital in 2009, confirmed that this family had the misfortune of being affected twice by SHD. The father shut down the village aid posts at Gweritimin village. He stated that the aid post failed to save his young son therefore should not operate and he used physical force to prevent the aid post from opening during his lifetime. These stories depict SHD as a rapidly fatal illness. The survivors linked their illness to sago consumption, but health workers were unaware of neither the disease entity nor its effects on the body. Failure to retrieve all the medical records was supplemented with survivors' histories of outbreaks, these were also verified by long term health workers who were involved and familiar with the survivors. Despite there being SHD cases series reports 40 years ago, health workers were unaware and unfamiliar with symptoms and treatment, which contributed to poor outcomes in cases. Moreover, SHD was yet to be described in the standard treatment book to familiarize health workers in Papua New Guinea.

Ever since the early reports of SHD four decades ago, no epidemiological study was ever undertaken detailing the incubation period, temporal association, dose-response effect, or food histories to identify the implicated food items. Blood transfusion is an urgent resuscitative intervention needed in SHD cases. Prompt blood transfusion replenishes the red cell population to improve oxygen transport and delivery to cells and effectively reverses the effects of profound hypoxia. The lack of recognition of SHD contributed to the lack of treatment by health workers. Lack of understanding of the emergency nature of SHD by health workers caused delays in administering blood transfusions, even when the treatment was ordered. The long-standing absence of doctors at Kiunga hospital over many years contributed to poor outcomes in the management of acute care for critically ill cases and that included SHD. In interviews with 5 survivors from past outbreaks they denied any prior exposure to treatment with anti-malarial medication, consumption of broad beans, and exposure to snake or spider venom. More importantly, they reaffirmed that they were well up to the time they consumed the implicated sago meal, described the quality of sago as fit for consumption, and confirmed that some of the implicated sago was bought from the Kiunga market.

There was sufficient evidence from the review that SHD affected males and females with equal severity, as there was no statistically significant difference in their age and pre-transfusion haemoglobin levels. However, the median age and pre-transfusion haemoglobin were different in addition to mortality favouring males. Predominantly male deaths occurred early during SHD suggested there could be an increased susceptibility of males to the effects of SHD. Females were more tolerant of acute anaemia and effects of hypoxia such that a younger female aged 2.75 years was able to survive the duration of time taken to travel to hospital for treatment with blood transfusion. On the other, males that were ≥ 8 years reached hospital for treatment as opposed to younger males < 8 years old who died within the first 6 hours of illness. This evidence may support the underlying genetic base for increased susceptibility resulting in higher mortality in males.

Apart from the clinical severity of anaemia, their mean haemoglobin was similar (49.3gm/L in males and 43.1gm/L in females) with a median of 47 gm/L and 46.5 gm/L respectively. The mean age of males was 28 years, and this differed to the mean age of 21.9 years in females with a median age of 28 and 19.5 years respectively. Deaths occurred early, and predominantly involved males, more so children < 8 years old and young men. On the other hand, younger female children and adult women who have lower levels of haemoglobin were able to tolerate and survive the effects of acute anaemia and hypoxia to withstand the time taken to reach the hospital and benefit from a blood transfusion. The greater prevalence of early deaths among males supports increased susceptibility of males to effects of haemolysis and hypoxia compared to females. The increased risk of fatal outcomes among males may bear some relationship with evolutionary changes acquired to protect against malaria as SHD occurs in malaria-endemic areas. The status of G6PD deficiency (glucose 6 phosphate dehydrogenase) was not tested for in cases. A test for G6PD would have to be done months post-illness to determine its level in red cells produced by the bone marrow of the cases, and not from donor cells received from the blood transfusion.

Blood transfusions prevented death in 20 out of the 40 cases but had to be promptly administered. That required cases to be immediately transferred to hospital in order to prevent many of the deaths that occurred in the first 6-12 hours. Fixed-wing aircraft transfer of cases was vital and contributed to the survival of cases. An example from Suki village occurred where a 14-year-old male died and his mother with a near-term pregnancy had a stillbirth. The severely affected mother survived with a blood transfusion but had associated hepatitis and renal failure. During the Ali village outbreak four people died (3 adult males, 1 adult female,

and 2 children) due to prolonged and delayed travel using a canoe as it took 7 days to arrive at the hospital.

Death also occurred in hospitalized cases that required urgent blood transfusion but did not receive it because blood transfusion was not ordered, or there was a delay in implementing the interventions when it was ordered. A lack of awareness of SHD and its nature as a medical emergency among health workers contributed to deaths in hospitals. Efficient transportation of cases early to hospitals and prompt blood transfusion were critical to the survival of cases as demonstrated in this review. This required operating village airstrips and existing light aircraft usage of these remote airstrips to provide rapid access to hospital-based health care. Furthermore, there must be efficient communication between village aid posts and health service providers to affect a rapid transfer of medical emergency cases to hospitals. Very High Frequency (VHF) radios were used to maintain communication between health care workers and health care providers. In some villages the Churches' contact point was the village pastor and in the Ok Tedi Project impact region, the village trustee has access to VHF radio to communicate with the mine radio operators to call for help in medical emergencies. Mobile phones were widely available, but the network coverage was limited as not all areas were able to receive mobile phone signal to make or receive telephone calls at the time of the study.

SHD an abrupt illness which gaves rise to a fulminate intravascular haemolysis that resulted in a 35% case fatality rate, predominately early deaths of males. The case review demonstrated the similarity of SHD severity between males and females, but the mortality differed significantly, skewed to males which was further supported by the differences evident in the minimum and median age and haemoglobin levels between males and females. The graphic illustration of these box plots for age and haemoglobin distribution shows that females can survive with low haemoglobin for longer and reach the hospital for treatment. In contrast, male children and young adult males were not able to withstand the low haemoglobin and therefore died early during the first 12 hours of illness. A young male presenting to the hospital within an hour from the onset of illness also died in the hospital without blood transfusion. Only older males that had sufficient haemoglobin were able to survive and reach hospital to benefit from a blood transfusion. Moreover, the increased susceptibility of males' results in more deaths and this supports a genetic basis to explain the increased fatality. Several reports in Papua New Guinea point to the presence of underlying glucose-six-phosphate-dehydrogenase deficiency, an X-linked genetic disease in the coastal lowland region which is endemic for malaria geographically at 15-22 % (Woodfield & Biddulph 1975;

Yenchitsomanus et al. 1986) and in other areas with a higher prevalence of 53% (Müller et al. 2003).

The high mortality was also due to the lack of recognition by health workers of the symptoms and signs of acute anaemic hypoxia that identify SHD as a medical emergency. This compounds the delay in treatment with blood transfusion. Blood transfusion is a replacement treatment to add erythrocytes to the patients' circulation and correct the anaemia to alleviate the symptoms and signs of acute hypoxia. This lack of education can be corrected through training health workers to recognise and treat medical emergencies. Prolonged travel time to reach hospitals was experienced when traditional forms of transport was used to travel long distances. There was a seven-day delay in the arrival of cases at the hospital due to the use of traditional transport like canoes and dinghies which contributed to more deaths. Immediate and rapid transfer of cases to hospital for treatment is essential to reduce early deaths and this requires the use of light fixed-wing aircraft. For this to be possible, an operating village airstrip is required at each remote community, and this should be supported by efficient communication between villagers, aid post health workers, and the health provider.

Undoubtedly, prevention of SHD is difficult given the lack of knowledge of the cause of SHD. Past studies on the microbiology of sago starch showed growth of various microbes including pathogens such as *Salmonella* and *Escherichia coli*. Therefore, it is advisable to promote fermentation of sago starch to sterilize and reduce bacterial growth and thereby make sago starch safe food for consumption (Greenhill et al. 2009; Greenhill et al. 2010a). There was also a need to identify risk factors for haemolysis among SHD communities to inform prevention strategies.

To resolve the lack of knowledge on SHD, the principal investigator communicated with administrators and health workers at the hospital, aid posts, and communities using the case definition formulated in this review. This not only elevated awareness but also provided instructions on how to treat cases with blood transfusion so that the acute anaemia is corrected as soon as possible at the hospital. Early transportation of patients to reach the hospital remains the main message. This information meant cooperation was maintained with health workers by villagers, and reporting occurred through the church, government, and mine radios available within communities. The radio operators were instructed to clearly state the problem so the owners of the radio could find ways to assist to transfer of the cases to the hospital for blood transfusion.

This study was a clinical epidemiological investigation on SHD outbreaks to identify the food item responsible for SHD, its incubation period, dose-response effect in addition to its clinical and pathophysiological features.The focus remained on tracing the disease survivors, the community leaders of affected villages, review of medical records of past and new cases affected by sago poisoning so we can find out more of the food types consumed and obtaine good history to the beginning of the illness. The principal Investigator was ready to describe the disease fully, identify all the complications and also confirmed the changes by laboratory results of haematology; biochemistry; oxygen saturation; acid-base balance and urine results as described in the above chapter.

6.6 Conclusion

There were multiple causes for the high mortality. Lack of treatment with blood transfusions, lack of recognition of SHD by health workers, and delays in reaching hospital from the use of less-efficient transport contributed to the 35% case fatality rate in this study.

Sago induced haemolysis affected males and females with equal severity but the difference in the median age of male and female SHD cases indicated that females could have greater tolerance to the effects of acute anaemic hypoxia compared to males. Therefore, males were less tolerant and most susceptible to and experienced early fatal outcomes during the illness, explained why more of them died in the villages. Early deaths occurred predominantly in male children and young male adults compared to older males. This difference could most likely be related to the quantity of sago consumed as older males have poor dentitions to eat as much sago as cooked sago were gelatinous but gets harder and hard to chew. Females were observed to be more tolerant, even with low haemoglobin, and could withstand delayed arrivals to the hospital. They survived when given a blood transfusion as evident in this study.

Health-worker and community education on SHD was undertaken by the principal investigator and this needs to be repeated to ensure health workers and the communities remain vigilant in detecting SHD. Whilst an outbreak in a family becomes easy to diagnose, single cases presenting with SHD may be missed. It was evident in the study that children who presented to Kiunga hospital and died soon after most likely had unrecognized SHD. Complacency in health workers can contribute to death of cases whilst in the hospital.

In 2008, the principal investigator met with hospital staff at Tabubil, Kiunga, Rumginai and Balimo hospitals. They were informed of the intended study on sago poisoning cases. Known

information about the symptoms and signs of the sago poisoning cases was shared, they were informed that patients needed blood transfusion to survive. They were asked to ensure blood donors were informed and that blood must be collected for cross-matching by the laboratory personnel. The remaining sago that was responsible for causing the illness must be brought on the same flight as the patient to be collected by the principal investigator for further laboratory testing. The cause of sago poisoning was unknown, so it was important to ensure patients and remaining sago arrived as soon as possible to the hospital at Kiunga. This information was repeated to remote villages along the Fly River. The study prepared all stakeholders, health workers, and communities that ensured surveillance required to facilitate the prospective study of SHD cases was provided. Through this setting a thorough clinical epidemiological investigation of outbreaks was possible to test hypotheses on identifying implicated food items and obtain accurate timeline of illness. A map was produced to include spatial distribution of SHD outbreaks for use in other studies.

7 Chapter 7 Prospective study of sago poisoning outbreaks

7.1 Introduction

Sago haemolytic disease was a presumed foodborne disease not widely known by health workers in Papua New Guinea. This study carefully gathered epidemiological evidence that was needed to confirm or refute the presumed association with sago consumption. One of the purpose of the study was to substantiate this relationship suspected by the earlier clinicians who first reported their case series (Taufa 1974; Donovan et al. 1976). Despite the reported morbidity and 19% mortality associated with SHD, health workers and doctors that have no prior experience of SHD were unlikely to recognize the disease and therefore cases continue to have worse health outcomes. A thorough outbreak investigation was undertaken to create a case definition as well as other epidemiological characteristics specific to SHD. This was done to improve understanding and familiarize health workers and communities alike with SHD so they can promptly recognize and refer cases to hospitals for rapid diagnosis and appropriate treatment.

7.1.1 Hypothesis

Since the early description of SHD, the relationship between sago and the illness remained a presumptive association. The hypotheses to be tested in this study are as described in Chapter 1 and below:

H_O: There is no relationship between mouldy sago consumption and SHD.

: Consuming mouldy sago ≠ SHD

H_A: There is a relationship between mouldy sago consumption and SHD.

: Consuming mouldy sago = SHD

7.2 Materials and Methods

This study of clinical epidemiology was approved by the Papua New Guinea Medical Research Advisory Committee in 2006 MRAC 09.08. The overall permission to access a government health facility was obtained from the Secretary of the Department of Health who was aware of the inception and intention of the study. Permissions for collaboration with hospitals and communities were sought by the principal investigator for visits to hospitals and communities. Written permission was obtained from the chief executive officer of Kiunga

Hospital as it was the main hospital that received medical referrals from remote villages for treatment and/or for referral to another hospital.

7.2.1 Observation study design used for prospective cases

The lethality of sago poisoning is appreciated by affected remote communities' where scarcity of food prevents them from discarding sago that may seem less than ideal for consumption and causes them to risk consuming it. It was highly unlikely for any form of experiment to be conducted; it would be unethical to carry out a trial of eating old or suspicious looking sago as this could potentially cause serious haemolytic illness and death. The only option was to conduct a close observation study that assessed verbal reports on the quantity of sago consumed as well as the exposure and an accurate timing of events, particularly an account of various symptoms on a timeline. Initially, the time that the stated quantity of sago was consumed to the time of onset of the first symptom (and each subsequent symptom) was recorded. This will provide the epidemiological evidence for the incubation and severity of illness compared to the quantity of sago ingested. A comparison of the intake of different quantities of sago to the clinical severity of illness can be explained on the basis of laboratory testing of full blood counts, renal function (urea, creatinine, and electrolytes), and liver function tests (bilirubin, albumin, liver enzymes) as well as considering bedside measurements of vital signs, oxygen saturation, and Glasgow coma scale monitoring of the effects of hypoxic injury to brain function. The Glasgow coma scale is used to measure the brain's response to head injury but in SHD, it is used to measure acute anaemic hypoxic effect on the patient's brain which reverses after blood transfusion corrects the systemic effects.

7.2.2 Commencement of SHD active surveillance

During the initial field work, the principal investigator had an awareness of sago poisoning symptoms and signs from managing two previous outbreaks. These symptoms and signs were made known to the health workers and clinicians. The staff and the hospital administration of the four hospitals were informed that the study has begun, and the principal investigator was conducting the study as a PhD project with the James Cook University. The principal investigator would maintain contact with the hospital administration throughout the period of the study because the study needed permission for access to patients and for collecting relevant clinical data on SHD cases. Hospital staff and administration was advised to store any remaining sago that was brought to the hospital by the patients for the principal investigator. They were also asked to pass a message over the radio asking for the remaining sago to be carried with patients on the same transport taking the patients to the hospital.

7.2.3 Active surveillance of SHD

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Available information on SHD was shared with health workers to maintain a high state of alert. In 2009, the successful treatment of the 2005 SHD outbreak was communicated to the health workers at Kiunga hospital. Health workers were informed that to prevent deaths from SHD they must be able to recognize the urgency of starting treatment with blood transfusion without delay after the patients arrive. Similar meetings with health workers were delivered to Tabubil, Rumginae, and Balimo hospitals. Health workers were provided with the following definition for SHD and were advised to record historical and clinical information on cases seen. Furthermore, health workers were asked to retrieve implicated sago to be sent to the laboratory for further investigation.

7.2.4 Case definition for sago poisoning used in this study

A sago poisoning case was defined as a person who vomits 10-15 minutes after a sago meal and develops a headache and/or dizziness, followed by rapid onset of generalized weakness and drowsiness then loss of consciousness with passing red urine. In an unconscious or drowsy patient, a clinical diagnosis of SHD would be supported by the presence of sallow complexion of palms of hands and soles of feet of mild jaundice that overshadows extreme pallor indicating anaemia, ,and passing a dark red sample of urine that tests positive for haemoglobin content will be elevated if measured.This can affect a group that ate the sago meal together or individuals who ate sago by alone.

The map of the Western Province shows information on the burden of past or retrospective cases, and prospective or new outbreaks of SHD. The heavy burden of SHD outbreaks (both

past and new cases) are in the North Fly District. The three stars indicated the prospective cases for this study. The red dots show locations of past cases of sago poisoning from medical records. The South Fly Outbreak occurred in 2007, at the beginning of the study. The cases were airlifted by fixed wing aircraft and were admitted to Balimo Hospital. Cases from the Timingondok village outbreak were admitted to Rumginae Hospital in a canoe. The Tarakbits village outbreak cases were airlifted by helicopter to Kiunga Hospital. T'minserap villagers were transported by road ambulance from Sare Kona as were those from the Sauga Kona outbreak. The three hospitals located in North Fly Districts, particularly Rumginae and Kiunga, received most cases.

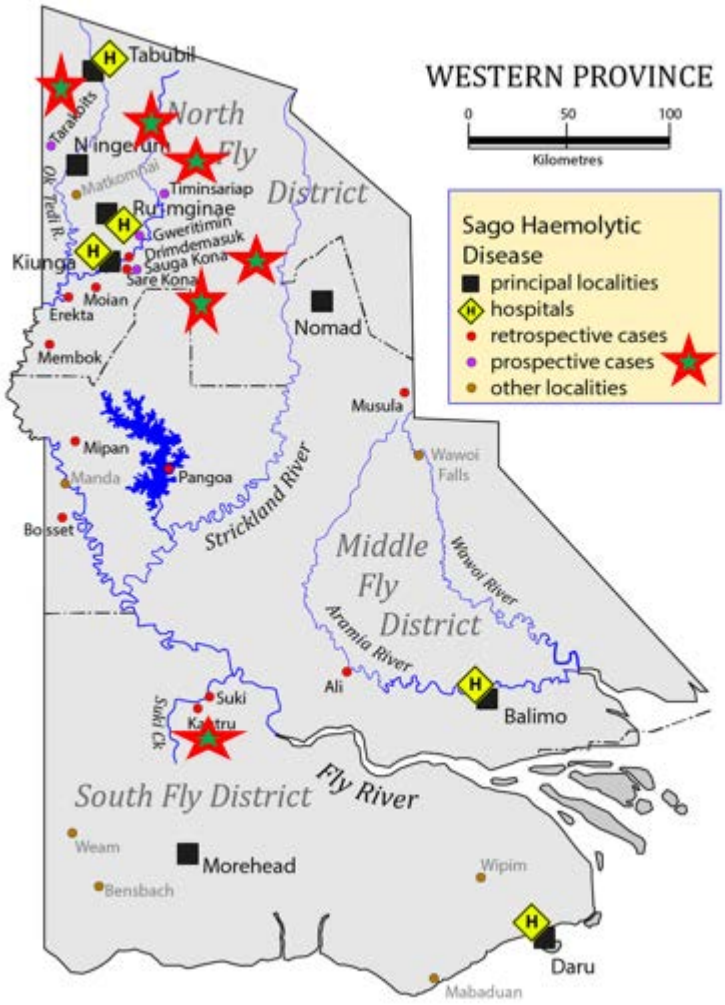

Figure 29 Six new outbreaks of Sago Poisoning in Western Province

A sago poisoning case was defined as a person who vomits 10-15 minutes after a sago meal and develops a headache and/or dizziness, then rapid onset of generalized weakness and

drowsiness followed by loss of consciousness and passage of red urine. In an unconscious or drowsy patient, a clinical diagnosis of SHD is supported by the presence of extreme pallor indicating anaemia, mild jaundice, and a dark red sample of urine that tests positive for haemoglobin of which the haemoglobin content is likely to be elevated if measured.

7.2.5 Risk communication strategy

Although the emphasis was on detecting new cases, messages on prevention were concurrently delivered to these communities to enlighten the community. Communities and health workers were mobilized to improve recognition, conduct investigations, and prepare for blood transfusion as treatment for cases with SHD. The complication of dehydration in an unconscious patient was stressed to hospital staff, this is counteracted by maintaining an intravenous line and rehydrating the patient whilst waiting for the preparation of cross matching blood by the laboratory staff. Failure to rehydrate the patient resulted in the onset of acute renal failure in patients who were admitted to the ward. The communities' mobilization created a high level of awareness and sensitivity to report, organize, and transfer cases as well as to send the implicated sago with the patients so that both patients and implicated sago arrive at the hospital at the same time. Due to the remoteness of the villages, retrieving the implicated sago after the arrival of the patient at the hospital proved difficult and ineffective due to the lack of regular fixed-wing flights and the implicated sago was most likely discarded by relatives to prevent others from ingesting it.

7.2.6 Communication strategy for medical evacuation

All communities were informed to effectively use VHF radios available in communities. Radios were held at health facilities for communication with the church, government, and resource developers such as Ok Tedi mine Ltd. Only the ECPNG Church and OK Tedi Mining Ltd were capable of providing airlifting services. The government and Catholic Health services did not have air services support to conduct medevac, so they continued to channel medevac requests to the ECPNG Church and Ok Tedi Mining Limited. The Mission Aviation Fellowship plays a critical role in medevac. Mission Aviation also flies medevac to Daru hospital.

In the experience of the principal investigator, radio communication by the pilot late in the afternoon is relayed to the residents of Daru Island by the hospital. This invites the town residents who own cars or trucks to align both sides of the airstrip with their head lights turned on, marking the length and width of the airstrips to allow the pilot to land the plane at night

with the sick patients on board. This was an experience that had remained with the principal investigator throughout their doctoring career in Western Province.

7.2.7 Strategy for the acquisition of implicated sago

Access to implicated sago samples was critical for the study to investigate the cause of SHD. Moreover, objective evidence obtained by laboratory investigations can accurately identify the aetiology that produces the pathophysiology of SHD. The history of SHD shows that implicated sago was not brought with patients or when brought in, there was no mechanism in place to fully investigate it. More often, implicated sago was discarded promptly by relatives to prevent others from consuming it and becoming ill. In order to obtain implicated sago, a collective approach between the community, health workers, and the principal investigator was required. Regular communications were maintained to secure transport of implicated sago with patients on medical retrieval. Two samples of implicated sago were obtained during the fieldwork through the assistance of health workers and laboratory technicians from Kiunga hospital.

Table 7.1 Villages visited to set up active surveillance

Sago haemolytic disease surveillance	
Year	Villages Visited
2007	Aewe Suki
2007	Ali Balimo market
2007	Boboa Lake Murray
2009	27 Fly River villages impacted by OTML project
2010	5 Ningerum villages
2011	6 Nomad and Lake Murray villages

Forty-four visits were made to villages and settlements during the study. In 2009, a larger community consultation on SHD was conducted as part of the Community Relation Department of the Ok Tedi Mining team. They visited 27 villages located along the 800 km length of the Fly River, eastern banks, and the Kiwai Islands. In 2010, SHD awareness was raised to rural remote communities of Ningerum, Nomad, and Lake Murray area and includes 5 large peri-urban Kona settlements surrounding the town of Kiunga.

7.2.8 Data analysis

Descriptive statistics were used to identify measures of central tendencies. Graph pad software was used to calculate the odds ratio for proportional data. T-tests were used to test for differences in means of clinical outcomes.

7.3 Results

7.3.1 Map of Western Province location of SHD outbreaks

The map of Western province in Figure 7.2 revealed the spatial distribution of prospective and retrospective SHD outbreaks by using their global position coordinates.

7.3.2 Western Province rainfall map and SHD outbreaks

Figure 7.2 shows the rainfall in 3 districts of the Western Province. The heaviest rainfall occurs in the North Fly and decreases in the Middle Fly with minimal levels in the South Fly District. The Lake Murray regions of Middle Fly and the Suki region as well as villages along the Aramia River of the South Fly are locations of SHD outbreaks.

A similar pattern was exhibited by the SHD outbreaks, most occur in the North. There were 3 outbreaks in the Lake Murray region of the Middle Fly and 3 outbreaks in Suki region of the South Fly District. The majority of the SHD outbreak sites (both prospective and retrospective) occurred in the North Fly District compared to the Middle and South district. North Fly District had the highest rainfall and had the highest number of SHD outbreaks with 61.1% (11/18) followed by the Middle Fly district with 36.2% (4/11) and the South Fly District with 27.3% (3/11). This SHD pattern coincided with the pattern of rainfall, which was highest in North Fly District and falls to very low levels moving further south of the province.

7.3.3 Prospective sago poisoning outbreaks in NFD during the rainy season

The prospective SHD outbreaks were from Tarakbits, T'mingondok, T'minserep villages and Sauga Kona, a peri–urban settlement of Kiunga. The prospective SHD outbreaks occurred during the wet season months (February-May and November) and the sites were confined to North Fly District where the rainfall was highest compared to the MFD, there was also one outbreak in Kautru in the Suki region of the South Fly District as depicted in Figure 7.2.The map also highlights the challenge of distance between the sites of outbreak and the hospitals where only fixed-wing or helicopter flights can overcome long distances to reach hospitals. Fortunately, the prospective cases were airlifted by the Ok Tedi Mining Ltd helicopter from Tarakbits. Road ambulance retrieved cases from the peri-urban settlements of Sauga and Sare

Kona. The three young males from T'minserep on the upper Fly River from were visiting Kiunga Town for a holiday and ate the sago pancakes cooked with sago that they had harvested in their village. They ate the same sago over 3 days despite being ill. Relatives and friends informed them to drink lots of fluid to improve but their illness worsened and they were hospitalized on the 4th day of illness. This was unlike other outbreaks where a single meal was detrimental to their health.

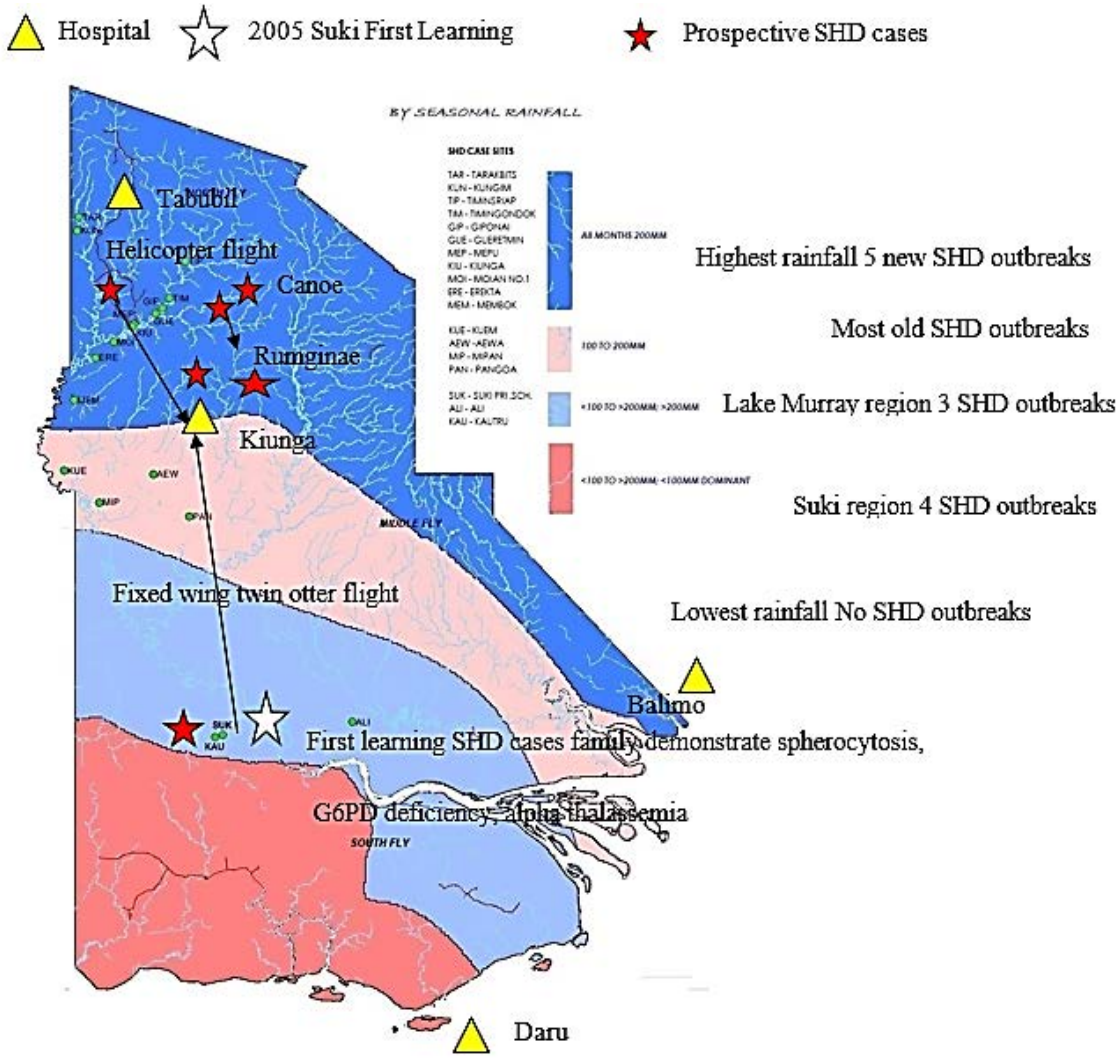

Figure 30 The rainfall differs considerably, high in north and less towards the south

Sago poisoning outbreaks were more common in high rainfall areas of the North Fly District shown as dark blue region. Fewer outbreaks occur in the drier regions of the Lake Murray in the Middle Fly District and Suki region of the South Fly districts. Water is essential for sago processing and may in part explain higher SHD outbreaks in the NFD where there is high

rainfall. But this may also have a causal relationship to the outbreaks. Temperature remains high throughout the year.

7.3.4 Epidemiological characteristics of prospective SHD outbreaks

Table 7.2 Characteristics of new outbreaks

SHD outbreak characteristics of 2005, 2009, 2012 and 2014						
Temporal association			Exposure status	Time of the first symptom	Quantify exposure	Severity of illness
Date	Village and storage surface	SHD symptoms	Exposure to implicated sago	Incubation period	Quantity of implicated sago consumed	Symptoms variability
25th May 2005	Suki Bag of sago stored on earthen floor	Yes	14-16 cm's sizes- sago pancakes	30mins-1hr	Single bite to full pancake	Severe symptoms and signs
		No symptoms	Chewed and discarded a mouthful of sago			Only Haemoglobinuria on day 3 tested
17th March 2009	Timingomdok Sago was stored on the receptacle of sago leaves stored in the ceiling.	Yes	Single exposure	Shortly after dinner	Mother ate most at a single meal	Severely affected
9th April 2009	Kiunga- Bag of sago stored on earthen floor of the kitchen	Yes	Affected only 2 that are 2/14 diners	15-20 minutes	One ate 1/4 , the other ate 3/4 sago pancake	Minimal symptoms, severe-fatal
19th November 2012	Tarakbits- Bag of sago stored on kitchen timber bench surface	Yes	Single evening meals	Shortly after meal	Ate the whole pancake	Severe symptoms and sign
24th of February 2014	T'minserap Bag of sago stored on timber floor	Yes	Repeatedly ate over 3 days while ill	Shortly after meal	Ate the whole pancake	Severe symptoms and sign ATE FOR 3 DAYS

Table 7.2 contains an estimate of time from exposure to onset of the first symptom as well as the severity of the illness compared to the quantity of sago consumed. This table includes data from the 2005 Suki outbreak as it contains more details of effects. This outbreak affected one family and illustrated the illness developing among family members who cooked and consumed the same implicated sago at different times. This includes the two siblings who just

tasted and then discarded the sago from their mouth because they claimed that it tasted too bitter to continue eating.

7.3.5 Radio report of SHD outbreaks

Radio communication is the main way rural communities talk with the church health services (Catholic and ECPNG) and government hospitals (Kiunga and Daru) in the Western Province during medical emergencies. Mine operations impacting Fly River communities also used their company-provided radio to communicate directly with the OTML community relations division for medical issues affecting them. The Catholic health administrators then communicated with the government hospitals who communicated with Ok Tedi Community Relations to initiate the helicopter transfer from Tarakbits village to the Kiunga hospital. Sago poisoning outbreaks occurring within peri-urban informal settlements usually send runners to the Kiunga hospital to alert the ambulance to be dispatched to collect the patients.

Kiunga hospital ambulance retrieved sago poisoning cases from Sauga and Sare Kona and took them to the Kiunga hospital within 10 minutes. The T'mingondok family travelled downstream in a canoe to Rumginai Hospital which took two days of travel.

A female adult case was transported by ambulance to Rumginai Hospital from Kiunga Hospital because her son died from sago poisoning at Kiunga hospital. During the late 1990's, this same family's 14 year old son, grade 10 student ate a single pancake for lunch when he became too unwell to return to school so the mother brought him to Kiunga hospital; but he died in the evening. The sources of sago were from the Kiunga market and the other was from their village on the upper Fly River.

Cases from the Suki region was communicated through the ECPNG health radio at their health facility in Suki. This is where the Mission Aviation Fellowship stationed at Rumginai arrived and airlifted cases to Balimo Hospital. In 2005, an Ok Tedi twin otter flight returning from Daru was able to transport the Suki family affected by sago poisoning cases to Kiunga hospital. This provided detailed data on the epidemiological and pathophysiological changes and genetic roles in this disease.

7.3.6 Learning cases: Suki 2005 outbreak

During the 2005 Suki outbreak, relatives informed the health workers who called the Kiunga Hospital radio. The call was then relayed to the Community Relation Department of Ok Tedi Mining Ltd and diverted one of its fixed-wing aircraft at Suki airport to transport cases. They

were transported on the third day of illness to Kiunga hospital managed by the principal investigator and health workers who provided the much needed clinical experience and expertise to investigate SHD. Investigations of erythrocyte membrane, enzymes, and haemoglobinopathy are reported in Chapter 6 on retrospective study of past case medical records. The detection of spherocytosis, presence of G6PD deficiencies, and α thalassemia were the first evidence of underlying genetic disorders of the erythrocytes as evolutionary protection developed against malaria by the population who live in endemic malaria regions.

7.3.7 Types of storage vessels used for implicated sago

The processed sago starch was stored in old, manufactured bags that were previously used for rice and chicken feed. The bags were stored on earthen and wooden floors. Only one was openly stored in a sago receptacle under the ceiling of a temporary garden house. Pictures of sago sold at Kiunga town market showed they were often stored in manufactured bags as seen in Figure 7.3. Smaller portions will be repackaged in plastic bags in to be sold to residents of the town. Manufactured bags are popular storage bags but those who do not have will have to weave baskets using sago plam leaves or other broad leaves and tie into a long bundle.

Figure 31 Bags of fresh sago starch at Kiunga market

Families in the villages would store their sediments of sago blocks in similar bags like the ones shown in the photograph above (Figure 7.3). The blocks of sago would be crumbled into powder and placed in smaller plastic bags for sale at the market.

7.3.8 Source of water used for extraction of implicated sago

The Sauga Kona family used the Kiunga town water supply to process sago extraction in 2009 which was responsible for the SHD outbreak that affected them (which would be an exception). The other 3 prospective SHD outbreaks used river water to extract sago starch. In lowland communities, swamp water provides a common source for sago starch extraction. Digging a hole in the ground in the lowland results in it rapidly filling with water, creating a well. This water is used to soak and squeeze the starch out of the macerated pith of sago. A collection vessel is used such as a supported plastic sheet. The sediment is collected and deposited into bags for storage and is used as food. Evidence of sago starch extraction sites and use of swamp water is shown in Figure 7.4 below. A sago receptacle was used as a funnel to drain the water and sago starch which flows down into collecting vessel for sedimentation. The water is poured off and sago starch sediment is collected and stored in bags as seen in Figure 7.3.

Figure 32 Sago processing site at T'moknai village

This is a typical evidence of sago starch extraction, withe rudimentary milling construction close to water source. Water source at theT'moknai village has multiple uses, firstly it used for sago processing, in addition to drinking, bathing, and washing clothes. The health team used this water source whilst others walked to the river. Sago is produced in the open environment as captured using traditional method so to consider sago poisoning as a food borne toxicosis one has to recall the source of the food production, storage and cooking the particular sago pancakes or pudding that families eat

7.3.9 Prospective study of SHD outbreak – full stories

Table 7.3 Hospital admissions and clinical outcomes

Date of outbreak	Villages	Number affected	Number dead	Hospital
17th March 2009	Timingondok	5	0	Rumginae
9th April 2009	Sauga Kona	2	1	Kiunga
18th November 2012	Tarakbits	6	1	Kiunga
1st March 2014	T'minserep	3	1	Kiunga
Total		**16**	**3**	

The case fatality of the prospective cases was 18.8% (3/16) with 2 deaths, a 20-year-old male and a 27-year-old female occurred and were hospitalized cases. A 2-year-old male also died 4

hours after the onset of the illness but this occurred in the village. Kiunga hospital received the majority of SHD cases. The prospective or new cases of SHD outbreaks occurred during the wet season months (November –May).

Sixteen cases were reported during the period of the study; only 15 were admitted to the hospital and a 2-year-old male died within 4 hours in Tarakbits village before the helicopter retrieval was undertaken the next day at 16 hours from the onset of illness. The Kiunga government hospital received 10 cases whereas the Rumginae ECPNG church hospital received 5 family members from Timingondok village as they travelled in a canoe downstream to the hospital. Another case from Sare Kona was transferred by ambulance to Rumginae hospital despite being in close proximity to Kiunga Hospital. These cases were admitted by the clinician on duty who is a health extension officer or doctor, but the initial assessment would have been undertaken by a community health worker or nursing officer. This is the usual arrangement of clinical practice in rural hospitals in Papua New Guinea. Secondary cases were not observed in any of the prospective outbreaks.

7.3.10 Witness account of Sauga Kona SHD outbreak

On the 9th March 2009, an SHD outbreak affected the family of a former councillor, Jonathan Boru living at Sauga Kona in Kiunga (North Fly District) of the Western province. The details of the SHD outbreak were provided by the sole survivor and corroborated by Councillor Boru. The fatal case was the sister-in-law and the hostess that prepared the family meal, she also cooked the sago for her and her friend that made them both ill and caused her death.

7.3.11 New epidemiological data on the timeline of outbreak: 2009 outbreak

For the very first time, data collected on the Sauga Kona SHD outbreak provided the first evidence of a timeline from the exposure to the appearance of the first symptom and subsequent symptoms. Additionally, a survivor of the outbreak was able to retell the story. A further witness was a former local government councillor who was able to confirm the story because Councillor Jonathan Boru was the brother in-law of the deceased woman. The husband of the deceased was Councillor Boru's brother. He and his wife planned the Sunday luncheon cooked by his wife and her girlfriend. They boiled rice, chicken, and greens in a stew in another pot. They served the meals on 13 plates, to mainly children and 5 adults. She realized there was no food left for herself so she pan-fried sago taken from the bottom of her sago bag stored on earthen kitchen floor. She shared the sago with her girlfriend who ate a quarter of the sago pancake whilst she ate three quarters (16cm). Table 7.5 shows the timeline

of exposure to developing the first symptom which was vomiting 10-15 minutes after the meal. She developed a headache, dizziness, and generalized weakness and laid down on the floor and she was then noted to have passed red urine.

7.3.12 Sago poisoning outbreak investigation symptoms and signs

Table 7.4 Timeline of exposure to onset of illness

Time	Case Age	Ate sago meal	Symptoms and signs
2.00 pm	F/27 years	3/4 of 16cms pancake	
2.15 pm			Profuse vomiting, headache, dizziness, weakness
2.30 pm			Drowsy, noted to pass red urine, fever
3.00pm			Unconscious and admitted to hospital
			No urine output and died
2.00pm	F/23 years	1/4 of 16 cms pancake.	Ambulance and transferred to Kiunga hospital.
2.40pm			Vomited after the physical exertion of carrying her critically ill friend to the ambulance, No fever
3.00pm			Passed red urine but fully conscious and ambulant
			In hospital
	12 Controls	Did not eat sago	All 12 controls were well

The rapid onset of symptoms and signs of SHD is illustrated in table 7.4 compared to controls who consumed other food items and were spared. Only the two cases that ate sago became ill. The one who ate the most (three quarters of the pancake) had a fatal outcome and the other who ate only a quarter of the same pancake survived with mild symptoms.

7.3.13 Calculate the attack rate of illness by food items

Table 7.5 Types of food eaten during the Kiunga Sauga Kona 2009 SHD outbreak

Food items	# Ate	# ill	% Attack rate	# Not ate	# ill	% attack rate	Attributable risk
Chicken	13	1	7.6	1	1	100	99
Rice	13	1	7.6	1	1	100	99
Green	13	1	7.6	1	1	100	99
Chicken soup	14	2	14.3	0	0	0	14.3
sago	2	2	100	12	0	0	100

7.3.14 Attributable risk of sago defined it as the implicated food

Contaminated sago consumption preceded SHD and had an attributable risk of 100%. For the first time this study has provided the epidemiological evidence that confirmed that sago was

responsible for causing the sudden haemolytic illness which was presumed association suspected by earlier clinicians. The inclusion of a control group that did not eat sago allowed meaningful comparison to the cases that ate sago therefore provides quantitative evidence confirming that a true relationship exists between contaminated sago consumption and SHD. Finally, 50 years later, contaminated sago is declared as the implicated food.so the next question is what is present in the implicated sago to produces the haemolysis?.

7.3.15 Confirmed incubation period for SHD.

The incubation period is the duration of time taken from consuming the sago meal (the exposure) to the appearance of the first symptom which was vomiting. Out of the 14 diners, only 2 women that ate sago became ill; one of whom also ate other food items as well. The woman that developed severe illness vomited within 10-15 minutes of the meal and 40 minutes later the woman with mild illness vomited after she physically carried the severely ill woman 40 meters to the roadside for the Kiunga Hospital ambulance to retrieve the patient.

Furthermore, consumption of the implicated sago precedes the onset of sago poisoning.This confirmed the temporal relationship; consumption of contaminated sago must precede the haemolytic episode and the associated symptoms of acute anaemic hypoxia responsible for the physical weakness and the state of unconsciousness.

7.3.16 Confirmed dose-response effect for SHD

Does a relationship between the quantity of sago pancake consumed and the severity of the disease remain to be discovered? The main effect was intravascular haemolysis, the destruction and loss of the erythrocyte population. The clinical effects were related to the level of haemoglobin in the remaining erythrocytes. SHD occurred in those who consumed the usual quantity of sago pancake for a meal. In order to determine a dose-response effect, the size of a whole sago pancake was determined first, then amongst those who ate less than a normal meal, they were asked to provide the fraction of a single pancake that they consumed. The reported quantity of sago consumed varied from a single bite, just chewed, tasted and discarded, a quarter, and three quarters of 16ms sago pancake consumed. In 2005 the first evidence was gained from the two members of the Suki family who chewed a single mouthful, tasted, then discarded the sago, and were unaffected by sago poisoning. But, their clear urine tested positive for haemoglobinuria on day four of the outbreaks.

In 2009, the Sauga Kona outbreak provided more evidence through a case that vomited, passed red urine, and became drowsy and recumbent within 10-15minutes after eating three

quarters of a 16cm sago pancake. She shared one quarter of the pancake with her friend who remained well. Her friend piggybacked her to the main road to await the Kiunga ambulance where her friend vomited 30 minutes later after the physical exertion. They both passed red coloured urine whilst at the hospital. The one who consumed a quarter pancake produced intravascular haemolysis without significant anaemia (haemoglobin 78gm/l) the one who ate three quarters of a pancake produced critical and florid symptoms of acute anaemic hypoxia (haemoglobin 40gm/l) that led to a fatal outcome. Those that consumed one or more contaminated sago pancakes were destined to be moribund and remain unconscious as in most reports of SHD outbreaks. This occurs until they receive a blood transfusion to replenish their erythrocytes to improve and maximize the oxygen transport.

In 2014, sago poisoning affected three young men from T'minserap village on the upper Fly River. The three men were in robust health who travelled to Kiunga town for a holiday. They harvested their sago and brought it with them as their only food source. Their good health protected against the severity of sago poisoning. They ate contaminated sago pancakes over three days before becoming so unwell that an ambulance retrieved them from Sare Kona, a peri-urban informal settlement.

The severity of illness was demonstrated by the Suki outbreak in 2005 and the Sauga Kona outbreak in 2009. The different sizes of sago pancake consumed and as well as just tasting and discarding of sago caused intravascular haemolysis detected by the presence of haemoglobinuria on urine tests, this was despite the urine colour visually looking normal 4 days after the outbreak. These 2 members of the family of 8 remained asymptomatic. The urine samples were tested and recorded by the principal investigator who managed the Suki outbreak in 2005. The haemoglobinuria was intense in the other 5 members of the Suki family. The 14-year-old son died on day 3 as the plane landed to airlift the family to hospital. The mother and 16-year-old daughter were pregnant; the mother delivered a stillbirth but term baby on day 3 of the illness. The daughter had asymptomatic SHD, she went into spontaneous labour after one week whilst caring for her family in hospital. She delivered a fresh stillbirth from facial presentation and a delayed second stage of labour. The 2005 and 2009 outbreaks confirmed the presence of intravascular haemolysis, the incubation period, and dose response effect that fully characterizes the natural history of SHD. These two outbreaks were the equivalent to a quasi-experiment where data on quantity of sago consumed were pooled to show the titrated effects of the different quantities of contaminated sago on the severity of illness. The severity of illness correlated well with increased intake of sago pancakes, clearly

showing that three quarters of sago to a single pancake were associated with fatalities. Haemolysis was evident in the urine of those who were not ill which showed that even small quantity of hypothesized preformed toxin destroyed the erythrocytes. This released the haemoglobin to be excreted into the urine and coloured it red in more severe cases. The incubation period was reported to be 10-15 minutes. The patients became ill at the end of eating the three quarters of a sago pancake.

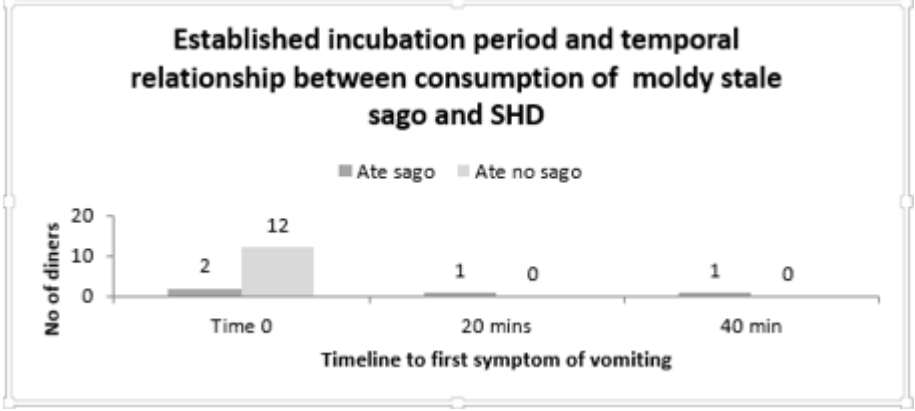

Figure 33 Incubation period and temporal relationship between sago consumption and SHD.

7.3.17 Glasgow coma scale use to monitor unconscious SHD cases

Glasgow coma scale is used to assess trauma induced head injury but is an instrument that was used to conduct clinical assessment of the altered state of consciousness induced by acute anaemic hypoxia in 14 SHD cases. A normal score of 15 was evident in 7.1 % (1/14), 57.1% (8/14) scored 6, 28.6 % (4/14) scored 7 and 7.1% (1/14) scored 11of the cases. Most of the cases were in an unconscious state and were recumbent until they received blood transfusion. They weren't abe to feed themselves so were fed food and fluid by the relatives as demonstrated by cases in the Mipan outbreak.

7.4 Reports of SHD outbreaks

7.4.1 Kiunga Sauga Kona SHD outbreak - 9th of April 2009

A post-mortem was requested by relatives who were concerned about domestic violence as a probable cause of death and gave permission to obtain tissues for testing. The surgeon and CEO of Kiunga hospital performed the post-mortem examination that did not reveal any blood

collection in body cavities and tissues. Tissues obtained from the oesophagus, stomach; kidney and pancreas were sent for histological examination at the Pathology services of Port Moresby General Hospital that reported that autolysis of tissues occurred which thereby prevented any interpretation.

The timeline provided by the survivor was able to inform this study of not only the incubation period, but also the temporal relationship between the implicated sago pancakes that transmitted SHD. This account also provided evidence of the dose-response effect in SHD. This relationship was accurate and definite with the inclusion of the control group that allowed analyses of the attributable risk as 100% illness in those exposed via sago pancake consumption.

There were three factors that greatly assisted the epidemiological investigation. Firstly, Outbreaks that occurred near the hospital helped immensely with the time of onset of disease and related well to the exposure confirming the temporal association. Unfortunately, the rapid transfer of cases to the hospital immediately after illness did not save the patients. Secondly, the outbreak occurred during the daylight hours aided greatly in obtaining an accurate timeline of exposure, clinical signs, and symptoms. The presence of doctor with training in epidemiology assisted in quantifying the exposure and linking the exposure to the effects of the disease. This also assisted in obtaining clinical samples to test urine samples, test blood for red cell abnormality, and to identify erythrocyte breakdown products in the urine. The clinical effects of acute anaemia hypoxia and the danger of dehydration and acute renal failure in patients were appreciated as the cause of death in sago poisoning. The reduction of the haemoglobin level on first blood test was noted, and urine was checked for the presence of haemoglobin as well as other breakdown products of bilirubin and urobilinogen. Moreover, the 2 cases of SHD from this outbreak provided both extremes on the spectrum of SHD clinical presentations. For the first time, this outbreak investigation alone provided not only detailed insight into the natural history of SHD but suggested the aetiology of SHD was related to preformed toxin(s).

During an interview conducted by the principal investigator with Councillor Jonathan Boru, he stated that he harvested the sago from a sago palm that grew in his back yard in Kiunga in December. He used the town water supply to extract the sago starch. He produced 24 bags from 10kg of sago starch and shared them with other families in the neighbouring houses. He confirmed that all sago was consumed within 2-3 weeks of harvest except for the implicated

bag of sago that was taken by his brother and stored on the earthen floor of his kitchen. His brother and his wife consumed the sago gradually over 4 months as they were a 2-person household with no children of their own. He confirmed that his sister-in-law died but her best friend survived. Councillor Jonathan Boru was one of the 12 people that did not eat sago, all 12 people remained well.

7.4.2 Tarakbits village SHD outbreak -19th November 2012

A family of 6 became ill during the night after eating sago for their dinner. The symptoms were vomiting and generalized physical weakness that was experienced soon after the meal. The sago had been recently harvested about two weeks old but stored in an old rice bag. A male child of 2 years old died that evening within 4 hours of illness. The next morning, 16 hours after the illness, 45 years old father, the 40-year-old mother and three sons aged 7, 9 and 11 years old were airlifted by Ok Tedi Mine helicopter to Kiunga Hospital where they received a blood transfusion. Blood and urine samples were collected and tested serially and used to monitor their management. For the first time during the study, an implicated bag of sago was brought to the hospital with the patients. Sago was the only food item eaten by the family for dinner and they all became severely ill within a short time after the meal with the death of the youngest son within 4 hours of illness in the village. A messenger was sent to the nearest health facility where radio communication was relayed to Ok Tedi and a helicopter was dispatched to the village where 5 surviving members of the affected family were transported to Kiunga hospital for treatment. Only sago was eaten that resulted in the SHD outbreak.

7.4.3 T'minserep village SHD outbreak - 24th of February 2014

Three men, aged 20, 20 and 25 years old from T'minserep village located in the headwaters of the Fly River planned to travel to the town of Kiunga and spend some time there. They prepared well by harvesting and processing their sago, which was stored in a manufactured bag formerly used to sell chicken feed. Within a couple of days, they travelled in a canoe downstream on the Fly River towards Kiunga with the bag of sago as their food supply to sustain them during their stay. Upon arrival, the bag of sago was stored on the wooden floor of the house at Sare Kona where they resided. Each day they used the sago to prepare their meals which consisted of dry pan-fried sago. Each meal was the same, where each man ate several sago pancakes with no other food item. Within 2 weeks of arrival, one evening meal of sago made them all ill but they continued to eat daily meals prepared from their bag sago for 3 more days. Other relatives encouraged them to drink more water during the 3 days they

had been sick, on the 5th day of illness the 3 men were transported by ambulance to Kiunga hospital. The symptoms and signs were immediately recognized as SHD by health workers at the hospital. Two men were drowsy, and one was unconscious and described to be breathing deep and rapidly. All 3 men had pallor signifying the presence of anaemia and were recumbent. Blood transfusions were administered to two men who gradually recovered, even the case that had acute renal failure improved over time. The third man was not only unconscious but had acute renal failure as well as having a high anion metabolic acidosis. This was explained by the description of a rapid deep sighing pattern of respiration. This is known as Kussmaul's breathing and is commonly associated with metabolic acidosis due to the presence of acute renal failure. This case had a fatal outcome upon receiving sedation (Idro et al. 2005; Morris & Low 2008; Kitabchi et al. 2009; Kraut & Madias 2010). For the first time, a high anion metabolic acidosis was identified in an SHD case that did not have acute renal failure. Blood transfusion was not administered nor was treatment for acute renal failure instituted. At the time of the study, treatment for acute renal failure by peritoneal dialysis or haemodialysis were not available in government hospitals in Papua New Guinea.

Table 7.6 Demographic and pre transfusion haemoglobin

N=24	Date of SHD	Village	Gender	Age in years	Hb gm/L	WCC/cm^3
1	30th of May Suki 2005	Suki	M	2.5	11.1	7100
2	30th of May Suki 2005	Suki	M	45	6.1	11000
3	30th of May Suki 2005	Suki	F	42	5.0	25000
4	30th of May Suki 2005	Suki	F	16	8.9	9700
5	30th of May Suki 2005	Suki	F	9	5.8	26700
6	30th of May Suki 2005	Suki	F	7	5.9	19300
7	30th of May Suki 2005	Suki	F	5	3.6	39800
8	9th of April 2009 dead in hospital, no blood transfusion	Kiunga Sauga Kona	F	26	4.6	11000
9	9th of April 2009	Sauga Kona	F	23	7.8	8000
10	7th March 2009	Timingondok	M	36	7.0	
11	7th March 2009	Timingondok	F	28	7.0	
12	7th March 2009	Timingondok	F	8	7.4	
13	7th March 2009	Timingondok	F	3	6.2	
14	7th March 2009	Timingondok	F	2	6.6	
15	19th November 2012-hypotension*	Tarakbits	M	45	2.7	12900
16	19th November 2012	Tarakbits	M	11	3.4	23000
17	19th November 2012	Tarakbits	M	9	2.9	44600
18	19th November 2012	Tarakbits	M	7	7.9	10000
19	19th November 2012	Tarakbits	F	40	4.2	20800
20	1st March 2014	T'minserep	M	25	5.8	9550
21	1st March 2014 -dead day 5 in hospital on sedation	T'minserep	M	20	6.2	11750
22	1st March 2014	T'minserep	M	20	6.6	8140
23	Dead -day 3 at village aid post	Suki	M	14	-	-
24	Dead in 4 hours of sago meal	Tarakbits	M	2	-	-

7.4.4 Demographics of SHD cases

Demographic details of the 24 hospitalized cases included age, gender, and pre-blood transfusion haemoglobin levels tabulated in Table 7.7. Deaths of 2 males, aged 2 and 14 years occurred in two different villages in two different outbreaks, these are not included in the analysis. Differences in the mean age and pre- blood transfusion haemoglobin were analysed to assess any gender differences. Hypothesis testing and statistics are as described below.

Determining gender differences in age and pre-transfusion haemoglobin:

Hypothesis testing

1 H_O Male Age = Female Age

H_A Male Age ≠ Female Age

2.H_O Male Hb=Female Hb

H_A Male Hb≠ Female Hb

Data for t-test analysis of age and haemoglobin by gender.

T-Test: Two-Sample Assuming Unequal Variances for age

Table 7.7 Data for t-test analysis of mean haemoglobin by gender

No.	Gender	Age in years	Hb gm/L	No	Gender	Age in years	Hb gm/L
1	M	2.5	111	1	F	42	50
2	M	45	61	2	F	16	89
3	M	36	70	3	F	9	58
4	M	45	27	4	F	7	59
5	M	11	34	5	F	5	36
6	M	9	29	6	F	26	46
7	M	7	79	7	F	23	78
8	M	25	58	8	F	28	70
9	M	20	62	9	F	8	74
10	M	20	66	10	F	3	6.2
11	M	14	-	11	F	2	6.6
12	M	2	-	12	F	40	42
	Mean	19.71	59.7			17.42	51.23

Statistical analysis

A t-test was used to check for differences in the mean pre-transfusion haemoglobin levels between males and females for both equal and unequal variances. The t-test showed no

statistically significant difference in the mean pre-transfusion haemoglobin. Both male and female haemoglobin levels were equally and similarly affected. The critical value for t was 0.381, with a p-value of 0.353 for equal variance. For unequal variance, the critical value for t was 0.4520 and p-value was 0.226. There was no statistically significant difference in mean age between males and females and therefore the study failed to reject the null hypothesis of no difference. Despite it being a small sample, sago poisoning affected males and females with equal severity.

There was no statistically significant difference between the mean haemoglobin of males and females therefore the study failed to reject the null hypothesis. Women and men were affected with equal severity by SHD thereby demonstrating similar mean haemoglobin. This evidence is in contrary to the evidence of higher survival in women compared to men. Therefore, this indicates that women tolerate or withstand the effects of acute prolonged hypoxia differently compared to men.

7.4.5 Calculation of odds ratio given exposure status

Cell A contains the 24 cases and cell B contains unaffected males from the Suki outbreak in 2005. Cell C includes a case with a blood transfusion reaction and an asymptomatic case from Suki. Cell D contains the 12 controls from the 2009 Kiunga outbreak.

The analysis revealed the odds of exposure in those that had SHD was 144 times higher than in the unexposed with a confidence interval of 11.8-1753 and a p-value of 0.0001. The relative risk was estimated to be 6.7 times greater for the exposed population compared to the unexposed with a significant confidence interval of 1.9 to 24.

Analysis of odds ratio by use of two-by-two table

Data analysed	SHD cases	No SHD	Total
Ate implicated sago	24	1	25
Did not eat implicated sago	2	12	14
Total	26	13	39

Results of analysis

One- or two-tailed	Two-tailed
Statistically significant? (alpha<0.05)	Yes
Strength of association	
Relative Risk	6.720
95% confidence interval	1.857 to 24.31
Odds ratio	144.0
95% confidence interval	11.83 to 1753

Rejection of the null hypothesis

Based on the attributable risk of 100% identified by the difference in the illness attack rate between sago ingestion and SHD, the study rejected the null hypothesis of no association between mouldy sago consumption. The study therefore accepts that mouldy sago ingestion was statistically significantly associated with the onset of SHD.

Summary of clinical outcomes

Table 7.8 Duration of SHD and time of death

	No	Alive	Dead	Death in 24 hours	Death 3-4th day	Mean age	Mean Hb
Male	12	9	3	2	1	19.71	55.08
Female	12	11	1	0	1	17.4	51.23
Total	24	20	4	2	2		

Deaths occur at 2 different time intervals; early deaths usually occur <12 hours from the onset of illness and late deaths occur on the 3rd to 4th day as acute renal failure develops.

7.4.6 Prospective study-Odds of exposure in SHD cases

Odds of death by gender for this group showed no statistically significant difference in mortality as shown by graph pad analysis below.

Table 7.9 Data for calculating odds ratio

Data analyzed	Dead	Alive	Total
Male	3	9	12
Female	1	11	12
Total	4	20	24

This analysis shows an insignificant p value, with an odds ratio of 3.7 was a good approximate for the relative risk of 3. More importantly, the confidence interval for the odds ratio is not significant at 0.32–41.6 because the 95% confidence interval contains 1.

Table 7.10 Odd ratio for the odds SHD given exposure of consuming contaminated sago

One- or two-tailed	Two-tailed
Statistically significant? (alpha<0.05)	No
Strength of association	
Relative Risk	3.000
95% confidence interval	0.3610 to 24.93
Odds ratio	3.667
95% confidence interval	0.3231 to 41.62

7.4.7 Assessing dose-response in SHD

From the historical evidence, it appeared that the greater the quantity of sago consumed the greater the severity of SHD symptoms and signs, this often resulted in a fatality. The history supports an early or rapid onset of illness and therefore a shorter incubation period in those who develop severe disease. Additionally, even a single mouthful of implicated sago (chewing and spitting out) was associated with asymptomatic intravascular haemolysis resulting in anaemia where urine tested positive for haemoglobin in the 2005 SHD outbreak. Further support of dose-response was obtained from the Kiunga (Sauga Kona) outbreak which demonstrated mild to moderate disease in the case that consumed a quarter of 12-14cms sago pancake. The patient reported feeling ill 40 minutes later whilst waiting for an ambulance. She was ambulant and had the physical strength to piggyback the severely ill case, female adult 400 meters to the roadside to be transported by ambulance. The severely ill case ate three-quarters of the sago pancake and developed vomiting within 15-20 minutes became too weak to sit up and became drowsy rapidly. She was noted to pass dark red urine within 30 minutes of the onset of illness.

7.4.8 Mathematical modelling of relationship between haemoglobin and consumed sago pancake

The simple linear regression analysis equation: $\beta_0 + B_1X_1 + \varepsilon$ demonstrates the type of relationship between the two variables of haemoglobin in sago poisoning cases (dependent or response variable) and the quantity of contaminated sago pancake consumed (independent or predictor variable). Furthermore, the magnitude of the change in the relationship can be predicted between the two variables.

Figure 7.6 firstly reveals the negative relationship between the size of sago pancake consumed and the patients pre-blood transfusion haemoglobin (gm/L). As the quantity of sago consumed increases, the pre- blood transfusion haemoglobin decreases. Secondly, the magnitude of the negative relationship is shown by the coefficient of – 0.2698 so taking the exponent of this means taking the reciprocal 1/0.2698 which removes the negative sign and the coefficient becomes 3.7X. The final interpretation is that the haemoglobin decreases 3.7gm for each square centimetre of contaminated sago consumed. Almost all cases would consume more than one sago pancake, estimated as 14-16cms in size. The area of 4 quadrants in a 16cm sago pancake is estimated as 200.96 cms^2 by the formula $= \pi r^2$. Therefore, a quadrant is 50.24cms^2 and three quarters is 150.2cms^2. The calculated area and the observed pre- blood transfusion haemoglobin is shown in the scatter plot of these two variables as the haemoglobin response to the quantity of consumed contaminated sago pancake. This is predicted follow the equation $Y = \beta_o + \beta_1X_1 + \varepsilon$ therefore the pre- blood transfusion haemoglobin would be reduced by 3.7 gm/L for each increase in one square centimetre of contaminated sago consumed

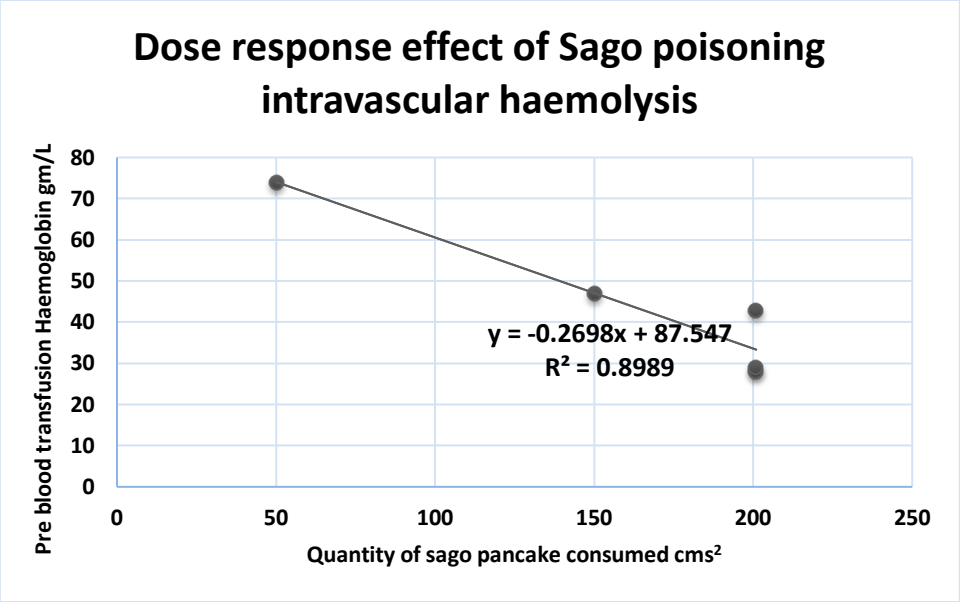

Figure 34 Demonstration of a negative dose-response relationship

Figure 35 Implicated mouldy sago responsible for 2014 SHD outbreak

7.4.9 Characteristics of implicated sago

The quality of sago from 2012 and 2014 was described as fit for consumption. Obvious specks of dark discolorations can be visualized from the photograph taken by the principal investigator of the implicated sago during the 2014 sago poisoning outbreak. The normal colour of sago usually is slightly grey. Sago haemolytic disease occurred in those that consumed the upper layer of sago that was recently harvested or old stale sago from the bottom storage layer that was 4 months older or more. The sago starch productions differed between outbreaks, from the villages located higher upstream of the Fly River, highland area of the Ningerum area and also along the Fly River as well as in land lakes of Suki and Mipan villages. The species of sago palm had not been investigated.

7.4.10 Duration of storage of implicated sago

The duration of storage of implicated sago from the 2012 and 2014 outbreaks was 2-3 weeks compared to the 4 months or more seen in the two 2009 outbreaks. Cases usually used the remaining sago for their meal and therefore rarely had any remaining to bring to the hospital.

7.4.11 Incidence of SHD

The population was recorded to be 62,850 in the North Fly District during the 2011 national census. There were 16 new cases from 4 SHD outbreaks confined to the North Fly District during the period of the study. Deaths occurred in 3 cases and acute renal failure occurred in 4 cases. The incidence for SHD was 26 cases per 100,000. The mortality was 5 cases per 100,000 and the incidence of acute renal failure was 6 cases per 100,000.

The case fatality rate was 18.75% with an incidence of 8.87 per 100, 000 population. Two adults died in hospital whilst a 2-year-old child died within 6 hours of eating an implicated meal. Arrival in the hospital was prompt for one outbreak which presented within one hour of illness at hospital. Another 2 outbreaks presented within 24 hours and the third outbreak presented on the fourth day. A helicopter was used to retrieve cases from Tarakbits, a canoe was used by the family from Timingondok, and a hospital ambulance was used to retrieve cases from informal settlements located in Kiunga. Refer to the outbreak map in Figure 7.3 for exact locations.

More deaths occurred within the hospital; one was from a lack of blood transfusion. The other fatality had severe metabolic acidosis and acute renal failure, and they were given sedation. The death of a 2-year-old male child occurred within 6 hours of a sago meal in the village. Five members of the family were transferred from the village to the hospital by helicopter the next day.

Table 7.11 Demographic details of prospective SHD cases

16 cases	Sex	No	Mean age	Standard deviation
9 Adult	Male	5	31	12.94
	Female	4	30	6.78
7 Children	Male	5	6.2	4.09
	Female	2	5.5	3.54

Table 7.12 Pre blood transfusion haemoglobin of 15 SHD cases

15 cases	Sex	No	Mean haemoglobin gm/L	Standard deviation
9 Adult	Male	5	56.6	17.14
	Female	4	59.25	17.46
6 Children	Male	4	52	24.34
	Female	2	68	8.49

The mean age between male and female adults and children differed slightly, with female mean age being lower than male mean age. There were 15 cases excluding a 2-year-old male that died in the village. The mean haemoglobin of females was slightly higher than males.

Intensive investigation and management were conducted on the 3 males affected during the 2014 SHD outbreak. Biochemistry and haematology analyses were conducted on blood and urine samples at James Cook University laboratory as described in chapter 7 on the pathophysiology of SHD.

7.5 Discussion

New epidemiological evidence on the of symptom onset identified the incubation period as at least 15-20 minutes. It also demonstrated the inherent dose-response effect on symptoms, signs, and pathophysiological changes. Additionally, it correctly identified mouldy sago pancake as the implicated food item in the 2009 SHD outbreak in Sauga Kona (Kiunga), which was unknown until that point. The attributable risk was 100%, which mean all people that were exposed became SHD cases and those that did not sago did not get sick. This demonstrated the true relationship between the mouldy sago and SHD. The odds ratio of 144 (11.8-1753) and its confidence interval and p-value of 0.00001 were all significant. The collective strength of the evidence strongly supports the SHD aetiology as being an intoxication illness. This is more appropriately called sago toxicosis or better still, following the locals it can be called sago poisoning. The locals correctly refer to the illness as sago poisoning and this has been used by local practitioners as a diagnosis even when they were not familiar with the name SHD, as described by early researchers. The symptoms of acute hypoxia followed such a short incubation period of 10-15 minutes and this suggested a rapid absorption of a suspected preformed toxin. It is thought this acts on the erythrocytes to disrupt the membrane to cause red cell haemolysis. The rapidity of clinical and physiological effects suggested that absorption may have also occurred through the buccal mucosa whilst chewing the sago. All cases were reported to be well and functioning normally in their daily activities before consuming the implicated sago meal. No cases reported a diarrhoeal-type illness suggestive of enteritis.

There were only two ways that cases with SHD presented. This was either as a sudden death or as a severely ill case who would readily die without receiving an urgent blood transfusion. Mild cases were those that consumed a smaller portion size of sago that varied from a single mouthful to quarter of a sago pancake. The restriction in intake was either self-imposed due to bitter taste or because there was only limited availability. The usual presentation followed a single exposure to a normal portion-size meal of sago, and this led to severe illness each time. It can be deduced that children and those that have comorbidities are likely to be severely affected and have fatal outcomes given the severity of the illness. Deaths in children may be the best indicator of SHD as a smaller portion size produces severe illness with a fatal outcome. Due to food scarcity, adults may consume smaller portion sizes, but this may prove fatal to children.

Males and females were both severely affected by SHD, but more males had fatal outcomes compared to females. Despite the lack of gender difference in age and pre-blood transfusion haemoglobin between males and females, the high male fatalities that occurred as early deaths strongly suggested that gender differences exist. This indicated that males were less tolerant of profound hypoxia, death occurred within 4-6 hours for male children and up to 12 hours for younger male adults.

The unknown preformed toxin(s) contained in the sago pancake was highly potent and that was illustrated in the 2005 outbreak. Even a small quantity or negligible amount of sago being chewed and spit out resulted in haemoglobinuria and an anaemia with haemoglobin of 87gm/L despite being asymptomatic of SHD symptoms and signs. Furthermore, the older sibling who cleared out the mouthful of sago from their 2.5-year-old younger brother using her finger also tested positive for haemoglobinuria, but his haemoglobin remained normal at 112gm/L. This provided the first valid evidence that not only supported the dose-response effect but also exhibited the high potency of the preformed toxin(s) as its aetiology. Moreover, the absence of secondary cases among those that assisted affected families also suggests SHD as a toxicosis which is therefore confined to those who were exposed by consuming the implicated meal of sago that contained preformed toxin(s).

Similarities can be drawn between the clinical effects of SHD and that of the cereulide toxin, this is associated with the emetic type of Bacillus cereus food poisoning reportedly associated with reheated rice and pasta consumption. Symptoms and signs were similar in that vomiting was the first symptom reported in disease, the incubation was similar at 10-30 minutes, neurological symptoms of acute encephalopathy was observed in both diseases, and deaths were reported within 6 hours of illness. However, that was where the similarities ended. The difference was at the site of action, cereulide toxins were confirmed to act on the mitochondria and its dominant feature was acute hepatic failure. In contrast, SHD acts on the red cell membranes causing intense haemolysis that severely depleted oxygen transport causing profound hypoxic clinical effects (Dierick et al. 2005; Shiota et al. 2010; Naranjo et al. 2011). Bacillus cereus is known to cause intravascular haemolysis but requires a focus on acute infections in immune-suppressed individuals where it mounts severe infection. This is quite unlike the SHD cases who have been well until their exposure to the implicated sago starch meal, they also do not show any signs of local infection (Ginsburg et al. 2003).

Remarkably, blood films of SHD cases failed to show oxidative damage in 2005 and 2014 outbreaks. This therefore points to the red cell membrane as the site of action where the toxins induce disruption, allowing the cells to rupture as opposed to oxidative damage which is discussed further in chapter 8. The natural progression of illness in cases to developing acute renal failure as a terminal event confirms the danger of intense haemoglobinuria that can predispose cases to acute renal failure, usually on the third day of illness, often compounded by dehydration. A post-mortem examination on the case did not reveal blood in the abdomen. Tissues sent to Port Moresby General Hospital Pathology service were stated to be unsuitable for histological examination due to the state of autolysis. The post-mortem was requested by relatives of the deceased woman as they were suspicious of internal bleeding that could have contributed to the death based on domestic violence.

Whilst this case provided maximum information adding immense value to existing knowledge of SHD, unfortunately, this severely affected SHD case died on day 3 of illness in hospital from severe anaemia and acute renal failure. This poor health outcome highlights continual challenges confronting patients that require urgent treatment in a rural hospital setting.

A personal prevention strategy involves paying attention to the following characteristics of the sago used in preparing sago pancakes. When presented with a meal of sago, one can use the senses to decide to consume or not to consume the meal. First, visually inspect the sago starch for discolorations. Second, use the sense of smell to detect bad odour emitted from sago. Finally, on taking a bite of the sago ascertain if it tasted bitter or different from the usual taste. The sago should be discarded if any one or all these features are detected to prevent SHD. During the 2005 outbreak, 2 out of 8 members of the family were spared because they discarded their bitter-tasting sago whereas the other 6 members of the family consumed the sago pancake and were severely affected, with one fatality.

Food scarcities among these rural communities were likely to prevent these communities from implementing the prevention messages of choosing hunger and discarding their only food. This is a difficult decision, and these communities are likely to take the risk of consuming mouldy sago. During communications on SHD awareness, communities admitted to consuming mouldy sago and reported that they were not adversely affected. Sometimes, the old sago is mixed with tapioca before preparing meals for families. The tapioca is fermented to flour by submerging it in the swamp over several days.

Based on the outbreak investigations, communities needed to be aware of outbreaks during the rainy season. Special care needed to be taken by families to ensure anaerobic storage of newly harvested sago starch to prevent colonization by bacteria and fungi. It was evident that both mouldy and stale sago was responsible for SHD outbreaks.

Clinicians and health workers needed to be aware and vigilant of SHD outbreaks during rainy season months, blood transfusion remains the best treatment to restore oxygen delivery and ensure that cases were not dehydrated. Advising families and communities to store sago safely in enclosed compact sago bundles or plastic prevents exposure of sago to the open air and prevents contamination by microbes.

7.6 Conclusion

Close observations of epidemiological details revealed several outbreaks were preceded by a meal of sago confirmed as the implicated food item as sago. Questions on portion size of the sago meals differed in two outbreaks. Two were not affected after discarded their first mouth ful of sago due to bitterness. Another outbreak affected 2 women who ate the sago, a quarter and 3 quarters of 16cms single pancake. One had mild symptomatic disease and the one that ate 3 quarters had a fatal outcome. All those that became severely affected had more than one sago pancake, considered as their normal portion sizes. This data was used to conduct a regression analysis between the size of sago as independent variable and pre blood transfusion. It also illustrated the dose-response effect as well as demonstrating that lethality of the hypothesized preformed toxin where there was no safety margin of eating contaminated sago. This indicated that a non-observable exposure level cannot be established making the hypothesized preformed toxin as the most lethal. Mathematical modelling showed the magnitude of change, as haemoglobin is predicted to reduce by 3.7 gm/L for each centimetre of contaminated sago pancake consumed. This is a near perfect description of the sudden fulminant onset of intravascular haemolysis that dramatically eliminates oxygen transport, the only way to provide oxygen to cells and remove carbon dioxide from cell metabolism. A normal portion size meal of sago produced severe life-threatening haemolysis and lead to a 35% fatality rate as reported in this study. The only treatment is a blood transfusion available at the hospital. Early interventions of emesis, or charcoal, are unlikely to help the patient as the toxin is likely to be absorbed rapidly by the mucous membranes directly into the blood stream, producing a fast and intense intravascular haemolysis.

This study declares that the first evidence of a 10–15-minute incubation period identified sago as the implicated food item responsible for producing SHD. It also demonstrated the dose response effect and the first confirmation of passage of red urine as haemoglobinuria which was evident from the 2005 Suki and 2009 Sauga outbreaks. The acute anaemic hypoxic effects appear suddenly at the end of a meal or whilst eating. The symptoms were reversed by blood transfusion after which patients were able to walk out of hospitals, they were discharged without any neurological deficits. Iron and folic acid tablets were given to patients to continue taking at home to replace the iron lost from the massive haemoglobinuria. Folic acid was given to aid the increased haemopoietic activities by the bone marrow in order to produce more erythrocytes.

8 Chapter 8 Pathophysiology of sago induced intravascular haemolysis

8.1 Introduction

There has not been a full-scale investigation into SHD outbreaks since the two-case series reports by Taufa and Donovan in 1974 and 1976, respectively. Taufa, working for the government, encountered these cases from the Maprik area of East Sepik while Donovan was working for Pioneer Missionary based at Balimo hospital recognized similar cases from Lake Murray and Suki areas of Western Provinces (Taufa 1974; Donovan et al. 1976). Balimo hospital later became part of Evangelical Church of Papua New Guinea (ECPNG) health services. This prospective study provided the ideal opportunity to reveal the pathophysiological changes in cases during the 2012 and 2014 outbreaks. The clinical samples were laboratory tested for full blood counts, urea, creatinine, electrolytes, bilirubin, albumin, and liver enzymes. In addition, the anion gap was calculated for evidence of the acid-base state.

A total of 5 SHD outbreaks occurred over the 5 years from 2009 to 2014. The two outbreaks in 2009 occurred too early in the study and yet provided important epidemiological evidence (as discussed in chapter 7) which revealed the spatial distribution of prospective cases shown in the North Fly District. The Kautru outbreak in the Suki region of South Fly District was admitted to Balimo hospital. The principal investigator interviewed the patient who recovered with a blood transfusion. The medical records could not be reviewed due to the need to fly to Balimo.

The laboratory results of haematology, biochemistry of clinical samples, and urine analysis from 2014 are presented and discussed with the inclusion of a case from the 2012 outbreak that developed hypotension and acute renal failure. Haematology and the biochemistry of blood and urine from the 2014 clinical samples was analysed at the James Cook University laboratory and compared to results obtained from the point of care hospital with limited biochemistry and haematology results.

Bedside clinical parameters of oxygen saturation were measured by a pulse oximetry device on a case from the 2012 SHD outbreak and illustrated with other recordings of the vital signs including blood pressure, respiratory rate, and pulse rate. Haematology results of SHD case

anaemia was compared to the population's anaemia results obtained during the community health assessment as described in chapter 5.

8.2 Data analysis

Descriptive statistics were used to identify measures of central tendency. The odds ratio was calculated for proportional data. T-tests were used to test for differences in means of clinical outcomes. Multiple regression analysis was used to predict SHD given age, gender, and pre-transfusion haemoglobin of the 3 prospective cases with 15 adults as control selected from the highland population who had no access to health care, like the 3 cases.

8.3 Results

8.3.1 Demographics of cases

Table 8.1 Date of outbreak and mortality of SHD by village

Date of outbreak	Villages	Number affected	Number dead
17th March 2009	Timingondok	5	0
9th April 2009	Sauga Kona	2	1
18th November 2012	Tarakbits	6	1
1st March 2014	T'minserep	3	1
Total		16	3

More deaths occurred in the hospitalized cases, one from lack of blood transfusion and the other had severe metabolic acidosis and acute renal failure and was given sedation. Case arrival at the hospital was within an hour or up to 4 days of from the onset of the illness. The death of a 2-year-old male child occurred in the village within 6 hours of consuming a sago meal. Five members of the family were transferred from the village to Kiunga hospital by helicopter within 16 hours from the onset of illness. Three men with SHD from T'minserap were transported by ambulance from Sare Kona to Kiunga hospital on the 4th day of illness despite living within a 20-minute walk to Kiunga Hospital.

Table 8.2 Demographic details of prospective cases of SHD

16 cases	Sex	No	Mean age	Standard deviation
9 Adult	Male	5	31	12.94
	Female	4	30	6.78
7 Children	Male	5	6.2	4.09
	Female	2	5.5	3.54

Mean age between male and female adults and children differed slightly with female age being lower than male age.

8.3.2 Haematology and Biochemistry of cases

Table 8.3 Pre blood transfusion mean haemoglobin of 15 cases with SHD

15 cases	Sex	No	Mean haemoglobin gm/L	Standard deviation
9 Adult	Male	5	56.6	17.14
	Female	4	59.25	17.46
6 Children	Male	4	52	24.34
	Female	2	68	8.49

The normal male haemoglobin of 144-166gm/L and 122-147 gm/L were normal range for developed countries (Gomella & Haist 2004). There were 15 cases excluding the 2-year-old male that died in Tarakbits village. The mean haemoglobin of females was slightly higher than males.

Biochemistry and haematology analyses of blood and urine clinical samples was undertaken at James Cook University laboratory, they were reviewed considering the management of 3 males affected during the 2014 outbreak.

The presence of intravascular haemolysis was confirmed by the elevated lactate dehydrogenase levels and presence of haemoglobin in the urine with a normal bilirubin level. Assessment of haptoglobin, haemosiderin and reticulocyte response had not been undertaken. Haptoglobin levels were markedly reduced in 2005 SHD cases as reported in Chapter 6.

The mean age of cases was 21.7 years with a standard deviation of 2.9. Mean haemoglobin was 62gm/L with a standard deviation of 4 and the mean lactic dehydrogenase level was 2861.5U/L with a standard deviation of 953.9. Levels of serum bilirubin remained normal.

Table 8.4 Biochemistry evidence of intravascular haemolysis

2014 outbreak T'minserap	**Haemoglobin gm/L**	**Lactate dehydrogenase u/L**	**Total bilirubin mmol/L**	**Unconjugated bilirubin mmol/L**	**Conjugate bilirubin mmol/L**
Normal range	14.4-16.6	<230	3.4-17.1	<3.4	<3.4
Male 25 years	58	2872.13	0.07101	0.0587	0.01233
Male 20 years	62	1902.24	0.04598	0.04099	0.00499
Male 20 years	66	3810	0.0756	0.065	0.0106

The normal values for biochemistry were obtained from the clinicians pocket reference book (Gomella & Haist 2004) in the absence of normal values for haematology and biochemistry values for Papua New Guineans.

Table 8.5 Elevated anion gap of SHD cases

Normal anion gap 8-16mE/L Formulae: [Sodium] - [Chlorine] + [Bicarbonate]

Cases	Sodium	Chlorine	Bicarbonate	Anion gap
SHD case 1	93.7	72.3	12.7	34.1
SHD case 2	129.3	96.1	13.8	47
SHD case 3	135	102.4	16.4	49

Anion gap was calculated for the 3 SHD cases and revealed the markedly elevated levels that indicated the presence of metabolic acidosis, the first evidence obtained by the study.

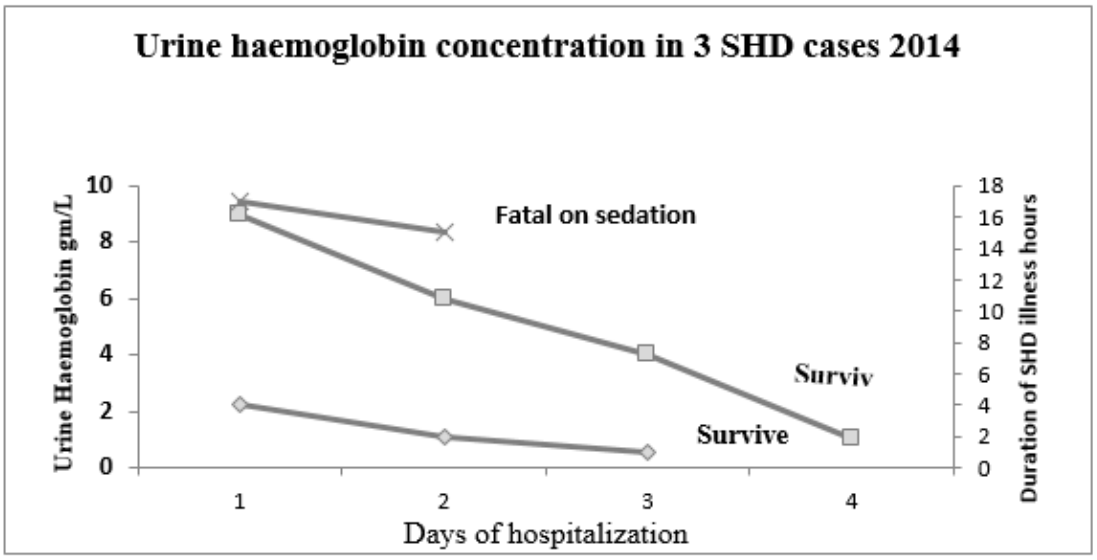

Figure 36 Levels of haemoglobin contained in urine samples of SHD cases. Depicted is the haemoglobin content of serial urine samples for two cases that declined over several days following treatment with a blood transfusion.

Figure 37 Serial collection of urine samples over 6 days in one SHD case. Intravascular haemolysis subsided within 6 days following treatment with a blood transfusion that replenished the red cell population.

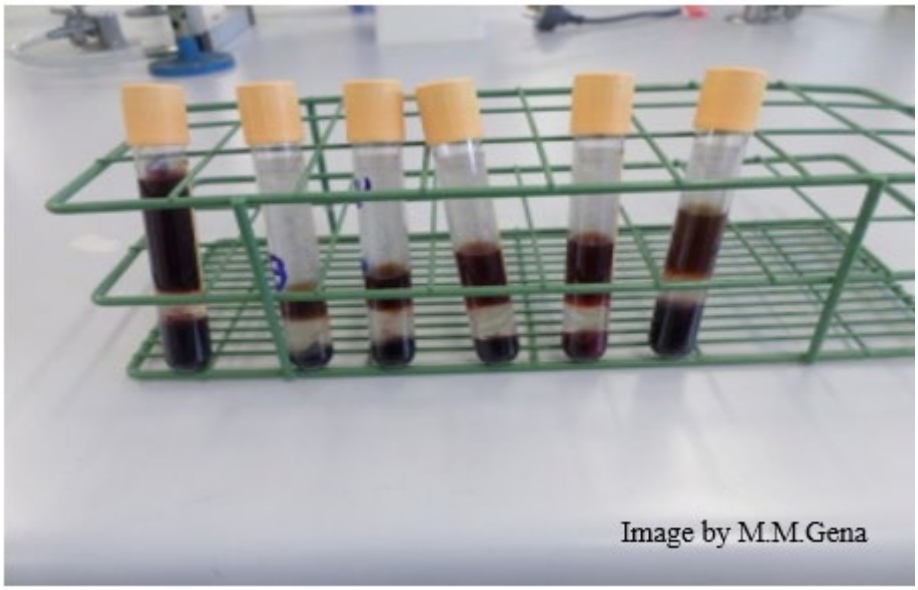

Figure 38 Blood samples of 3 cases of SHD in 2014

There yellowish discoloration in the blood samples of 3 prospective SHD cases captured in Figure 8.3 was due to the intravascular haemolysis. Jaundice was a clinical feature of sago haemolytic disease described by early reports, which also reported bilirubin in the urine (Taufa 1974; Donovan et al. 1976, 1977). Bilirubin was detected in only one case, in a postpartum mother that had mild hepatitis. This was out of 5 cases that had urobilinogen and

haemoglobinuria in the 2005 SHD outbreak. Skin discoloration was described as sallow and resembling a lemon-yellow skin complexion prominent in the palms of hands and soles of feet as well as light yellow discoloration of the sclera. These signs were present in SHD cases with copious urobilinogen and haemoglobin in the urine and commonly associated with haemolytic haemolysis of any aetiology (Packman 2001; Freedman 2015). The yellow or sallow appearance of the feet is easily recognizable on the wards and was used by the principal investigator to screen the patients on the ward for undiagnosed cases of SHD.

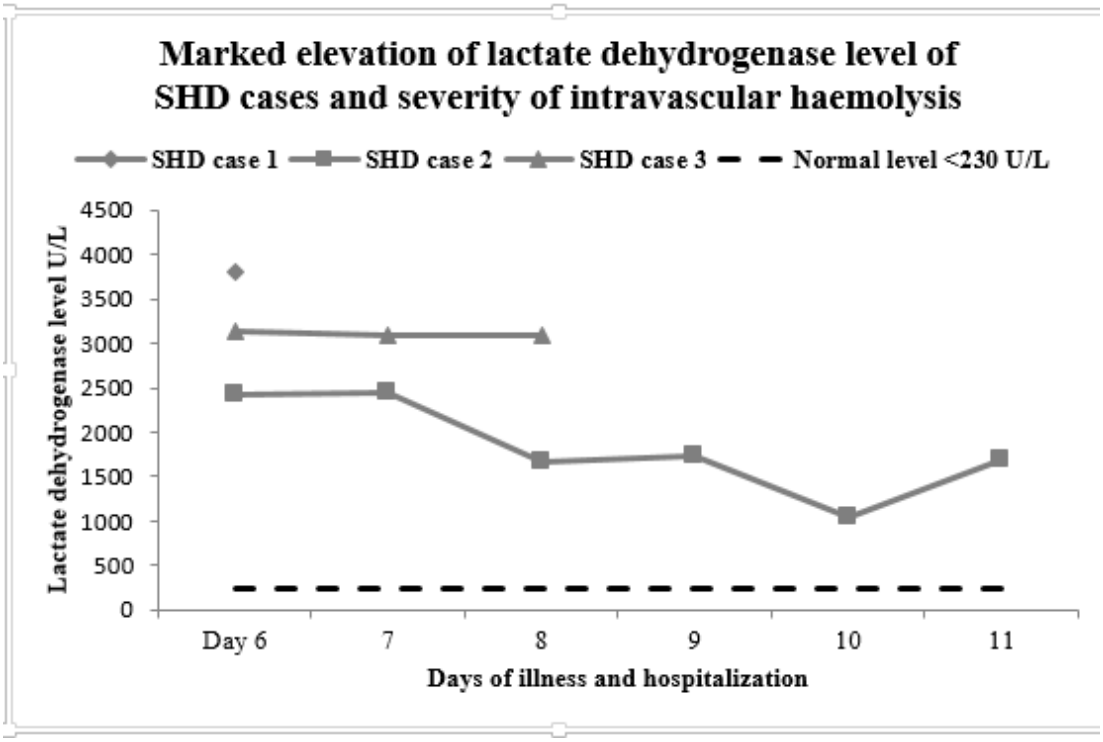

Figure 39 Elevated lactate dehydrogenase levels of 3 males with SHD

The marked elevated levels of lactate dehydrogenase correlate with severity and quantity of the red cell haemolysis in SHD cases, which reduced over time with cessation of intravascular haemolysis as evident in cases 2 and 3 in Figure 8.4 above.

8.3.3 Metabolic acidosis in SHD cases

Low serum bicarbonate levels were seen in all three cases of SHD and provided evidence of metabolic acidosis, with a mean anion gap of 45.1 instead of a normal value of 8-12. Anion

metabolic acidosis was present in all three SHD cases, including 2 with acute renal failure and one without.

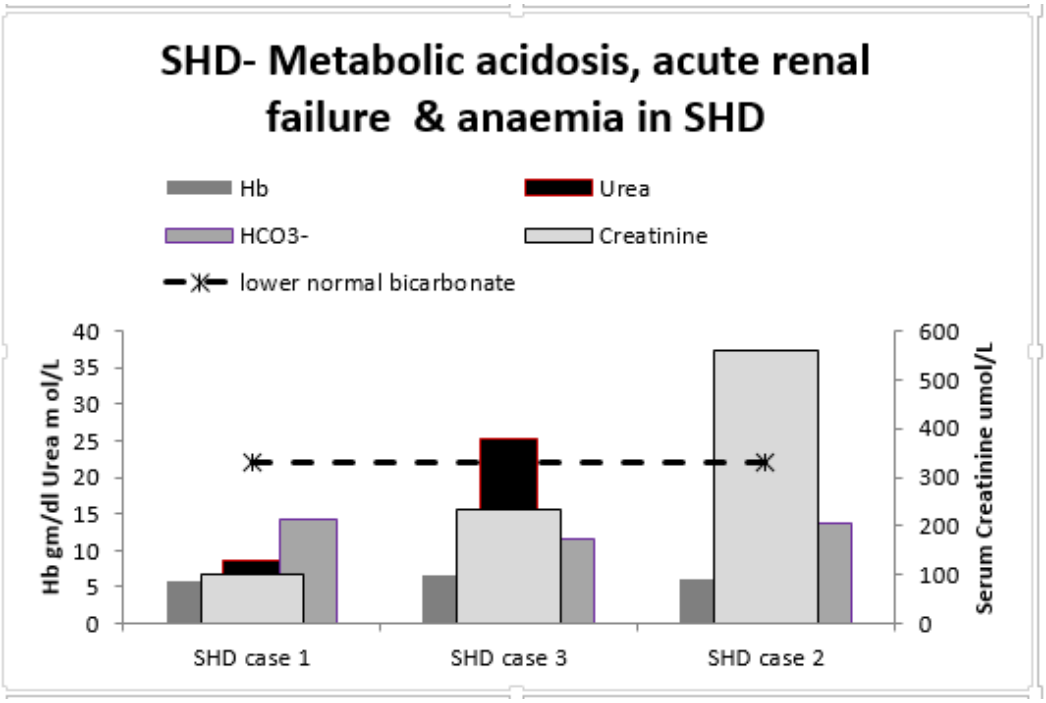

Figure 40 Physiological derangement in SHD

The first evidence of physiological disturbances associated with SHD is revealed in Figure 8.5 above. All three cases had acute anaemia with similar haemoglobin levels, two developed acute renal failure but all three had anion metabolic acidosis. Metabolic acidosis was revealed for the first time through serial tests that show low bicarbonate levels present in all 3 cases with SHD, including the one that did not have acute renal failure in

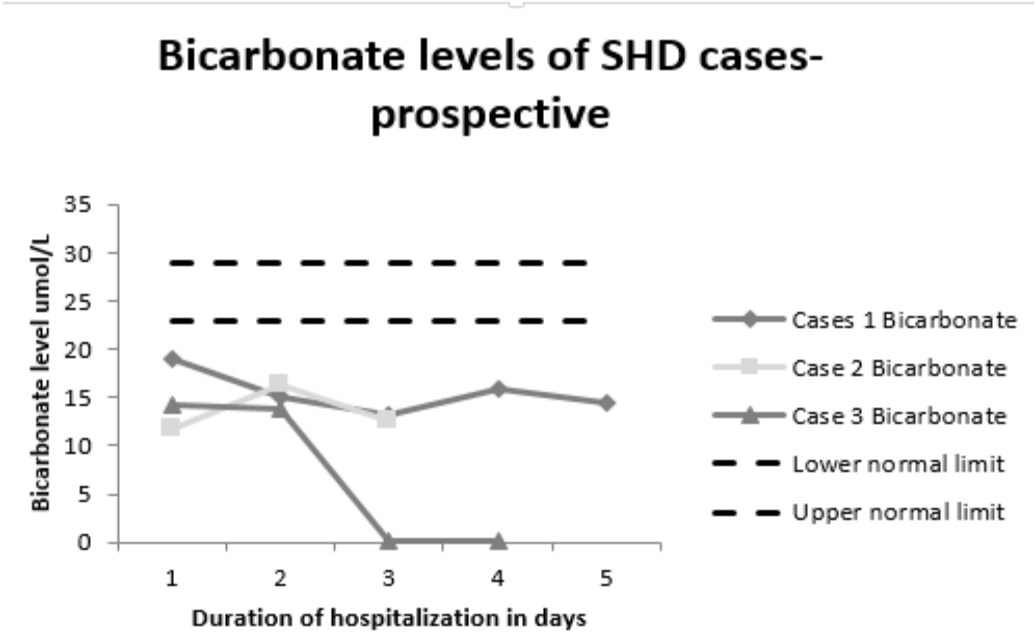

Figure 41 Serum bicarbonate levels of 3 SHD cases

Whilst all bicarbonate levels were low, case two had a fatal outcome upon administration of sedation as they developed a compensatory respiratory response to control the acidosis by blowing off the carbon dioxide. This compensatory respiratory response to systemic acidosis is known as Kussmaul's respiration.

8.3.4 Acute renal failure in SHD cases

Acute renal failure occurred in 26.7% (4 /15) of SHD cases. Three adult males were confirmed to have elevated creatinine and blood urea nitrogen. The fourth case of acute renal failure occurred in a 27-year-old female during the 2009 outbreak. She was hospitalized within one hour of illness and had a haemoglobin of 47gm/L but did not receive a blood transfusion or intravenous rehydration. On the third day, she developed anuria and had a fatal outcome despite her early arrival at the hospital. Only single haemoglobin was obtained, and the laboratory was unable to conduct biochemical tests.

8.3.4.1 Hypotension and acute renal failure

Described below was the iatrogenic induced hypotension in an SHD case from the 2012 SHD outbreak from Tarakbits where cases were medically retrieved by use of an OTML helicopter. The effect of hypotension occurred in a 45-year-old male in response to intravenous diuretics. These were administered with a blood transfusion and precipitously reduced the blood

pressure that then led to acute renal failure. The case was hospitalized within 24 hours of illness and had a haemoglobin of 27gm/l. A sudden drop in the blood pressure of a 45-year-old man with critically low haemoglobin of 27gm/L precipitated acute renal failure, with a concurrent drop in oxygen saturation which can also become a terminal event. This case demonstrates a combination of lethal conditions of acute anaemia, hyperkalaemia, hypotension, acute renal failure, and metabolic acidosis.

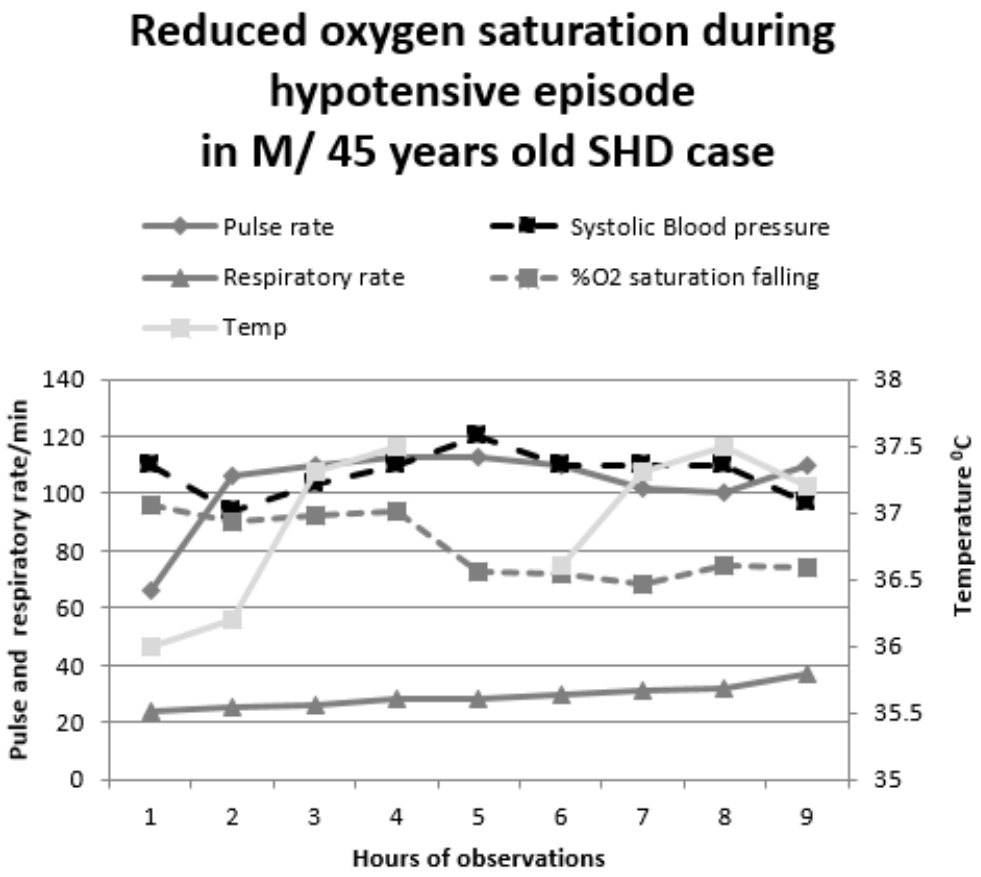

Figure 42 Changes in vital signs following hypotension

The skills of the attending emergency physician meant they were able to resuscitate the patient, resolve their low blood pressure, treat the hyperkalaemia and improve oxygen saturation of the patient allowing their body to resume homeostasis. The patient's condition gradually improved, and they were discharged without any motor or neurological deficit. However, they were found to have unilateral pleural effusion as a comorbidity and were

started on treatment for tuberculosis pleural effusion. The hypotension was induced in the patient by the administration of Lasix (a diuretic), which is a standard practice to all patients that received blood transfusion. In SHD, the patients are also dehydrated, understanding that will ensure that a diuretic is not used.

8.3.4.2 Hyperkalaemia and acute renal failure

One case from a 2012 outbreak had iatrogenic induced hypotension precipitating acute renal failure as well as the added feature of acute hyperkalaemia, a known cause of the lethal arrhythmia. The case was urgently treated with intravenous glucose and insulin that resolved the acute danger and facilitated the recovery of kidney function throughout hospitalization.

In the 2009 and 2012 outbreaks, results were scarce due to the lack of laboratory resources and the lack of tests undertaken by clinicians which were improved in the 2014 outbreak.

During the 2014 outbreak, evidence of acute renal failure was evident. Two out of the 3 cases developed elevated levels of blood urea nitrogen and serum creatinine in the 4 days of illness illustrated in the following figures.

8.3.4.3 The rising level of blood urea nitrogen

The sudden increase in blood urea nitrogen level after hospital admission indicated the cause as being iatrogenic. It is important to be aware of the acute anaemia and pre-existing dehydration in cases that develop sudden onset of unresponsiveness and unconsciousness not due to trauma. This guides the management plan for maintaining or improving vital signs to ensure physiological conditions are optimized to make sure cases recover. Poor hydration from lack of intake of oral fluids during acute illness can worsen with routine standard treatment such as the use of diuretics with blood transfusion. Clinical judgment on hydration status and the need for rehydration can be based on the blood urea nitrogen level in well-resourced rural hospital laboratories as evident in Figure 8.8 below.

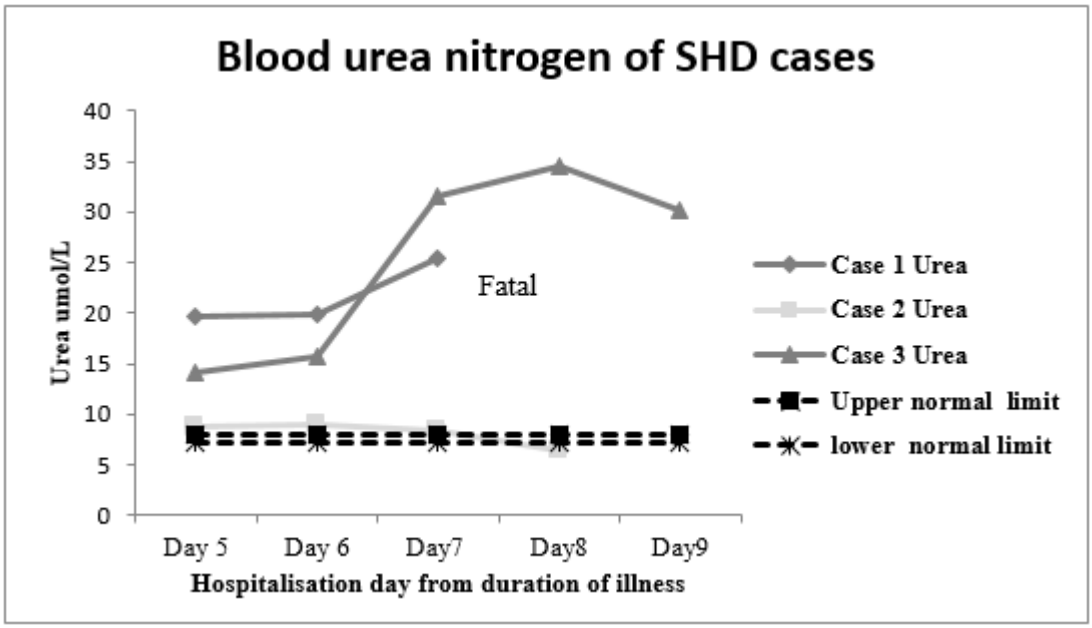

Figure 43 Daily blood urea nitrogen of 3 SHD cases

Figure 8.4 demonstrates the onset of acute renal failure in 2 out of 3 cases on the second day of hospitalization (which was day 6 of SHD illness) with one fatal outcome. In one case iatrogenic induced interference altered physiological respiratory compensatory mechanisms, whilst the other case blood urea nitrogen level remained normal.

8.3.4.4 The rising level of serum creatinine

Acute renal failure causes a concurrent increase in the blood urea nitrogen and serum creatinine levels as indicated in Figure 8.9 below. The cases were admitted to the hospital with normal levels of blood urea nitrogen and serum creatinine. Resuscitating SHD cases to maintain normal blood pressure remains central to recovery. Actions taken to the contrary such as giving diuretics with blood transfusion dramatically reduced blood pressure in a case and required administration of intravenous fluid to increase the blood pressure and stabilise the patient. Sago poisoning cases suffer from acute and prolonged hypoxia and maintaining a good blood pressure is critical to delivery of oxygen to tissues and survival of patient. Physiological derangements such as metabolic acidosis respond well to blood transfusion. As evident in this study, patients survived when given care by skilled clinicians in emergency medicine who were able to reverse the changes of primarily acute anaemic hypoxic effects.

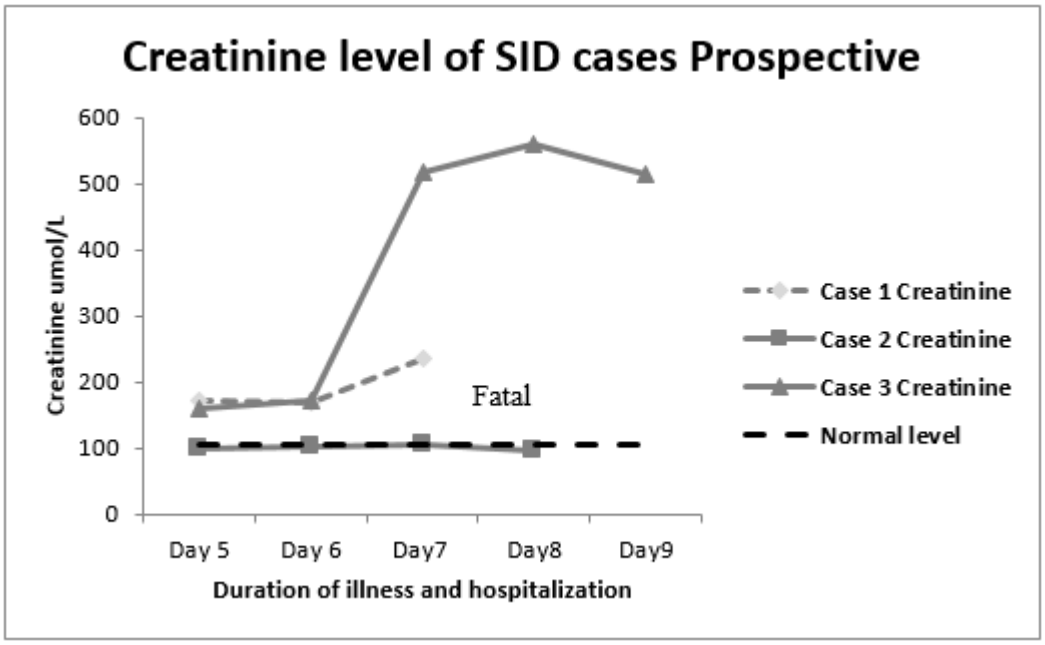

Figure 44 Daily creatinine level indicating acute renal failure

In the 2014 outbreak, 3 cases had repeated exposures as they ate sago pancakes that were cooked from the same bag of two-week-old sago for 3 days whilst being ill. They were transported to the hospital after the third day where two developed acute renal failure, one had severe metabolic acidosis that led to a fatal outcome upon sedation. The recovery of two cases and the fatal outcome in the other case is depicted in Figure 8.9.

8.3.5 Presence of comorbid conditions in cases from 2012 SHD outbreaks

Figure 8.10 below illustrates the sudden increase in blood urea nitrogen, in the case with the lowest haemoglobin being 27gm/L in a 45-year-old father upon receiving diuretic whose vital signs are demonstrated in Figure 8.7. This is compared to his 3 male children who were just as ill as their father but had haemoglobin levels that were higher. A unilateral pleural effusion was also diagnosed in the father after successful resuscitation efforts that reversed the hypotension, improved oxygen saturation, and reversed the acute hyperkalaemia. The potentially dangerous acute physiological derangement can be further potentiated by the presence of comorbidities, as evident in this case. The skills of the attending physician averted the death of this case.

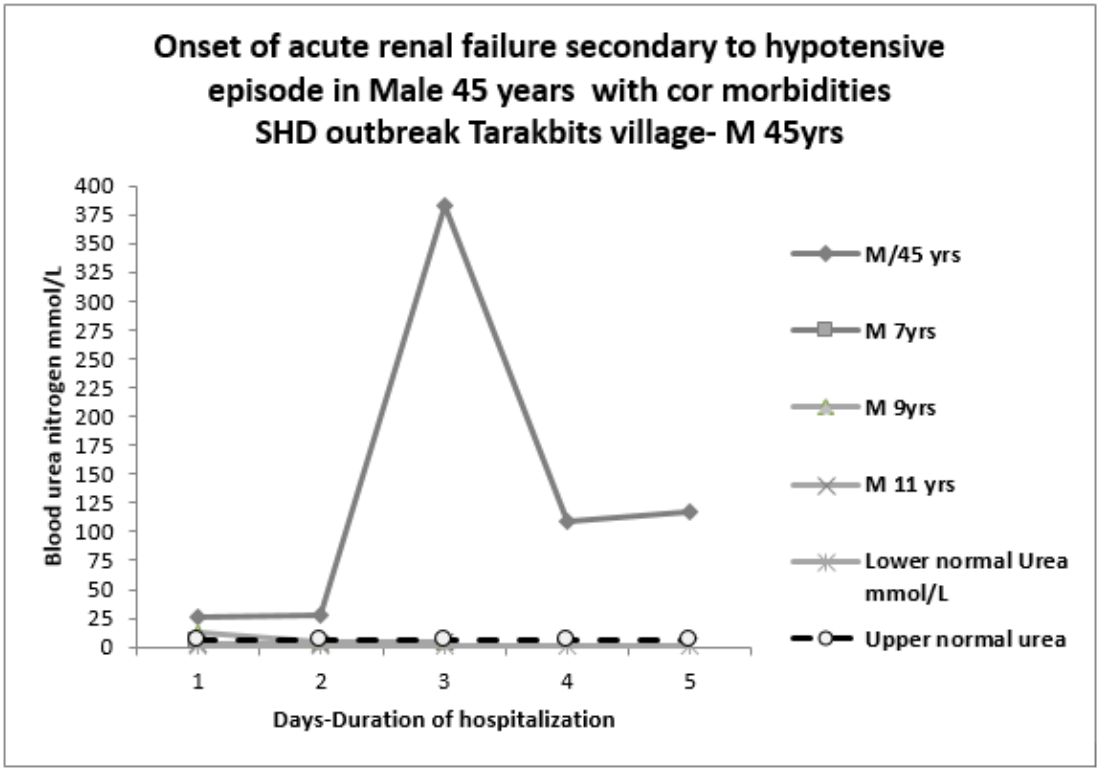

Figure 45 Hypotension induced acute renal failure in response

Figure 8.10 shows more evidence of the iatrogenic cause of hypotension causing acute renal failure. Caution should be exercised with the use of an intravenous diuretic as it will cause diuresis thereby induces hypotension that reduces the perfusion pressures at the cellular level that further aggravates effects of severe anaemia (such as in SHD). Hypotension cannot be tolerated well in cases with anaemia and or dehydration. This case demonstrates the danger of hypotension in cases with acute anaemic hypoxia in SHD therefore health workers will have to make a judgment call not to use diuretic during blood transfusion in sago poisoning cases. The patient was successfully resuscitated by doctors trained in emergency physician training program.

8.3.5.1 Comorbidity

A unilateral significant pleural effusion was diagnosed in the 45-year-old male case that developed acute renal failure secondary to iatrogenic acute hypotension. The aetiology of the pleural effusion was assumed to be tuberculosis based on the prevalence within the community and anti-tuberculosis regimen was instituted. Upon his discharge from the hospital, he continued his anti-tuberculosis treatment as an outpatient through the TB clinic for 6 months.

8.3.6 Nutritional status and immune response

8.3.6.1 Summary of total serum protein, albumin, and globulin

Table 8.6 Nutritional and immune response indicators in SHD cases

2014 outbreak	Albumin	Total Protein	Globulin	Albumin: Globulin
Units	umol/L	g/L	g/L	Ratio
Normal male	35-50	60-80	20-35	1.7-2.2
Male 25 years	35.38	60.65	25.27	1.4
Male 20 years	41.03	75.54	34.51	1.19
Male 20 years	40.17	74.37	34.2	1.17

For the first time, these levels of serum total protein and albumin were normal as were the globulin levels as demonstrated in the three young men with robust health who developed SHD. The albumin and globulin ratio was in the lower end of the normal range normalof 1.7 - 2.2 that clearly shows the lack of the immune system response to the sago poisoning effects on the body. To the best of my knowledge this is the first case report that had repeated exposure over three days, a pattern not reported in the past. They were able to withstand the effects that seemed to worsen over repeated exposure. This may explain the single exposure producing maximum effect in a single exposure. This was alluded to by the Greenhill study suggested poor nutrition level could potentiate effects of disease affecting the body. Poor nutrition was prevalent among the cases from 2005 and 2012 outbreaks, but their blood was not tested for total protein and albumin due to severe limitations in the capacity of laboratory resources in remote rural hospitals

8.3.6.2 Serum albumin level in 3 young men in robust health with SHD

Further evidence of low total protein and albumin levels is illustrated in Figure 8.11 and Figure 8.12 below in 3 men of robust health. Of these, 2 had levels below the normal upper limit and one was on or just above the lower limit of normal. They were acutely ill with SHD for 3 days prior to hospitalisation.

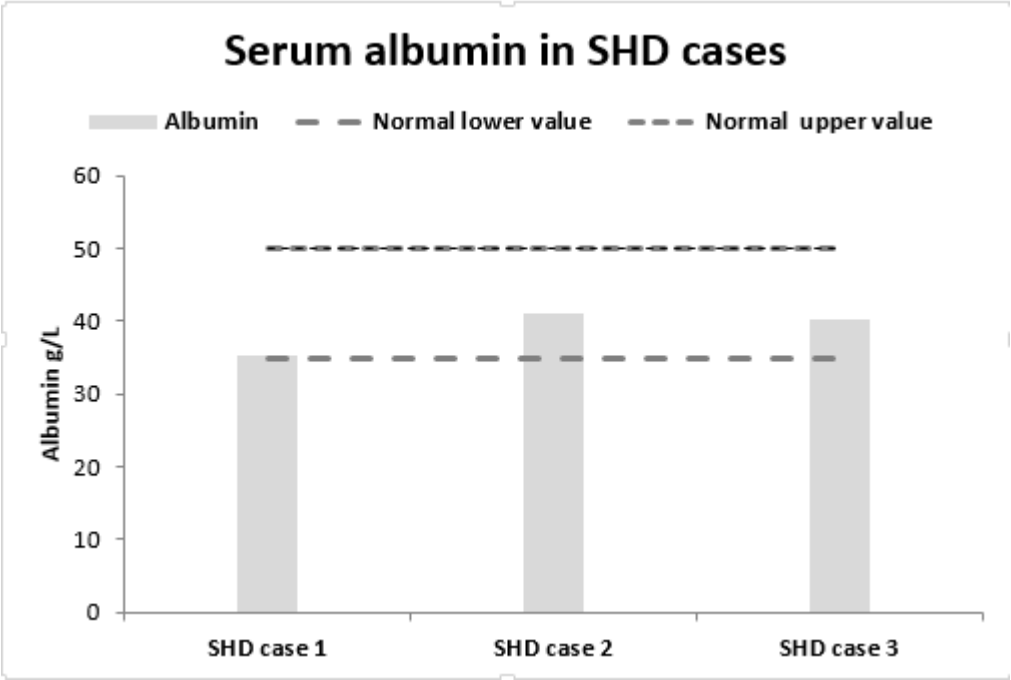

Figure 8.11 Serum albumin level in 3 SHD cases

8.3.6.3 Total serum protein in 3 men of robust health with SHD

The total protein levels of the 3 SHD cases was lower than the upper limit of normal and on or above the lower limit, similar to serum albumin levels. Their adequate level of total protein and serum albumin may have lessened the effects of SHD whilst they continued to ingest the implicated sago for three more days before presenting to the hospital. In most outbreaks a single meal of sago produced severe SHD, as seen in those with poor nutrition in the 2005 and 2012 outbreaks. These were managed by the principal investigator and emergency physician respectively.

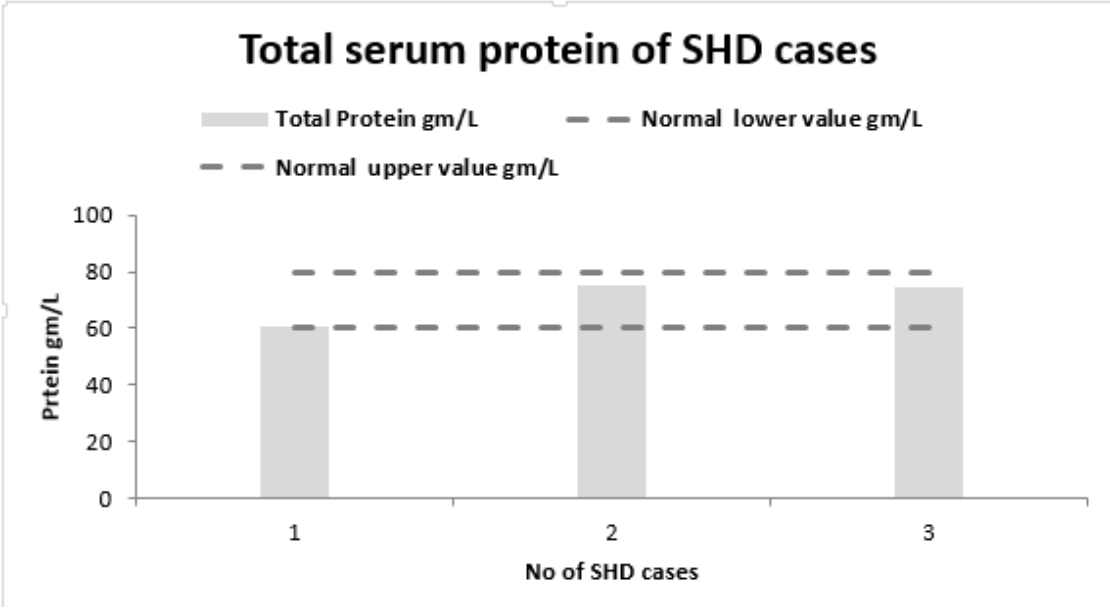

Figure 8.12 Total serum protein level of 3 SHD cases

Total serum protein levels for the 3 SHD cases were within the normal limits of 60-80gm/L except for one that had was at the lower limit of normal albumin. Albumin is an acute phase reactant in the immune response and therefore can be reduced in acute illness. However, in this instance albumin binds the preformed toxin(s) yet to be identified in implicated sago that responsible for causing SHD.

8.3.6.4 Globulin levels in 3 men in robust health with SHD

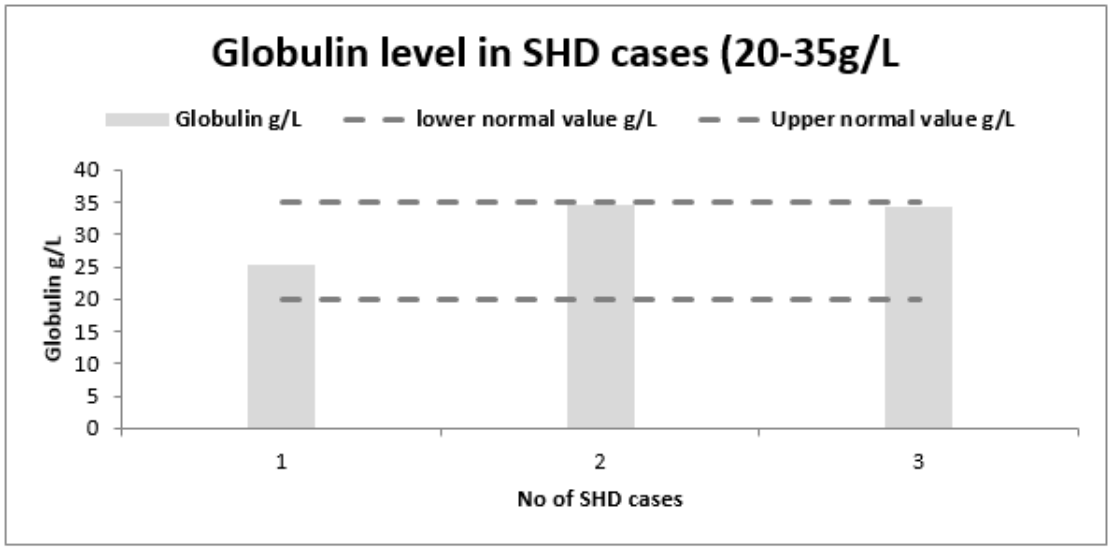

Figure 8.13 Serum globulin level of 3 SHD cases. The serum globulin levels of the 3 SHD cases were within the normal limits of 20-25 gm/l with a significantly lower than normal level for one case.

8.3.6.5 Albumin: globulin ratio

The albumin:globulin ratio was low at 1.17-1.4 compared to the normal level of 1.7-2.2 and it was hypothesised by the Greenhill study to be based on the poor nutritional status of rural communities which this study confirmed (Pearson et al 202; Russel et al 2020; Li et al; Groeger et al 2019; Novak et al 2008). Consistently low albumin and globulin need further investigation as this can occur in renal, hepatic, and bone marrow disorder. In SHD the prevalence of poor nutrition could explain the low albumin:globulin ratio (Forse & Shizgal 1980).

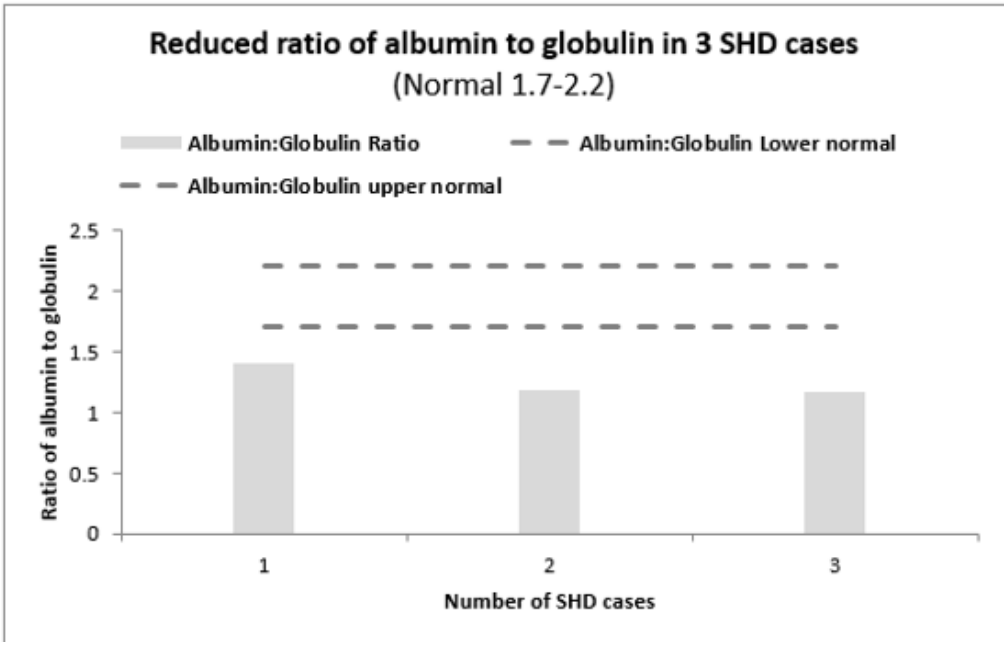

Figure 46 Reduced ratio of serum albumin to globulin ratio

An increase in albumin to globulin ratio can result from increased production of globulin by an immune reaction which seems to be absent in SHD cases which may indicate that intoxication illness is due to a natural preformed toxin(s) that was present in the implicated sago which was not destroyed by the cooking process. Effects of SHD were due more likely to

ingested preformed toxin(s) and not to a focus of infection in the SHD case hence no increase in globulin. It may be said that there was mucosal entry whilst chewing process was undertaken hence rapid absorption into the systemic circulation due to its incubation period of 8 -12 minutes (Pearson et al 202; Russel et al 2020;Li et al; Groeger et al 2019; Novak et al 2008).

8.3.7 Consciousness level and duration of illness

The duration of illness varied from one hour to several days before haemoglobin levels were checked for cases. The severity of anaemia differed by their exposure level. Figure 8.15 below show the different levels in cases from the same outbreaks. During the 2012 outbreak, members of the family were poorly nourished. They experienced the death of their young son < 2 years old. The father had the lowest haemoglobin of 27gm/L compared to his wife and 4 sons. Only one son with a haemoglobin of 80gm/l was conscious as he ate a smaller quantity of sago compared to the other severely affected members of the family. They were unconscious as they had eaten more of the sago pancakes.

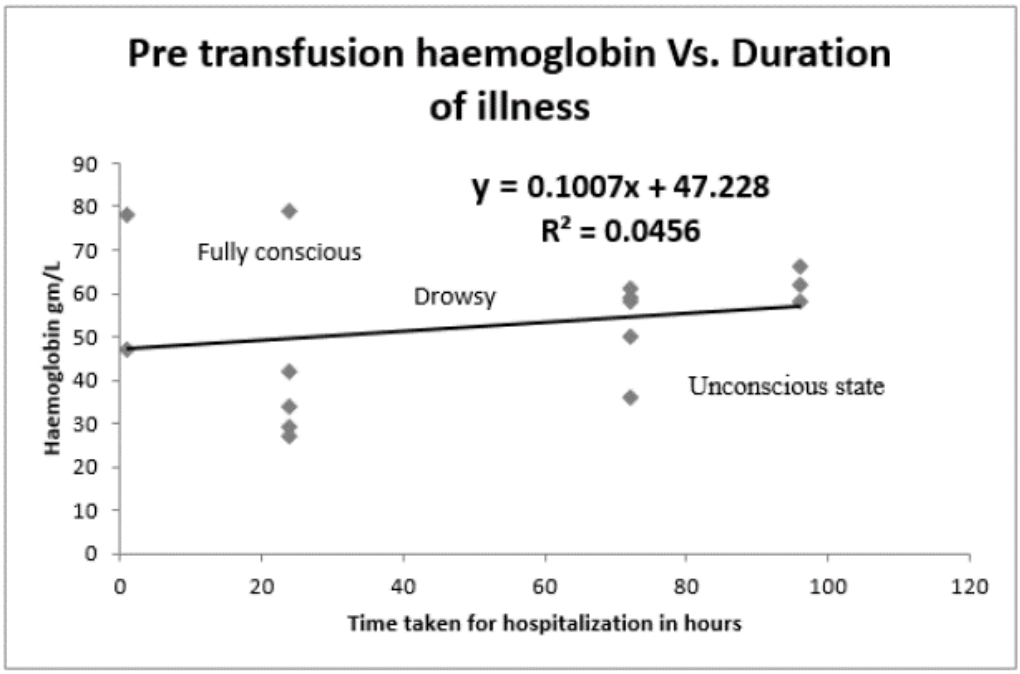

Figure 8.15 Pre transfusion haemoglobin and state of consciousness.

The demarcation in haemoglobin level needed to maintain consciousness and be ambulant was 78gm/l, as seen in a case that ate a quarter pancake of implicated sago. Patients become unconscious with haemoglobin of 47gm/l; this was seen in a case that ate three quarter of a

16cms pancake. These effects were demonstrated by the 2009 Kiunga outbreak. In Figure 8.15 above, those cases with haemoglobin < 78gm/L but above 47gm/L conscious level were described as drowsy and unaware of their surroundings. Unlike other medical emergencies where there may be obvious changes that capture the attention of the health workers or relatives, SHD can be missed as cases remain in a state of drowsiness and or unconsciousness that can be interpreted as sleeping, especially when single person is affected. Children with SHD are most likely to be missed and lead to sudden deaths as opposed to outbreaks affecting more members of a family.

8.3.8 Dose response effect of sago meal and clinical symptoms

There was a significant correlation between the quantity of sago pancake consumed and the severity of anaemia represented by haemoglobin levels in SHD cases. Cases described in Chapter 7 demonstrated the size of pancake and disease outcome.

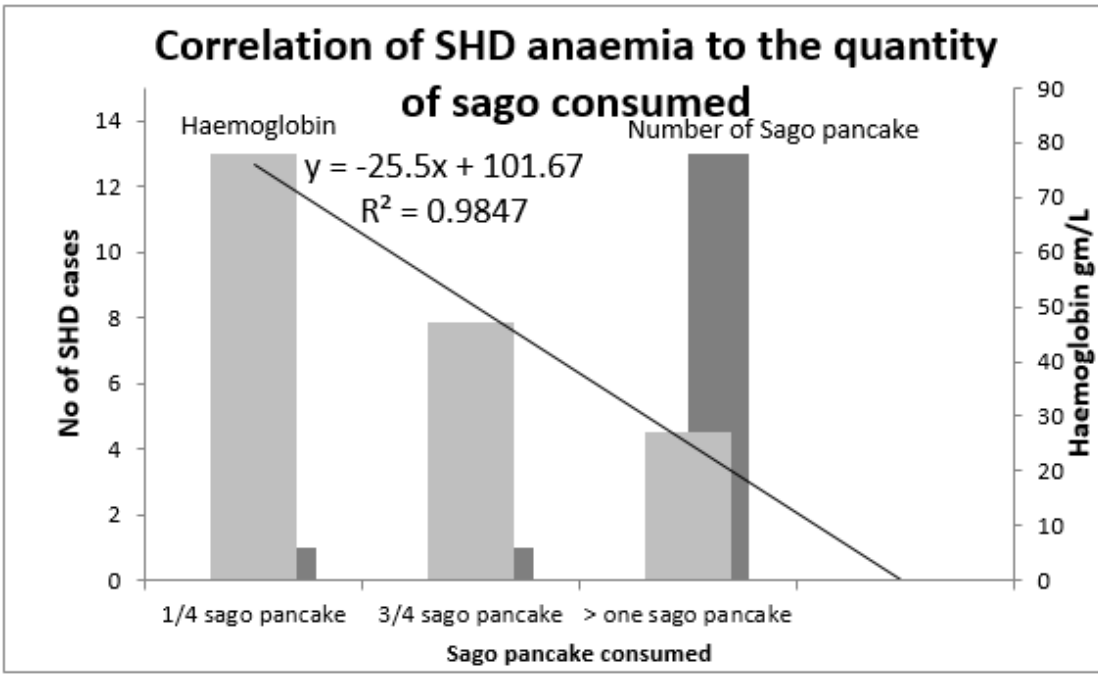

Figure 47 The more sago pancake consumed the severe the anaemia

The haemoglobin level highly correlated with the quantity of sago consumed, equates to a R^2 score of 0.98. The more sago pancakes eaten the lower the haemoglobin and vice versa. A dose response effect is based on these phenomena described by the observational study that

explained by the level of haemoglobin in these patients correlated to the quantity of sago they consumed. The expected haemoglobin in cases that were ambulating was likely to be ≥74gms/l compared haemoglobin of ≤50gms/l to be drowsy, unable to ambulant and unconscious. To be able to survive means eating less which is less likely. The ones who ate less were restricted by availability of sago and others selected not to eat anymore due to the extreme bitterness of the sago. The study was fortunate to obtain these evidence that demonstrates the lethality of SHD highly dependent on the number of sago pancakes consumed. A normal portion size of a meal would be several sago pancakes 14-16cms, therefore, will produce more serious life threating outbreaks with fatalities among rural communities who depend on sago as their staple food.

The study compared SHD anaemia to Non SHD anaemia as measured during the community health assessment of the SHD affected communities. The line graph below shows 2 different groups of anaemia showing a steep decline by the SHD induced anaemia compared to anaemia as measured in the adults in the communities. By statistically testing the two means using the ttest showed that they are statistically significantly different. The visual difference is demonstrated in Figure 8.17 below. The data used to generate Figure 8.17 is in the ttest results in the Appendix.

Table 8.7 below compares the haemoglobin and red cell counts of SHD cases to those identified with haemoglobin <100gm/L to have anaemia during the community health survey described in Chapter 4. The haemoglobin and the total red cell counts differ on inspection, SHD cases had lower haemoglobin and lower red cell counts compared to those found to have anaemia that were identified in adults during the health assessments of remote rural communities. A t-test analysis tested the two means of haemoglobin of the two groups found that mean haemoglobin level was statistically significantly different with a t value of 8.807 with a p value of 0.000000048. The t-test was conducted for both equal and unequal variances placed in the Appendix. The scatter plot in figure 8.17 graphically illustrate the differences between SHD cases and those with anaemia identified during the remote communities' health assessment.

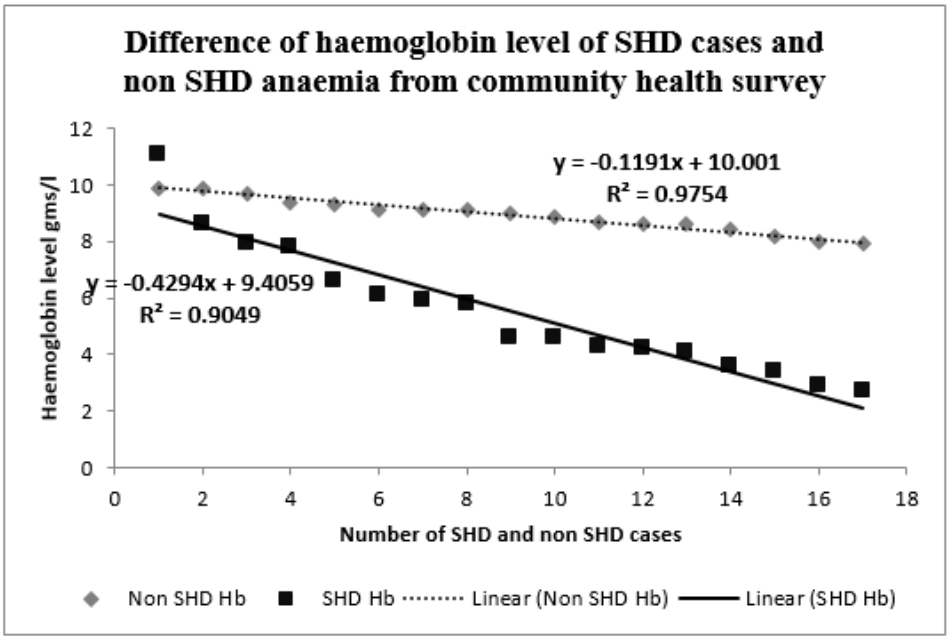

Figure 8.17 Difference in haemoglobin levels of SHD and non-SHD anaemia

Table 8.7 SHD and non-SHD haemoglobin and red cell count

No	Non-SHD Hb	Non-SHD red cell pop	No	SHD Hb	SHD red cell
1	99	4000002	1	79	
2	99	3000088	2	78	
3	97	3000084	3	66	2050000
4	94	4000084	4	61	1000016
5	93	4000032	5	59	1000008
6	91	4000084	6	58	100066
7	91	4000001	7	46	1000008
8	91	4000043	8	46	
9	90	4000067	9	43	1000081
10	89	3000095	10	42	
11	87	3000042	11	41	100023
12	86	4000045	12	36	910000
13	86	3000027	13	34	3400000
14	84	3000009	14	29	2900000
15	82	3000044	15	27	2700000
16	80	4000029			
17	79	3000047			

8.3.9 Comparing haemoglobin levels of SHD cases by their nutritional status

The nutritional level of SHD cases of prospective cases was measured as indicated by total protein and albumin but these values were not tested in past cases of SHD due to poor laboratory resources. The clinical nutritional assessment of past cases was poor. All family members of the 2005 and 2012 outbreaks were too lean at the time of hospital admission. A t-test analysis was conducted on haemoglobin levels of SHD who were considered malnourished and the group of 3 men considered to be in robust health that was affected by SHD and had normal total protein and serum albumin levels. The difference in the mean pre blood transfusion haemoglobin was statistically significantly different supporting an association that existed between poor nutrition and severity of haemolysis experienced by SHD cases. Similar two-tail t-test analyses of haemoglobin of the 3 men and haemoglobin of 6 cases from the 2012 SHD outbreak showed a two-tail critical t value of 2.365 and a p-value of 0.0371. When sample the sample size was increased with the 2005 SHD outbreak showed a stronger association with t statistic of -4.771 and a p value of 0.000182 as reflected in the Appendix.

8.3.10 Haemoglobin level and nutritional state of SHD cases

The result of the t-test analysis showed that there was a strong association between nutrition state and effects of SHD. The 3 men had a higher level of pre-transfusion haemoglobin even though they had consumed sago meals prepared from the bag of implicated sago for 3 days before presenting to the hospital. For the majority of SHD cases, a single exposure produced severe illness.

8.3.11 Summary of exposure level, dose-response effect & clinical outcome

A single meal of implicated sago produced serious illness in 93% (14/14) of cases but 3 males had repeated meals over 3 days, a phenomenon not known to occur previously (Table 8.8). Three cases died, one death of 2 years old occurred 4-6 hours of illness but the other 2 died from acute renal failure one that had clinical and biochemical evidence of anion metabolic acidosis.

Table 8.7 Repeated exposure level, dose-response effect and clinical outcome

Place of outbreak	<1 sago pancake	Normal sago meal portion size	Repeated exposure> one meal	Mild disease	Serious illness	Death
2009-Kiunga 2 cases	¼ and ¾			1	1	1
2009 Timingondok		4			4	
4 2012 Tarakbits 6		6			6	1
2014 T'minserap 3		3	3		3	1
Total	2(13.3%)	13(87%)	3	1	14(93%)	3(20%)

8.3.12 Pathophysiological changes observed in SHD.

Table 8.8 Pathophysiological changes in 29 sago poisoning cases

	Pathophysiology changes detected in SHD	No of cases	%
1	Acute severe anaemia	14	93.3
2	Acute mild anaemia	1	6.7
3	Acute renal failure	5	33.3
4	Combination of anaemia, metabolic acidosis, renal failure	3	20
5	Haemoglobinuria (urine sample tested)	3	20
6	Early death first 4-6 hours	1	6.7
7	Late death due to renal failure without treatment	2	13.2

The table above shows the frequency of cases with anaemia, acute renal failure, anion metabolic acidosis, haemoglobinuria, and fatalities. Early deaths occur soon after the onset of illness and late deaths occur from the 3rd day onwards, this is related acute renal failure in those not given a blood transfusion. Due to lack of testing of all cases, not all features could be identified. The samples of the 3 males from the 2014 outbreak were tested at the Port Moresby Hospital laboratory and also at the James Cook laboratory. The universal features of

SHD include severe anaemia and haemoglobinuria which can progress to acute renal failure. All had underlying anion metabolic acidosis identified associated with the severe hypoxia. This was evident clinically by the onset of generalized weakness associated with drowsiness and the sudden onset of an altered conscious state progressing to unconsciousness.

8.3.13 Simple linear regression model

A simple linear regression model has been used to explain the clinically observed dose-response effect between the pre- blood-transfusion haemoglobin and the quantity of contaminated sago consumed. The pre- blood-transfusion haemoglobin is the dependent variable also known as the response or outcome variable. The independent variable (also known as the predictor) is the quantity of contaminated sago consumed by sago poisoning cases. The relationship between these two variables was analysed and the magnitude of the relationship can be predicted by examining the coefficient.

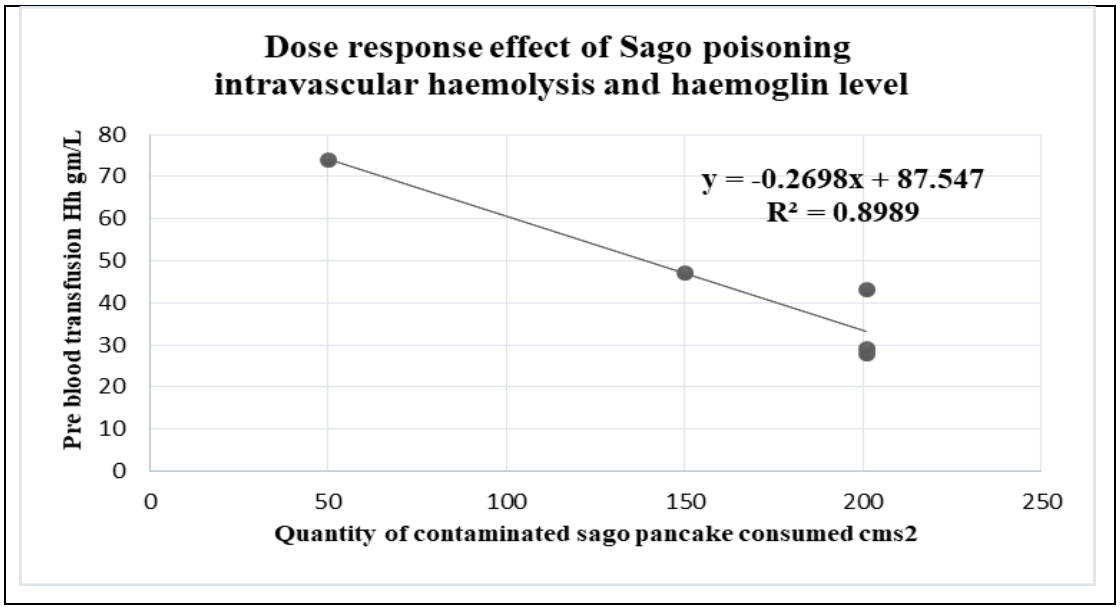

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Figure 8.18. Dose response effect of Sago poisoning intravascular haemolysis and haemoglobin.

8.4 Discussion

Hypoxia has long been known to be a significant physiological threat to survival. It has been studied extensively in mountain climbers, deep-sea divers and in aviation to delineate its effects and outline effective training and necessary equipment to protect against its damaging effect on physiological functions in the human body (Hornbein et al. 1989; Duplain et al. 1999; Ferretti 2001; Jansen et al. 2002; Basnyat & Murdoch 2003; Cable 2003; Smith 2005; Fitz-Clarke 2006; Smith 2008; Lindholm & Lundgren 2009; Goetze et al. 2013).

The physiological consequences of profound hypoxic effect on survival were best described in a statement by AS Haldane:

'Hypoxia not only stops the machine but wrecks the machinery' also described as '*Oxygen lack not only stops the metabolism but it wrecks the machinery'* (Kelman 1969; Petty 1989; Malone & Agutter 2008; West 2008).

The primary effect of SHD was the massive destruction and depletion of the red cell population that diminished oxygen delivery. This was due to the significantly smaller population of red cells therefore severe anaemia was described 40 years ago (Taufa 1974; Donovan et al. 1976). This study identified the secondary consequences of profound hypoxia relating to severe anaemia as being severe anion metabolic acidosis. This meant there was a propensity towards acute renal failure without treatment with blood transfusion and also correction of dehydration with adequate intravenous rehydration. The well-known dangers of hypotension in the presence of acute anaemia have been demonstrated in an iatrogenic case of hypotension from the use of an intravenous diuretic that had been part of a standard protocol with blood transfusions. The clinical conditions of SHD cases universally will be severe anaemia, dehydration, and unconsciousness. The study advocates for rehydration and blood transfusion to improve perfusion pressure and increase oxygen delivery to cells. The use of diuretics as a standard protocol is withheld until case blood volume has been adequately resuscitated. This will prevent precipitating acute renal failure which has no set system for treatment within the Papua New Guinea healthcare system. Administering diuretics produced grave consequences of acute renal failure and hyperkalaemia. Monitoring and treating acute renal failure takes more clinical skills that are unlikely to be possessed by clinicians not trained in emergency medicine or internal medicine training. Monitoring such cases would require frequent serial blood tests and cardiac monitoring which are quite intensive and may be beyond rural hospital capacity. These hospitals lack the level of acute care required in

intensive care units. Whilst resuscitative efforts were successful under the management of emergency physicians, undoubtedly these skills may be beyond the limits of other health workers in rural hospitals that have to manage SHD cases.

Continuing medical education with particular emphasis on the management of acute medical conditions for health workers would be a worthwhile exercise to maximize clinical improvement for severely ill cases. Understanding the damaging effects of hypoxia and ensuring training of health workers to recognize the hypoxic symptoms and signs (like those that present in SHD cases) will improve their clinical acumen and practice.

During the study, improvements in monitoring critical ill patients were noted. Monitoring of vital signs included pulse, respiration, and blood pressure which required regular checks by the nurses. Pulse oximetry was used for the first time in SHD cases to monitor oxygen saturation. Furthermore, a cardiac monitor was available in the operating theatre and could be used with proper training of nursing staff to visually monitor critical ill patients on the wards. Rural hospital laboratories equipment was installed including biochemistry and haematology analysers and an adequate supply of reagents. This was coupled with appropriate training to effectively operate the analysers. All of this provided an elevated the level of care to critically ill patients, particularly sago poisoning cases.

The electrolyte, acid-base disturbances, the elevated blood urea, and nitrogen would not be known without the results provided by the biochemistry analyser. Acute care to sustain life requires intensive monitoring of biochemical and haematological parameters at regular intervals. This is in order to prompt the use of appropriate interventions which saves lives, as demonstrated in this study. Failure or delay to provide treatment has also contributed to death as demonstrated in this study. Ensuring that laboratory technicians are trained and competent to operate the equipment remains crucial as biochemistry results that were incomplete and or reported as malfunctions were unhelpful with negative consequences to patient care.

Identifying genetic susceptibility by testing for G6PD deficiency was not undertaken in this study. Future studies can identify the reasons for the increased mortality of males compared to females. Evidence obtained in this study showed that men were more severely affected compared to females which may be explained by red cell enzymopathy and or haemoglobinopathy.

Red cell morphology reportedly was normal, but only one case had ovalocytosis among 7 blood films of family members during the 2005 outbreak. Moreover, blood films of 2005 and 2014 cases did not show any oxidative changes in Heinz bodies of ghost cells.

SHD occurs among lowland communities where malaria is endemic, its natural selection effects on red cell membranes, enzymes, and haemoglobin may exaggerate the effect of intravascular haemolysis of SHD. This may explain the gender difference of mortality by deficiency of glucose-6-phosphate in males as it is an X linked that invariably affects males and homozygous females with heterozygous females as carriers (Chockkalingam et al. 1982; Ganczakowski et al. 1995; Ruwende & Hill 1998; Nkhoma et al. 2009). The study reports that blood films of SHD cases do not exhibit evidence of oxidative damage. The profound hypoxia may induce greater haemolysis of red cells in those that have deficient glucose-6-phosphate dehydrogenase as the red cells do not have the support of mitochondria, therefore red cells are unable to generate adequate levels of NADH for glutathione reduction and its antioxidant properties (Ruwende & Hill 1998). The severity of intravascular haemolysis evident in SHD may in part or wholly be explained by the underlying abnormality of the red cell membrane, enzymes, and/or haemoglobin.

There have been beneficial effects reported in populations that lack Glucose-6 phosphate dehydrogenases where the severity of heart failure was reduced with fewer deaths from heart disease (Hecker et al. 2013). This may explain the severity of anaemia and tolerance of cases that reached the hospital. Blood film examination for malaria was routine for cases with anaemia and no SHD cases were found to have malaria.

The use of results obtained in this study can increase clinicians' and health workers' confidence to rapidly assess and promptly administer a blood transfusion to SHD cases to reverse the physiological consequences of hypoxia and return cases to normal homeostasis.

The swiftness of the haemolysis in both males and females and the lack of oxidative changes points to the presumed pre-formed toxins, which disrupt the red cell membrane bi-lipid layer causing haemolysis either through its action on the ion channels or on the membrane proteins.

Other causes of lactic acidosis needed to be considered as a differential diagnosis, these included intoxication by methanol or alcohol, medications, conditions such as diabetic ketoacidosis and acute renal failure. None of these conditions was present in the SHD cases.

Given the remote setting, exposure to other causes of metabolic acidosis would be negligible to non-existent.

In SHD, metabolic acidosis was prevalent in all 3 cases but only 2 developed acute renal failure that would explain the metabolic acidosis. Therefore, lactic acidosis occurred in all three cases as a result of the profound hypoxia.

The histories of SHD cases stated they denied alcohol consumption in addition to having not taken regular prescribed medication, particularly anti-malarial medications. They had not consumed broad bean or mushroom before their illness and were not exposed to the venom of snakes or spiders. Moreover, they denied a history of renal disease, liver disease, or diabetes mellitus as comorbidities before their illness.

At the time of the study, there were no renal dialysis services in the government hospitals in Papua New Guinea. Peritoneal dialysis is not commonly practiced. Without the availability of such equipment for haemodialysis, and mechanical ventilators, appropriate laboratory work remains essential to provide critical care in emergencies where a doctor's skills are required. Rural hospitals provided by any organization should be supported by the government through the outlay of essential equipment to save the lives of vulnerable and disadvantaged communities. Discriminatory practices by the government through their unwillingness to support church operated hospitals deprives rural communities of their right to doctor-level care that is supported by objective scientific results of clinical samples. Geographical isolation, lack of access to clinical consultation by practitioners in rural hospitals, and lack of essential medical equipment will continue to impair optimal care for seriously ill cases.

The results of pathophysiological changes in SHD provide an educational tool for clinicians and health workers to understand and appreciate the threat to survival confronting SHD cases. The acuteness and the emergency nature of SHD requires a rapid response in organizing and administering a blood transfusion to replenish the oxygen transport to cells. Moreover, ensuring all health workers become familiar with SHD through the dissemination of results of this study can remove barriers that contribute to the high mortality of SHD.

Time is of the essence in the treatment of SHD cases therefore, understanding the basis of the pathology of SHD may prompt health workers to improve their clinical acumen and fast-track investigation and treatment without undue delay upon arrival of SHD cases.

Rural hospital laboratory services provide essential support in investigating patients that present with medical issues, more so in those that present with life-threatening illnesses. Sufficient training of medical technicians to operate laboratory diagnostic equipment with a high level of skill, coupled with training of health workers to recognize medical emergencies, will increase the understanding of urgency in administering interventions such as blood transfusion to SHD cases. Strengthening clinical service delivery and prevention of complacency among health workers will improve clinical outcomes for patients.

Poor access to health care equates with poor health outcomes for the remoteness of SHD endemic communities. They live on the fringe of, or beyond health services and experience hardships in travelling to access treatment for medical emergencies of varying causes (SHD being one of them). Even those fortunate few that manage to reach distant hospitals may have fatal outcomes due to the lack of familiarity of clinicians and health workers with SHD. Families must retrace the treacherous journey to return the dead body to the land of their death for burial. Burying dead bodies on land other than their birth land is frowned upon and leads to mental anguish on those who choose to do so. Villagers of Baniso located in the Nomad area reported having to transport their ill pastor on a stretcher to a distant health facility for treatment where he died. Villagers decided to bury the body there and have been tormented by their action even years later (Lohmann 2005; Stewart & Strathern 2005). A rural community steeped in traditional beliefs about the care of dead relatives and loved ones will not only suffer a physical loss, but also suffer from anxiety over not observing traditions relating to burial. Preventing the death of SHD cases whilst in hospital will reassure and protect the mental health of families from remote communities (Schneider & Lindenbaum 1987; Cole 1988; Lohmann 2005; Stewart & Strathern 2005). The villagers have made repeated requests for villages' aid posts to be built in their village to any organization that can listen, as there is no government service in the Nomad area.

The treatment for SHD is simply an urgent blood transfusion. SHD cases must be transported without delay to the hospital for treatment. Fixed-wing aircraft are needed to provide efficient transfer, but helicopters are required where there was no operating airstrip. Needless to say, Mission Aviation provides air services to and from rural remote communities and conducts medical retrievals too. The service requires budgetary support from the government to assist its operation. Resource developers operating in the area provide ad-hoc support with medical retrievals in the absence of a formal government system.

8.5 Conclusion

Sago haemolytic disease decimates the oxygen transport system and deprives the cells of oxygen to sustain their metabolism. Therefore, it produces lactic acid from anaerobic respiration causing anion metabolic acidosis. The treatment for SHD is to restore the oxygen transport by blood transfusion and rehydrate cases to sustain sufficient perfusion to deliver the oxygen to cells. It is important to avoid the use of diuretics in SHD cases as well as avoid the use of sedation in critically ill cases where patients cannot be mechanically ventilated. In Papua New Guinea, ventilators are used in operating theatre settings. Acute care and accident emergencies do not have access to ventilators. Acute renal failure can be treated by providing peritoneal dialysis to cases with sago poisoning. Training doctors to conduct peritoneal dialysis would provide lifesaving treatment to sago poisoning cases as the kidneys are provided time to recover their function.

8.6 Recommendations

The study advocates continuing medical education on recognizing symptoms and around hypoxia and the management of SHD as well as its inclusion in the standard treatment book. AS Haldane is a British physiologist, their 1912 statement of ‘Oxygen lack not only stops the machine but wrecks the machinery’, needs to be understood by all categories of health workers in Papua New Guinea so they can translate and relay this in their communications to the decision makers and politicians.

9 Chapter 9 General Discussion

9.1 Objectives and hypotheses

The main objective was to conduct a clinical epidemiology study on sago poisoning, ultimately can be called sago toxicosis was accomplished. There were 5 main objectives that guided the study.

The first objective was the clinical epidemiology study which consisted of characterizing the disease by a case definition, derived from the retrospective study and refined by the prospective study of sago toxicosis outbreaks then established an incidence rate for the affected population. Essentially, it was a foodborne toxicosis therefore enabled an outbreak investigation that clearly identified the incubation period, temporal association, clinical features and dose response relationship as well as confirmed implicated contaminated sago as the exposure.

The second objective was to determine the pathophysiology of sago toxicosis which was achieved and reveled a purely biochemical disturbances of acid base balance directly related to the extreme acute anaemic hypoxic state that resulted in lactic acidosis due to anaerobic metabolism the body was forced to encounter as a result of exponential intravascular haemolysis.

The third objective was to determine the pre-morbid health status of sago toxicosis affected communities was achieved revealed the population to be in a dehydration state enmass. This was an unanticipated finding that can compromise patients' haemodynamically once they develop any acute illness. The biochemical health profile was healthier for both men and women that had operational village health facilities compared no health care facility or nonoperational.

The fourth objective was to enable statistical testing of relationship on the data collected on the clinical cases compared to controls obtained during health assessment of affected communities.

Access to health care between rural to rural populations with and without operational village health facilities was not statistically significant similar to peri urban settlements and rural Fly River communities' access to health care was not statistically significant. The biochemical health profiles of communities were statisticaly significantly different for many variables by

gender on the basis of operational village health facilities.The study confirmed the abscence of chronic renal failure that was suspected by practicing clinicians Western Province. It was highly likely that the dehydration state identified in this study readily induced acute renal failure in patients that were admitted for other acute illnesses.

The fifth objective was to call to action on the plight of remote communities by evidence based logistics challenges confronting rural remote communities'to access to health care which was advocated for at every opportunity within and outside of the medical fraternity.

9.2 Hypothesized causes of sago toxicosis

First and foremost, the aetiology of foodborne toxicosis remains unknown. To overcome the lack of awareness, this study proose to use sago toxicosis as the medically name to facilitate health workers retain and use this term to diagnose and manage sago poisoning cases with blood transfusion as soon as possible and rehydrate intravenously whilst waiting. This study postulates preformed toxins as the most likely cause as it behaves as a type II exotoxin but occurred in the absence of a local infection. Despite it being a foodborne illness, the presentation was of a systemic type signs and, non gastrointestinal symptoms highly suggestive of ingestion of highly potent of preformed toxin that absorbed directly by the buccal mucosa whilst chewing as the incubation period was only 8-12 minutes. The other cause to consider was exposure to arsenic to produce the same symptoms in a population who had existing susceptibility towards increased haemolytic tendencies. The Suki family outbreak of sago poisoning in 2005 had blood level of arsenic of 0.6μmo/l was near the non toxic level of 0.7μmol/l 48 hours after the onset of their illness. Arsenic level reduces rapidly by distributing into tissues within hours of ingestion from where it gradually excreted into the urine over a week. Arsenci could be present in the ground water used in dissolving sago starch granule in the sago pith. Both of these causes needed to be investigated in future studies.

9.3 Significance of Immune system stimulation

Immune system has become so important particularly during the Covid 19 pancdemic. Urgent decision was made to bring the pandemic undercontrol through the vaccination process by creating new vaccine. Immunology was recently developed and understood by those that academically studied this new field of medicine in the 1960. Covid was a respiratory mucosal disease which becomes systemic when the lowere respiratory tract such as alveoli becomes involved to produce the cytokine storm that destructs lung tissues and proved fatal. The

hypothesized preformed toxin that causing sago toxicosis passes through the buccal mucosa and entered the circulation ensured a rapid haemolytic process that depleted the erythrocytes population decimating the oxygen transport system. The downstream effect was systemic as acute anaemic hypoxic lactic acid induced metabolic acidosis. IgA is responsible for mucosal immunity. The short incubation period of 8-12 minutes indicated rapid absorption from the buccal mucosa by passing first pass through the hepatic circulation. The physical force of chewing of the contaminated sago did not produce local lesions in the buccal mucosa; instead produced an exponential haemolytic crisis depleted the erythrocyte population. The acute anaemic hypoxic state triggered anaerobic cellular respiration. That change in the sago toxicosis case led to central nervous system depression with loss of all voluntary movement and consciousness as a fatal outcome. Survival was assured by replenished oxygen transportation through blood transfusion. The reversal of anaerobic cellular respiration to aerobic can only occur with urgent blood transfusion needed to be taught to health workers.

Red cell cytolysis induced a biochemical change of acute anaemic hypoxia with lactic acidosis that did not seem to stimulate the immune inflammatory reaction. Due to the presence of global hypoxia – ischaemia, these patients appear to be in deep sleep state, had no gastrointestinal system involvement, no coagulopathic lesions and were not in renal failure at the time of hospital admission. Despite its acute medical emergency presentation, it does not resemble anaphylactoid shock, an allergic response, a hypersensitivity type reaction which can easily be recognised by the health worker (Uhr 1966; Hopp 2020; Srevastava 2003). Similarly, it does not resemble Haemolytic uraemic syndrome (HUS), a condition that was often suggested by other doctors during conferences. It consisted of a triad of haemolytic anaemia, thrombocytopenia and acute kidney injury related to enteric disease (Schering et al 2008; Noris et al 2005; Goldwater et al 2012). Could this be complement activation? It had not triggered the coagulation system as there were no clinical features suggestive of it. The four hypersensitivity reactions were considered but these induced intracellular changes which do manifest clinical symptoms and signs unlike sago toxicosis case (Suankratay 1999; Chapin et al 2016). Their skin remained warm and dry. It may resemble blood transfusion reaction resembles an allergic type reaction but the sago toxicosis patients had not been in patients (Pineda et al 1978; Chowdhury et al 2008).

Finally, sago toxicosis induced a biochemically led derangement in the physiological functions orchestrated on the oxygen dissociation curve in response to the critical depletion erythrocyte population, the means to transport oxygen. The acute anaemic hypoxic lactic

acidosis reduced pH affected the acid base balance thereby not detected by the immune system. The lactic acidosis indicated by a high anion gap was due to the critical lack of oxygen and anerobic cellular respiration (Goodkin et al 1980; Narins et al 1980; Lim 2007). The other causes of methanol intoxication, diabetes ketoacidosis, uraemia and infection. Intake of medications such as iron, isoniazid, and salicylates were known causes of lactic acidosis as was the homicidal or suicidal intent of ingestion of propylene glycol and ethylene glycol. For remote communities had no access to these medications and poisons who had been previously well until the sago meal that rapidly rendered them immobile and unconscious, the diagnosis was not obvious but after this study, more diagnosis were ca able to diagnosis and treat these patients with blood transfusion hence survival of from this lethal disease. Moreover, the uraemia did develop on day 3 as patient developed acute renal failure from being dehydrated or not administered blood transfusion for varied reasons described in the thesis.Cases were diagnosed and transfused with blood thereby saving them was a positive outcome of this study.

The first hypothesis was to identify the implicated food item proven to be contaminated sago therefore confirmed as a foodborne Sago induced toxicosis by this study. It is a non – gastrointestinal illness but has systemic effect of acute anaemic hypoxia that renders patients unconscious with fatal outcome. The aetiology remains unknown; this study hypothesizes preformed toxin, more likely, an exotoxin type II as the contaminant in the sago. The production site of for the harvest of logs of metroxylyn sagu palms, their debarking, maceration of fibrous pith containing sago starch, milling process using ground water to disolving sago starch and the sedimentation process occurred in the natural environment as opposed to a factory staged manufacturing process of sago starch. In the ecological environment and its microbial life forms and genetic material transfer between microbes could account for such a disease. This remains speculative and warrants future studies to identify the aetiological agent responsible for depleting the erythrocyte population exponentially with fatal outcome not described previously.

The second hypothesis was proven that nutritional status plays a significant role in the severity of the sago poisoning. The protective effect of albumin inhibiting haemolysis has been described in the literature.Whilst the sago toxicosis is a lethal disease, those who were malnourished had greater severerity of the illness and experience more fatality should they not be promptly given blood transfusion (Igisu;1993;)

The third hypothesis test resoved that blood transfusion protects against death and renal failure as shown in this study. This is understandable due to improved blood circulating with more erythrocytes delivers more oxygen to cells to maintain aerobic respiration thereby correct the anaemia associated lactic acidosis and improve the physical state of the patient where becomes conscious and be able to ambulate without any physical or neurological deficits.

An additional finding of the study was the enmass dehydration status of the population which endangers their survival should they develop an acute illness. Literature discusses the lethal combination of hyoxia and hypotension. The sago poisoning cases clinical outcome supports reflect the deaths occur in two peaks, early in the first 4-12 hours and late as on the third day. Dehydration may play a big role in explaining these deaths on the bases of being acutely hypoxic and also be dehydrated to the beginning of illness a well as getting dehydrated as the cases unconscious and not able to rehydrate themselves (Spaite et al 2017; Low, 1993)

In doing so, hypotheses raised were tested. A summary of the results of the statistical tests is provided together for an an overview. A short description, the sample size, the variable being tested, the name of the statistical and whether or not the test was statistical significant.

Sago poisoning produces the worse physiological derangement involving depletion of erythrocytes; causing anaerobic cellular respiration causing elevated lactic acid production that affects the acid base balance leaving the patient in a perpertual state of acute anaemic hypoxia; could easily be compounded by acute renal failure without urgent blood transfusion C Sanghavi et al 2023; Foucher et al 2023). The primary problem was the depletion of erythrocyte population as a perculiar but specific effect of sago poisoning. Whilst lactic acidosis is expected in critically ill patients that signals imminent death; likewise, sago poisoning case has less red cells so, the cellular metabolism is reversed from aerobic to anaerobic produces lactic acidosis secondary to the acute anaemic hypoxic that is easily corrected by replenishing the red blood cells by blood transfusion. This is a frightfully lethal condition (Suetrong 2016; Kim et al 2024; Possemiers 2021; Smith et al 2019).

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9.4 Summary of hypotheses test and results

Description	N - Sample size	Variable	Statistical test	P value	Significance status
Disease severity by poor nutrition	Male : 10 Female: 12	Mean of Pre transfusion Hb	T test	<0.001	**Significant**
Implicated sago	2 outbreaks	Has disease	2 x 2 table	100% Attributable risk	**significant**
Mathematic modelling of lethality of sago poisoning	Pre blood transfusion Hb as dependent variable Independent variable as quantity of contaminated sago consumed	Bivariate regression analysis	**Regression coefficient** - 0.1990759 - T stat 2.545614566 - Standard error0.07820347	<0.001 **1 cms^2** contaminated sago **reduces Pre blood transfusion Hb by 3.7gms/L**	**Significant**
Disease difference by age	Male 12 Female 12	Mean age	T test	1.7	Not Significant
Disease severity by gender	Male 6 Female 10	Mean pre blood transfusion **Hb similar**	T test	0.22	Not significant **Equal severity**
Mortality by gender	11 male death	Equal number of deaths	Odds ratio	6.8 (1.4-32.8)	**significant**

	Total deaths 14				
Description	**N Sample Size**	**Variable**	**Statistical test**	**P value**	**Significant Status**
Blood transfusion and death	Male 18 Death 8 Female 17 Death 2	Protective against death	Medcal-online Odds ratio	0.04 (1.049 -34.3)	**significant**
Compare anaemia of SHD and Non SHD	SHD 11 Non SHD 17	Compare mean Hb of two groups	T test	P <0.001	**Significant**
Health assessment Dehydration status of rural population	Sample size Male 210 Female 182 Total 392	Elevated Urea with normal serum creatinine and uric acid level	Ttest two tail by gender by access to operating aidpost	Male P < 0.01 Female P < 0.01	**Significant** Population in a **state of perpetual dehydration**

9.5 1: Does nutritional status affect the severity of sago poisoning?

The Suki family and the Tarakbits family were poorly nourished compared to the three robust healthy young men from T'minserep. The severity of acute anaemic hypoxia was worse among the Suki outbreak cases of 2005 and Tarakbits outbreak of 2014 compared to the T'minserep/Sare Kona outbreak of 2014. The young men from T'minserep residing in Sare Kona repeatedly ate sago pancake cooked using the implicated sago brought with them from the village. They challenged themselves with more meals of sago and became severely affected. Being away from their village, the only food source was the sago they harvested and brought with them for food while they had a short holiday in Kiunga Town.

9.6 2: Was sago the implicated food item in sago poisoning illness?

The 2007 Sauga Kona outbreak of sago poisoning affected 2 women that consumed sago spared 12 others that did not eat sago produced the first evidence of sago as the implicated food item. Added more evidence on dose response effect.The 2014 T'minserep outbreak

provided clear evidence that implicated sago that they harvested from upper Fly River region, a different location and brought to Kiunga town to sustain them during their stay before they return to their village. The inclusion of the control group with the 2 women that ate sago confirmed that contaminate sago contained the cause for sago poisoning. The confidence of diagnosis and recognition increases with each outbreak since this study began.

9.7 3. Predict dose response effect by mathematical modelling

The lethal effect of sago poisoning was determined by the bivariate regression analysis on the pre blood transfusion haemoglobin, the dependent variable to the independent variable as the quantity of the contaminated sago consumed. The regression analysis mathematically demonstrated lethality by reducing the haemoglobin 3.7 gm/L for each square centimetre of contaminated sago pancake ingested. This clearly described would render some one unconscious and or die particularly as normal meal of sago would far exceed that quantity. The state of unconsciousness and death was explainable on the basis of the rapid onset exponential haemolysis of the red cells induced acute anamic exteme hypoxia associated lactic acidosis progesses to acute renal failure when patiens were dehydrated.

9.8 4: Is SHD anaemia comparable to other anaemia?

The anaemia of SHD had debilitating effects that has asudden onset unlike the anaemia affecting others who ambulant without restriction. There exists a statistically significant differeance in their two mean haemoglobin represented as two distinct groups as depicted on the scatter plot of haemoglobin, one as an acute form for the sago poisoning cases and the other insidious onset of chronic anaemia cases.

9.9 Natural history of sago poisoning

The natural history of sago poisoning is described as a foodborne toxicosis. It can be more accurately described as sago induced intravascular haemolysis that produces acute anaemi hypoxic symptoms occur within 10-15 minutes of consuming a sago pancake cooked with contaminated sago sago flour. The temporal association was confirmed, sago poisoning symptoms were preceded by a sago meal, mostlikly contaminated with hypothesized preformed toxin. The mechanism of the anaemia is a sudden intravascular haemolysis of the erythrocytes exceeding the clearimg system of haptoglobin.This was thereby detected as haemoglobinuria and reported as passage of red urine reported by relatives which was witnessed during hospitalization. The loss of the erythrocytes depleted the oxygen transport

system and proved lethal for cases that did not receive a blood transfusion. It is essential to replenish the oxygen transport system through administering blood transfusion as a life saving treatment. Dehydration must be avoided in these patients.

Consuming a contaminated sago meal that incapacitates the person within extremely short incubation period matter of less than 15 minutes; a disabling level of physical weakness associated with sudden loss of consciousness. Clearly, the vehicle for sago posiong was present as a contaminant or preformed toxin in the sago flour prior to the prepared meal. Sago starch produced using traditional milling process of the fibres extracted from the pith of the stem of the metroxyline sagu. This illness reaches it maximum effect within 10-15 minutes of The symptoms of acute anaemic hypoxia were headache, dizziness, extreme fatigue, becoming recumbent, with central nervous system depression as unconscious state in a patient. The giveaway sign was the passage of red coloured urine indicated the loss of erythrocytes where urine haemoglobin increases as the erythrocytes in the circulation rapidly depleted. The haemolytic anaemia produces the yellow sallow appearance on the palmar surface of the hands and the soles of the fee that over shadows the pallor of severe anemia thereby prevents the health worker to fully appreciate the presence of severe anaemia and associated it with the central nervous system depression. Seeing sallow appearance in dark skinned individuals may be harder for those not familiar with looking for sallow appearance (lemon yellow).

The complications of sago poisoning were evident in the results of the full blood counts, urea, creatinine, and electrolytes and these best explained the clinical findings. The pathophysiological evidence supports the presence of life-threatening acute anaemia, hypoxia, and high anion metabolic acidosis. This explained the early deaths occurring at 6-12 hours in males and late deaths on the 3-4 day of illness from acute renal failure. These are preventable deaths through administering a blood transfusion as early as possible. Lack of availability around supportive renal failure management such as peritoneal dialysis and haemodialysis prevents rescuing and salvaging those that need it.

Genetic susceptibility towards developing haemolysis may exist in the SHD affected community. The Suki family outbreak provided evidence of alpha thalassemia and red cell membranopathy of spherocytosis, supported by morphological abnormalities of anisocytosis, poikilocytosis, and microcytosis. The use of collection of blood spots on the filter paper to test for erythrocyte enzyme deficiency needs to be investigated. Moreover; regarding this study’s

hypothesis of preformed toxin(s) as the aetiology, the mechanism as proposed was to occur at the ion gated channels to cause osmotic changes to explain the exponential speed of the intravascular haemolysis. The presence of hypoxia can worsen the situation further (Grygorczyk et al 2017; Buehler et al 2010; Tozoni et al 2019).This requires further investigation in the future. The behaviour of the preformed toxin resembled that of preformed exotoxin type 11. The diseases of exotoxin aetiology require an ongoing infectious site to produce the toxin.In sago poisoning; the evidence of scepticaemia was absent. Moreover, the source of outbreak does not always mean old sago; recent harvest of 2 weeks old was source of the source of sago poisoning outbreaks during the 2012 and 2014. Despite samples of implicated sago obtained, the search for toxicological studies was not pursued.

9.10 Benefits of operating aid posts in villages

Access to health care by remote communities was predominantly provided by non-government's organizations such as the Church health services by the Catholic and ECPNG Churches as well as the resource developer Ok Tedi Mining Ltd. This study shows that any operating health facility was better than having closed aid posts as people do access them for their health care. This access to health care is reflected by the results of the health assessments where those who have access have normal parameters in their haemoglobin and biochemistry results. The range of values considered normal was taken from tests books which are most likely for developed countries. Determination of normal values for remote communities will require consideration by health authorities. Access to bed net distribution and use by the communities was also demonstrated, they need more rather than less. The burden of malaria species and microfilaria increases as distance increases from towns to remote communities. The urban population greatly benefits from rapid access to treatment for malaria and also from the use of bed nets. Data from the Tabubil Public Health sector shows the rapid reduction of slide positivity since the increased availability of bed nets from the global fund. The benefits will be lost if bed nets are not retreated or replaced. This study demonstrates the reduction in malaria and microfilaria burden in urban and peri urban communities and shows how this burden remains high in remote communities furthest from the town of Kiunga. This evidence shows a lack of access to bed nets and treatment for malaria.

From the evidence gathered on health service providers and regions of their operations, this study advocates for church health services to be supported by the government through budgetary provision to run all health facilities in the region of their operations. This will

improve access to health care by remote communities. Air transport is essential to health and education services to remote communities and therefore, the study advocates for budgetary support for Mission Aviation Fellowship (MAF). Moreover, if the government has the transport logistics to facilitate government services reaching remote communities, so to use the same logistics be used to transport medical emergencies as well as for the educational needs of students and teachers.

This clinical epidemiological study provided the first-ever evidence that characterised Sago poisoning as a foodborne toxicosis because the onset of illness occurs after a meal of sago pancakes. This is presumed to be contaminated with a hypothesized microbial preformed toxin, or multiple toxins. The short incubation period (identified as 10-15) minutes strongly supports the suspected aetiology of preformed microbial toxins. The ensuing symptoms of acute anaemic hypoxia directly reflected the rapidity of intravascular haemolysis at such an exponential speed that it proved lethal. This lethality was especially true for male children and young adult males, despite female children and women being affected by the same severity of intravascular haemolysis they were able to reach hospital for blood transfusion and fully recover. At a presentation of the results of the study, the audience even suggested that women should be the first to eat the meal to taste the safety of the sago pancakes as they were more likely to survive. Alas, such will be unlikely due to cultural positioning and practices that honour boys and men above women and girls. The biggest portions of any meal are served to men and boys before women and girls eat their lesser portions.

This study confirms a normal portion of sago pancakes, which is usually more than one 14-16cms sago pancake, proves lethal and causes near-death acute anaemic hypoxia. It was extremely fortunate that different sizes of contaminated sago pancake were seen, from just chewing, tasting and discarding the mouthful of sago up to consuming a quarter, three quarters, or one single pancake or more. This related closely to cases experiencing asymptomatic to symptomatic with symptoms of acute hypoxia and fatal outcomes constituting the very first evidence of the dose-response effect. Furthermore, this demonstrates the lethality and specificity of the action targeting a single cell line damage on the erythrocytes. The blood films do not show evidence of oxidative changes of erythrocytes as the mechanism for the intravascular haemolysis of erythrocytes. The blood films demonstrated evidence of membranopathy as spherocytosis. Furthermore, the morphological changes of poikilocytosis, anisocytosis, and microcytosis of erythrocytes supported the

presence of thalassemia that was confirmed as alpha thalassemia with the presence of haemoglobin H.

This study showed that the past reports of old mouldy sago being the cause of the reported sago haemolytic disease were not wholly true. Sago poisoning also occurred in those who ate recently harvested sago of two weeks as shown in Figure 7.7 on page 203. The sago was stored in manufactured bags formerly used as rice bags sold in the shops. This study was the first to confirm the true existence of the temporal relationship between consuming the new hypothesized preformed toxin in contaminated sago pancakes and the onset of severe intravascular haemolysis after 10-15 minutes. Symptoms include vomiting, dizziness, extreme physical weakness, lethargy associated with drowsiness to unconsciousness and death. The early deaths were attributed to extreme acute anaemic hypoxia and metabolic acidosis. The later deaths were due to dehydration exacerbating the tissue perfusion and acute renal failure which cannot be reversed with peritoneal dialysis in rural remote hospitals. Patients with severe acute anaemic hypoxia survived after receiving blood transfusion, but if this was delayed then deaths in the hospital occurred as demonstrated in this study. All health workers must be knowledgeable about severe intravascular haemolysis and the urgent need to give a blood transfusion to replace the massive loss of the red cell population. Health workers were unfamiliar with symptoms of acute anaemic hypoxia when they were confronted with cases. The anaesthetists and emergency trained doctors and nurses will now be able to recognize these and have contributed to the rapid and appropriate resuscitation and treatment of the latest outbreak from the Tarakbits village in 2012. The patients were able to survive, even the one case that was administered a diuretic, a usual treatment to all patients that are given a blood transfusion. In this situation, Lasix was the diuretic used which is contraindicated as the patients were volume-depleted, and therefore this treatment caused the patient to become hypotensive. They were successfully resuscitated with rapid fluid replacement. The emergency physician training positively contributed to the survival of sago poisoning with comorbities and others who were able to walk out of the hospital without any permanent sequelae from acute prolonged hypoxia. This was a much appreciated and relief to the principal investigator.

Furthermore, the study confirmed the natural history of SHD by demonstrating the dose-response effects of asymptomatic haemoglobinuria with no anaemia as negligible exposure, to mild disease in minimal exposure, and severe intravascular haemolysis with a dramatic reduction in haemoglobin and life-threatening acute anaemia in those that have eaten three-

quarters (14-16cms) of a single pancake or more. Sago haemolytic disease has an aetiology which fits that of preformed toxin(s). Therefore, the cooked sago pancake contains heat resistant preformed toxin(s) which are yet to be identified in the microbial and toxicological study of implicated sago. There were three clinical presentations of SHD which occur following a normal portion size meal of sago: these occur firstly as early fatalities, secondly, as a severe illness that can become fatal without early treatment, and thirdly, mild cases were evident but only rarely as these occur in those that consume less than a normal meal. Mild cases were captured in this study as they were the controls for cases, thereby identifying features of intravascular haemolysis in them. Despite obtaining 2 samples of implicated sago, these studies were not undertaken.

This study established risk factors for developing sago poisoning as being poor nutrition (indicated by malnutrition, low albumin, low total protein levels), and being male. The evidence that supported this relates to the severity of anaemia and increased mortality in cases of poor nutrition compared to cases that had robust health. Furthermore, a single exposure was sufficient to cause severe disease in malnourished cases compared to cases with robust health. More robust cases maintained a higher level of pre-blood transfusion haemoglobin and could tolerate meals from the implicated sago for a further 3 days before becoming severely ill.

There was a significant gender difference where more males died earlier at 4-12 hours during the illness, which suggests an underlying genetic difference where males had a reduced tolerance level for acute anaemia and hypoxia. This may be due to the presence of glucose six phosphate dehydrogenase deficiencies is a prevalent condition among malaria-endemic lowland communities of Papua New Guinea where SHD occurs. This study was not able to access male survivors to test for this condition. Red cell morphology of cases was normal except for the occasional case of ovalocytosis.

The main treatment for SHD consists of rehydration and a blood transfusion administered to resuscitate acutely ill cases. This study recommends multiple first aid treatments, firstly the use of charcoal ingestion during the early stage of the illness may allow binding of excess unknown toxin, this can be undertaken in the village or upon arrival at the hospital. Other forms of treatment such as administering albumin infusions in SHD cases when they arrive at the hospital to bind excess unknown toxin(s) in the circulation as its binding properties of volume expander could be attempted, knowing well that erythrocytes numbers needed replenishing as soon as possible and prior binding of existing toxins can be prevented form

haemolysis as it seems so rapid and instantaneously that could favour survival and reduce the need for more blood transfusion.

During the community health assessment, three factors were identified as comorbidities. These were pre-existing conditions of poor nutrition, anaemia, and dehydration. Poor nutritional status was endemic, but there was a slight improvement in communities that had access to health care and used bed nets compared to communities without access to health care. The burden of anaemia was reduced significantly by the use of bed nets and access to treatment for malaria by the communities. Biochemical analysis during the health assessment revealed prevalent state of dehydration affected the population which can easily precipitate hypotension in acute febrile illness or diarrhoea and vomiting. Even worse effects were observed in SHD where dehydration reduces perfusion even further leading to onset of acute renal failure that can be fatal. Dehydration was a new comorbid condition identified and could pre-empt the onset of acute renal failure which as was alluded to by doctors practicing in Western Province. Using a community education strategy to mitigate these comorbidities seems like the next step to take. Educating the community to drink more water throughout the day can help to prevent dehydration. Other actions include promoting access to more bed nets by communities without access to health care and ensuring that all village aid posts were operating so that early treatment was provided for malaria, the endemic disease that contributes to anaemia.

Poor infrastructure development in the Western Province will continue to be the main factor in the delay of patients accessing life-saving treatments in hospitals and will continue to contribute to fatal outcomes in cases with treatable conditions. Air transport operated by OTML and MAF had saved lives of SHD cases that were transported to the hospital. A formal retrieval system to serve the medical emergency needs of rural remote communities and support existing MAF services needs to be addressed by the Western province administration.

This study on SHD updated its description from the early version provided by Taufa and Donovan's case reports (Taufa 1974; Donovan et al. 1976, 1977). It affects rural remote communities that heavily depend on sago as their main staple food in addition to having poor access to health care. Physical barriers imposed by difficult geographical terrain are well known in the Western Province and other parts of Papua New Guinea and are recognized as the major obstacle to the delivery of goods and services to many isolated rural remote communities. The lack of infrastructure development maintains the isolation of remote

communities and prevents them from accessing health care. Without existing road networks and modern river transport, government-driven village-based development activities have lagged or are non-existent. Hence, the lack of visibility of government services among rural remote communities.

Churches health services were visible and prevalent among remote communities, filling this vacuum left by the government. They sustain this service by use of fixed-wing flights to overcome the geographical barriers and appear the only way to sustain essential to moving cases to hospital and was vital to sustaining the operation of its health facilities in these remote communities. Catholic health services ceased their fixed-wing flights following the crash of its only aircraft and the subsequent death of a priest pilot. This led to the disuse of many of their village airstrips. The Evangelical Church of Papua New Guinea (ECPNG) is a major health service for rural communities and was preferred over other health service providers as seen in increased attendances to its hospital. They provide obstetrics, surgical, and medical care with an increasing number of doctors. In partnering with Mission Aviation Fellowship (MAF) flights, the ECPNG Church health services sustain their health services to remote villages in a wide region of the North Fly District. Mission Aviation Fellowship (MAF) has a long history of providing regular flights to deliver goods and personnel involved in health and education services and do medical emergency retrieval for remote communities without roads in Papua New Guinea.

Resource developers operating in the Western Province overcome the geographical barrier by operating their logistics of ships, trucks, regular fixed-wing, and helicopter flights to sustain operations in such unforgiving geographical settings. Hence, they assist remote communities by providing mercy flights for medical emergencies when required.

To carry out any detailed study into the clinical epidemiology of sago haemolytic disease in such a setting remained an impossible task. This can only be achieved with appropriate logistical support to access study sites. Executive management decisions by Ok Tedi Mining Ltd provided the resources and a research grant to James Cook University for this study on the clinical epidemiology of sago haemolytic disease. They supported the principal investigator and allowed access to the use of logistics like fixed-wing flights and a ship that facilitated travel to reach many remote communities located along the Fly River, downstream from Kiunga Ok Tedi wharf to its estuary, including the North banks and Kiwai Islands. Meetings on raising awareness of the case definition of SHD, and the need to initiate an early transfer of

cases to a hospital for blood transfusion, were imparted to remote communities and health workers of 4 hospitals (Tabubil, Kiunga, Rumginai, and Balimo). Visits to Ali village on the Aramia River were also undertaken as the SHD outbreak reported there had more deaths due to a delay in arrival at Balimo Hospital. This was caused by the use of ineffective transport over long-distance travel by canoes. These talks established surveillance by communities and health workers around new cases to enable a rapid response in reporting and transferring cases to hospital for investigation and prompt institution of a blood transfusion.

Results of a baseline health assessment on rural remote communities were obtained through the generous support of the community relations manager from Talisman Energy Niugini Ltd (TENL). As an oil and gas exploration company, it facilitated the delivery of health care under its community investment program to those communities impacted by its exploration activities. They did this by supporting the principal investigator to lead the health team to reach out to these communities. Financial and logistical support with medical supplies and transport was provided by TENL. Fixed wing and predominantly helicopter flights were used to transport health teams and their supplies to remote villages to conduct mobile clinics and health assessments of these rural remote communities. This established the baseline village health data that was not available from the health information system of the government.

The outcomes achieved were successful delivery of health care to remote communities that lacked access to health care, established village-based health data of all segments of the communities, provision of bed nets and personal clinic books. Most of all, valuable time was spent with remote communities through conducting health education programs on promoting health. This was conducted by a team of health professionals with different skills sets who put an emphasis on the important health needs during different phases of life. This study demonstrated that the use of the right types of logistics can achieve health care delivery even if that was on a temporary or one-off basis to these remote communities. It also affirms that health care delivery was achievable with the use of air transport to overcome geographical barriers.

Following ethics approval, a case definition of SHD was established following a retrospective review of medical records from 4 hospitals (Tabubil, Kiunga, Rumginai, and Balimo). A total of 40 cases were identified but only 16 medical records were retrieved as shown separated by hospital (Tabubil 3, Rumginai 2, Balimo 5 and Kiunga 6). Twenty-four records were not located in Kiunga hospital, the main referral point for cases. Poor storage of medical records

contributed to the retrieval of fewer records. Regardless of this, health workers (particularly nurses) were able to identify cases that were verified by the ward admission register. Nurses easily recalled deaths of SHD cases due to confrontation, physical assault, and damage to hospital property carried out by grief-stricken relatives.

The retrospective review revealed a case fatality rate of 35% (14/40), 71% (10/14) of which occurred among male children and young men in the first 12 hours of illness. This is compared to women and female children who had a lower fatality rate despite having similar severity of illness. An odds ratio of death was 6.8 with a 95% confidence limit (1.4-32.8) and $p < 0.001$ among those that did not receive blood, and an odds ratio of 0.15 with 95% confidence limit (0.03-0.7) and $p > 0.05$ in those that did as a blood transfusion had protective effects against the odds of death. The minimum age of children admitted to hospital differed between males (8 years) compared to female children (4 years). Male children <8 years died within 6 hours of illness before travel arrangements were made to the hospital, this suggests that females were more tolerant of low levels of haemoglobin compared to male children and young men as evident in Figure 5.5 and 5.6. The higher risk of death in males with SHD suggests a genetic basis for this increased susceptibility. The annual incidence rate was 1.3-5.8 per 100,000 which was highly likely affected by under-reporting due to the lack of transport that impedes access to health care. SHD outbreaks were common during the wet season and were more common in North Fly District with a monthly rainfall of 200mm compared to other areas that had less rainfall.

Two instances of field work were undertaken earlier in the study to educate health workers and communities on the sago haemolytic disease case definition as defined in chapter 5.3.8. This was undertaken to prepare all participant health workers and communities so they could fully engage in the prospective study of SHD cases. Facilitating rapid reporting and transport of cases to hospital as well as ensuring health workers promptly recognize, investigate, and treat cases with blood transfusion not only improves survival of cases, but also provides the opportunity to study this elusive disease.

Results of the prospective study on SHD revealed the incriminating food item, its temporal relationship, incubation period, and dose-response relationship that effectively construct the natural history of SHD. It begins with consuming dry pan-fried sago pancake(s) prepared from mouldy sago flour which that precedes the onset of SHD. Only those that ate implicated sago became ill, therefore it was confirmed as the implicated food. This established the

temporal relationship between consumption of sago and onset of SHD, which was a presumed association since the early case reports 40 years ago. The most accurate incubation period was determined as 15-20 minutes; this is the duration of time taken from ingestion to the appearance of the first symptom of intense vomiting. Full clinical effects render cases recumbent and unconscious and these occur within 30 minutes of ingestion of implicated sago. Deaths due to SHD occur in 2 peaks, the most susceptible group was identified as male children and young men who died within 6 hours of the onset of illness compared to the second peak of deaths that occur on the third to fourth day of illness, resulting from acute renal failure. Hypotension was recognized to precipitate acute renal failure. Dehydration from a lack of intake of oral fluids and delayed treatment contributed to hypotension. Moreover, hypotension was iatrogenically induced by administering an intravenous diuretic with blood transfusion, this is a standard treatment approach to prevent overloading a patients' circulation. The study discourages the use of diuretics in patients with SHD who require blood volume expansion, resuscitating with blood and fluids improves perfusion and increases oxygen delivery.

Anaemia was the main sign of SHD and was always present. However, careful interviews revealed asymptomatic individuals that had negligible exposure levels compared to serious cases that had higher exposure levels and significant symptomatic anaemia requiring a blood transfusion. Furthermore, debilitating anaemia was described in cases that survived SHD without treatment, they had such severe anaemia that it prevented them from ambulating for 2 weeks after the illness. They recovered upon receiving a blood transfusion. This study showed that cases that had robust health before the illness and maintained a haemoglobin level 50-60gm/L higher had different outcomes compared to those with a greater severity of anaemia with a haemoglobin level of 26gms/L in cases with poor nutrition.

9.11 Dose-response and aetiology of SHD

This study demonstrated that the severity of SHD was closely correlated with the quantity of contaminated sago consumed by cases. Reduced exposure by tasting or chewing a single mouthful of implicated sago and discarding it produced asymptomatic haemoglobinuria and normal colour urine without affecting the cases. Eating a quarter (14-16cm) of an implicated sago pancake produces dark red urine and asymptomatic anaemia with haemoglobin of 78gm/L this did not affect the case. Eating three-quarters of implicated sago rendered a case drowsy and recumbent with haemoglobin of 47gm/L. Those that ate one or more implicated

sago meals developed loss of consciousness with lower levels of haemoglobin. Furthermore, hyperhaemolysis continues to occur in severe cases during blood transfusion that suggests the presence of a preformed toxin interacting with donor red cells which ceases upon its depletion. Considering the dose-response, level of exposure, and the speed of symptoms onset, it suggests a highly potent natural toxin to be the aetiology of SHD.

9.12 Pathophysiology

This study confirmed evidence of massive intravascular haemolysis of haemoglobinuria, depleted haptoglobin, marked elevation of lactate dehydrogenase, and normal bilirubin levels. Hyper haemolysis of red cells decimated oxygen transport and critically reduced oxygen delivery to cells as a result of instantaneous acute severe anaemia and profound prolonged hypoxia. The cumulative effects of profound hypoxia underpins the neurological and musculoskeletal effects of the disease as well as newly identified evidence of high anion severe metabolic acidosis (Gnaiger et al. 1995; Erecińska & Silver 2001; Leach & Treacher 2002; Gerrah et al. 2003). The accumulation of lactic acid due to anaerobic glycolysis was the most likely cause for the metabolic acidosis and this would revert to normal instantaneously by increasing oxygen delivery to cells. This can be done by replenishing the red cell population by blood transfusion and maintaining hydration status to sustain normal perfusion into cells.

9.13 Genetic susceptibility

Increased susceptibility in male children and young men was presumed as an explanation for the observed early deaths in the first 6 hours of illness; overall high mortality had not been explored in this study. SHD occurs among malaria-endemic communities that also have a high prevalence of red cell abnormalities as membranopathies, enzymopathies and haemoglobinopathies as ways to protects against malaria (Srivastava & Beutler 1968; Yenchitsomanus et al. 1986; Jarolim et al. 1991; Tilley et al. 1991; O'Donnell et al. 1998; Bruce et al. 2000; Mueller et al. 2003; Mueller et al. 2007). The genetic susceptibility would need to be investigated in future studies.

This study measured the burden of malaria in SHD affected communities as described in Chapter 4. The malaria prevalences tend to be lowest in communities who lived around the Kiunga Township but dramatically increased as the distances increased to the most distant remote villages nearing the provincial boundaries to the eastward. Malaria prevalence was 4%

among the Kiunga Township communities compared to 8.2% among the highlands and Fly River communities that are located within a day's travel. Malaria prevalence increases to 38.2 - 42.1% among the Strickland and Nomad populations whose villages are only reachable by air. The Chi square test of independence analysed the prevalence of malaria between urban and rural villages of Strickland River communities was statistically significantly different due to large test statistic of 11 for one degree of freedom and an alpha of 0.5. The dramatic reduction of malaria was attributed to Bill and Melinda Gates Foundation distribution of bednet that were easily obtained by the population living in the town compared to distant communities. Furthermore, bednets had been distributed by Ok Tedi Mining Ltd to local communities for a fee since its operation in 1984 reduced malaria burden in communities living around the mine lease area as well as the surrounding communities of Kiunga town. The dramatic reduction in malaria burden was reflected by the malaria monitoring program at Tabubil Public Health section in Figure 4.15 and Figure 4.16.

9.14 Improving access to healthcare and hospital-based care

Improving health care access by rural remote communities can be achieved by overcoming the geographical barriers through use of fixed-wing flights as well as community development activities that link with logistics of travel by river and road transport by government or resource developer projected. This will require serious consideration by responsible provincial and national governments. Whilst resource developers assist by transporting medical emergencies using their logistics of fixed-wing and helicopters, sustained delivery of health care to remote communities needs efficient transport on a regular schedule. Mission Aviation Fellowship (MAF) provides flights into remote communities and conducts medical evacuations. Support for such services by the government may alleviate poor access by transporting the health team to deliver health care in the disadvantaged rural remote communities. The use of fixed-wing flights and helicopters was essential to accomplish medical retrievals to the hospital by the most direct route, in the shortest possible time. This was the preferred rapid response to call-outs by health workers who refer cases with a life-threatening illness to the hospital for medical evacuation and life-saving treatment. Services delivered through charities fills that could be acknowledged and formalized by the government through budgetary support. Decision makers at provincial and the national government lack ability to focus on reaching and serving remote communities.

9.15 Training of health workers on medical emergency

To reduce mortality associated with medical emergencies, all categories of health workers need the training to recognize and treat medical emergencies promptly. This should be done using appropriate interventions as means to stabilize the condition of patients and to promptly institute specific treatment. Strengthening consultations between different categories of health workers is required to give quality assurance on patient care. Lack of knowledge and delays in treatment contributed to poor outcomes in this study. Training of all categories of health workers to recognise and treat medical emergencies is required. Emergency trained physicians successfully resuscitated and treated SHD cases during the prospective study described. SHD has been fully characterized and its pathophysiology revealed and, treatment with blood transfusion is known but the risks and aetiology of SHD remain yet unknown. This is despite the progress made in a laboratory investigation of haemolytic compounds found in a microbiological study on the basal microbial composition of sago (Greenhill et al. 2007a; Greenhill et al. 2007b; Pue et al. 2008; Greenhill et al. 2009; Greenhill et al. 2010b). There is a need to further investigate implicated sago to determine if it contains other natural toxins besides the free fatty acids identified (Pue et al. 2008).

9.16 Impact of this study

This study confirmed that transferring medical emergencies from remote communities to hospitals by air transport saves lives. The use of fixed-wing aircraft was essential to operate the delivery of health care or any type of services to remote communities. Furthermore, the study confirms the spatial distribution of SHD outbreaks among riverside villages along with the upper Fly River suggests ecological factors may also play a role in the aetiology of SHD. The reported outbreaks were more prevalent in the North Fly District that has 40 mm of rainfall monthly as opposed to drier regions of Middle and South Fly Districts where earlier reports of SHD outbreaks were seen. This study observed new epidemiological evidence that were not known previously suggested a highly potent preformed toxin may be responsible for producing such the exponential intravascular haemolysis. The presumed high potemcy was supported by evidence of asymptomatic haemoglobinuria upon ingesting a minimal quantity of contaminated sago (such as chewing, tasting and discarding a single mouthful). Additionally, increasing the quantity of ingested sago escalates the severity of effects associated with the disease. Ultimately, this also suggests that there was no margin or

threshold of safety, marking implicated sago as containing one or more highly potent natural toxins.

In the absence of effects of oxidative damage (Greenberg 1976), the site of action of the preformed toxin was likely to be at the red cell membrane. The mechanism of action is likely to be disrupting the cell membrane ion channels that draw in fluid, expanding and rupturing the red cells or had pore forming properties of the erythrocyte membrame. This is similar to natural toxins in marine animals that produce intense symptoms rapidly upon exposure by affecting the ion channels of membranes (Russell 1975; Bagnis et al. 1979; Frenette et al. 1988; Butera et al. 2000).

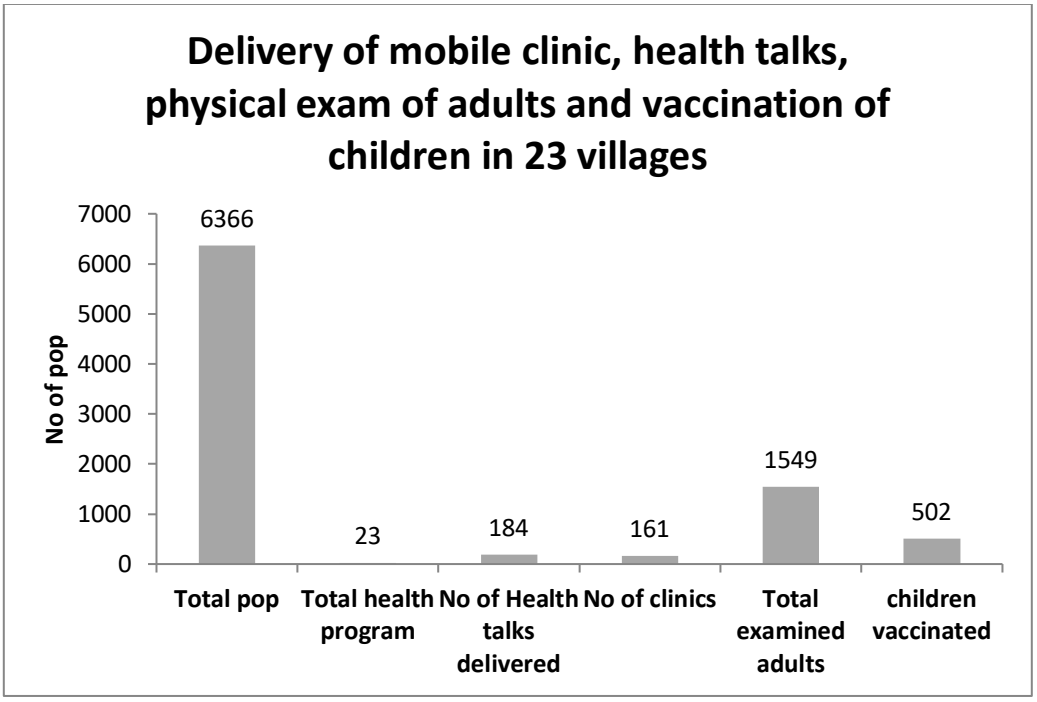

Figure 9.1:A number of beneficial outputs delivered to communities

Ensuring reciprocal benefits between communities and researchers assured better relationships by respecting the needs of others, particularly disadvantaged communities. With appropriate support, the results of this study would have to be disseminated to those villages that participated. The results have been presented to the medical fraternity during the Papua New Guinea Medical Symposium in 2013. A special visit was made to present the results to health

workers from Kiunga and Tabubil hospitals. Presentation of the results was made to the executives of Ok Tedi Mining Ltd. Separate presentations were made to the Community Relation Department of Ok Tedi that will inform the Fly River communities. Results were presented to Talisman Energy Niugini and its impacted communities in 2016.

9.17 Limitations of this study

Study on less known disease affecting humans had to be observed on humans as such clinical epidemiology study of sago poisoning amongst rural remote communities in PNG. Laboratory tests on clinical samples continued to be problematicin the the poorly resourced laboratories in rural hospital settings in Papua New Guinea, The biochemical analysis eluded to the effects of lactic acid and arterial blood gases were not analysed to reflect the profound hypoxia that formed the basis of biochemical and physiological disruption of homeostasis. The prospective cases blood was evaluated at James Cook University Laboratory. Analysis of glucose 6 phosphate dehydrogenase deficiencies was not determined for SHD survivors as it could explain the high mortality of males' during the early part of SHD illness. The patient reveived urgent blood transfusion therefore could be part of a future study.

Microbiological study was undertaken by principal investigator revealed the growth of *Escherichia coli* and *Bacillus cereus* variant; both were known to cause haemolysis. Future studies could do ecological studies to identify toxins producing microbes given the environmental conditions for harvest and milling process.

Retrival of toxins on clinical samples of urine and blood be considered as well as from implicated sago by use of bioassay, Eliza, receptor binding assays and cytotoxicity assays. Mass spectrometry base analytical technique could have determined the compounds in the contaminated sago. The study missed a golden opportunity to subject the contaminated sago to laboratories with updated molecular diagnostics to identify the compounds contained within it and lastly but not the least the prolonged length of study from 2007-2014, no different to other epidemiological study that consumed resources generously provided by resource developers operating in these remote areas of PNG for which the principal investigator appreciated and indebted to.

9.18 Recommendations

SHD had a spatial distribution and could be investigated by ecological studies towards identifying the aetiology of SHD. This can be coupled with investigating survivors

susceptibility based on red cell disease studies of membranopathy, enzymopathy, and haemoglobinopathy among communities and survivors of SHD (Valentine 1975) to highlight as part of community education on SHD. Implementing community-based interventions on the prevention of SHD can be done through alerting people to the risks of severe haemolysis based on inherent risks of poor nutrition, dehydration, anaemia, and red cell disease when exposed to contaminated sago consumption. SHD remained a clinical diagnosis that had to be considered in those that suddenly beome unconscious, sallow appearance, pale and passed red urine. Ask the relatives whether the patients consumed sago prior to the onset of illness. That will facilitate the clinical diagnosis sago toxicosis. The effects both clinical and pathophysiological were documented by this study but fell short of identifying the aetiology. This study hypothesized that the effect of exponential intravascular haemolysis fits that of preformed microbial type II toxin as a foodborne toxicosis with systemic effect in the absence of any localized disease.

There were no distinguishing characteristics evident on the contaminated sago and those that weren't. Only taste bitter so this study supported the advice provided by Dr Kath Donovan to avoid the consumption of bitter tasting sago since 1976. This study echos the same advice, a bitter taste of the cooked sago could indicate presence of hypothesized preformed toxin contamination and the meal should not be eaten. This was a tough advice to those who had food scarcity most or all the time without access to other food alternatives.

Protection against SHD required improved nutrition, normal haemoglobin levels, normal hydration status, and improved and rapid access to hospital. In malaria-endemic regions such as the lowlands, use of bed nets and rapid access to anti-malarial treatment will maintain reasonable levels of haemoglobin, and therefore assure survival for long enough that cases could reach a hospital to receive a blood transfusion to replace the erythrocytes to reverse the pathophysiological changes and correct the metabolic acidosis. Many communities still exist on the fringe or out of reach of health services operators in the region. Both the inhabitants and health service operators need government action to not only improve access to health care for disadvantaged communities but also to adopt and implement non-medical public health interventions such as increasing food production, access to clean water, and improved sanitation practices and ongoing treated bednet distribution. What other interventions could add value to the storgage of sago starch safely to be consumed over time. This would make a difference (along with value-adding activities such as producing energy for remote

communities) that would improve the health of the greater majority of the population in Papua New Guinea.

10 References

Andrade C. (2020). Sample Size and its Importance in Research. Indian journal of psychological medicine, 42(1), 102–103. https://doi.org/10.4103/IJPSYM.IJPSYM_504_19

Adrogué, H. J., & Madias, N. E. (1998). Management of Life-Threatening Acid–Base Disorders. New England Journal of Medicine, 338(1), 26–34. https://doi.org/10.1056/NEJM199801013380106

Alderman, H., & Lavy, V. (1996). Household responses to public health services: cost and quality tradeoffs. The World Bank Research Observer, 11(1), 3–22. https://doi.org/10.1093/wbro/11.1.3

Allen, B., Bourke, R. M., & Gibson, J. (2005). Poor rural places in Papua New Guinea. Asia Pacific Viewpoint, 46(2), 201–217. https://doi.org/10.1111/j.1467-8373.2005.00274.x

Alpers, M. P. (1979). Epidemiology and ecology of kuru. Slow Transmissible Diseases of the Nervous System, 1, 67–90.

Alpers, M. P. (2005). The epidemiology of kuru in the period 1987 to 1995. Communicable Diseases Intelligence, 29, 391–399.

Alpers, M. P. (2008). The epidemiology of kuru: monitoring the epidemic from its peak to its end. Philosophical Transactions of the Royal Society B: Biological Sciences, 363(1510), 3707–3713. https://doi.org/10.1098/rstb.2008.0071

Amyx, H. L., Gibbs, C. J., Gajdusek, D. C., & Greer, W. E. (1981). Absence of vertical transmission of subacute spongiform viral encephalopathies in experimental primates. Experimental Biology and Medicine, 166(4), 469–471. https://doi.org/10.3181/00379727-166-41092

Aoyama, S., & Kolff, W. J. (1957). Treatment of renal failure with the disposable artificial kidney. The American Journal of Medicine, 23(4), 565–578. https://doi.org/10.1016/0002-9343

Ashwell, H. E. S. (2008). Evaluation of a program to improve the interaction between community and health systems in Papua New Guinea: its impact on improved maternal and

child health (PhD). Charles Darwin University, Darwin. Retrieved from https://espace.cdu.edu.au/eserv/cdu:9259/Thesis_CDU_9259_Ashwell_H.pdf

Ashwell, H. E. S., & Freeman, P. (1995). The clinical competency of community health workers in the eastern highlands province of Papua New Guinea. Papua and New Guinea Medical Journal, 38(3), 198–207.

Ashwell, H. E. S., & Barclay, L. (2009). A retrospective analysis of a community-based health program in Papua New Guinea. Health Promotion International, 24(2), 140–8.

Ashwell, H. E. S., & Barclay, L. (2010). Problems measuring community health status at a local level: Papua New Guinea's health information system. Rural Remote Health, 10, 1539.

Atagazli, L., Greenhill, A. R., Melrose, W., Pue, A. G., & Warner, J. M. (2010). Is Penicillium citrinum implicated in sago hemolytic disease? Southeast Asian Journal of Tropical Medicine and Public Health, 41(3), 641.

Baird, J. K., & Surjadjaja, C. (2011). Consideration of ethics in primaquine therapy against malaria transmission. Trends in Parasitology, 27(1), 11–16. https://doi.org/10.1016/j.pt.2010.08.005

Ballif, M., Harino, P., Ley, S., Coscolla, M., Niemann, S., Carter, R., … Beck, H.-P. (2012). Drug resistance-conferring mutations in Mycobacterium tuberculosis from Madang, Papua New Guinea. BMC Microbiology, 12(1), 191. https://doi.org/10.1186/1471-2180-12-191

Barss, P., & Blackford, C. (1982). Medical emergency flights in remote areas: experience in Milne Bay Province, Papua New Guinea. Papua New Guinea Medical Journal, 26(3–4), 198–202.

Basnyat, B., & Murdoch, D. R. (2003). High-altitude illness. The Lancet, 361(9373), 1967–1974. https://doi.org/10.1016/S0140-6736

Benjamin, A. L. (2001). Community screening for diabetes in the National Capital District, Papua New Guinea: is betelnut chewing a risk factor for diabetes? Papua New Guinea Medical Journal, 44(3/4), 101–107.

Benjamin, A. L. (2007). Body size of Papua New Guineans: a comparison of the body mass index of adults in selected urban and rural areas of Papua New Guinea. Papua New Guinea Medical Journal, 50(3/4), 163–171.

Beracochea, E., Dickson, R., Freeman, P., & Thomason, J. (1995). Case management quality assessment in rural areas of Papua New Guinea. Tropical Doctor, 25(2), 69–74. https://doi.org/10.1177/004947559502500207

Beutler, E. (2002). Glucose-6-phosphate dehydrogenase. Hoboken, NJ, USA: John Wiley & Sons, Inc. Retrieved from https://doi.org/10.1002/0471203076.emm0056

Black, R. E., Allen, L. H., Bhutta, Z. A., Caulfield, L. E., de Onis, M., Ezzati, M., … Rivera, J. (2008). Maternal and child undernutrition: global and regional exposures and health consequences. The Lancet, 371(9608), 243–260. https://doi.org/10.1016/S0140-6736(07)61690-0

Botes, L., & Van Rensburg, D. (2000). Community participation in development: nine plagues and twelve commandments. Community Development Journal, 35(1), 41–58. https://doi.org/10.1093/cdj/35.1.41

Bracht, N., & Tsouros, A. (1990). Principles and strategies of effective community participation. Health Promotion International, 5(3), 199–208. https://doi.org/10.1093/heapro/5.3.199

Bradley, R., & Wilesmith, J. W. (1993). Epidemiology and control of bovine spongiform encephalopathy (Bse). British Medical Bulletin, 49(4), 932–959. https://doi.org/10.1093/oxfordjournals.bmb.a072654

Braga, A., Oliveira, M., Feliciano, G., Reiniger, I., Oliveira, J., Silva, C., & Bernardo-Filho, M. (2000). The effect of drugs on the labelling of blood elements with technetium-99m. Current Pharmaceutical Design, 6(11), 1179–1191. https://doi.org/10.2174/1381612003399897

Brownson, R. C., Fielding, J. E., & Maylahn, C. M. (2009). Evidence-based public health: a fundamental concept for public health practice. Annual Review of Public Health, 30(1), 175–201. https://doi.org/10.1146/annurev.publhealth.031308.100134

Brownson, R. C., Baker, E. A., Leet, T. L., Gillespie, K. N., & True, W. R. (2011). Evidence-Based Public Health (2nd ed.). Oxford: Oxford University Press.

Bruce, L. J., Wrong, O., Toye, A. M., Young, M. T., Ogle, G., Ismail, Z., … Tanner, M. J. A. (2000). Band 3 mutations, renal tubular acidosis and South-East Asian ovalocytosis in

Malaysia and Papua New Guinea: loss of up to 95% band 3 transport in red cells. Biochemical Journal, 350(1), 41. https://doi.org/10.1042/0264-6021:3500041

Brus, I., & Lewis, S. M. (1959). The haptoglobin content of serum in haemolytic anaemia. British Journal of Haematology, 5(4), 348–355. https://doi.org/10.1111/j.1365-2141.1959.tb04045.x

Buehler, P. W., & D'Agnillo, F. (2010). Toxicological consequences of extracellular hemoglobin: biochemical and physiological perspectives. Antioxidants & redox signaling, 12(2), 275-291.

Buor, D. (2003). Analysing the primacy of distance in the utilization of health services in the Ahafo-Ano South district, Ghana. The International Journal of Health Planning and Management, 18(4), 293–311. https://doi.org/10.1002/hpm.729

Burkot, T. R., Garner, P., Paru, R., Dagoro, H., Barnes, A., McDougall, S., … Spark, R. (1990). Effects of untreated bed nets on the transmission of Plasmodium falciparum, P. vivax and Wuchereria bancrofti in Papua New Guinea. Transactions of the Royal Society of Tropical Medicine and Hygiene, 84(6), 773–779. https://doi.org/10.1016/0035-9203(90)90073-N

Butera, R., Prockop, L. D., Buonocore, M., Locatelli, C., Gandini, C., & Manzo, L. (2000). Mild ciguatera poisoning: Case reports with neurophysiological evaluations. Muscle & Nerve, 23(10), 1598–1603. https://doi.org/10.1002/1097-4598(200010)23:10<1598::AID-MUS20>3.0.CO;2-P

Cable, G. G. (2003). In-Flight Hypoxia Incidents in Military Aircraft: Causes and Implications for Training. Aviation, Space, and Environmental Medicine, 74(2), 169–172.

Carvalho, J. J., Baruzzi, R. G., Howard, P. F., Poulter, N., Alpers, M. P., Franco, L. J., … Elliott, P. (1989). Blood pressure in four remote populations in the INTERSALT Study. Hypertension, 14(3), 238–246. https://doi.org/10.1161/01.HYP.14.3.238

Chapin, J., Terry, H. S., Kleinert, D., & Laurence, J. (2016). The role of complement activation in thrombosis and hemolytic anemias. Transfusion and Apheresis Science, 54(2), 191-198.

Charlwood, J. D., & Graves, P. M. (1987). The effect of permethrin-impregnated bednets on a population of Anopheles farauti in coastal Papua New Guinea. Medical and Veterinary Entomology, 1(3), 319–327. https://doi.org/10.1111/j.1365-2915.1987.tb00361.x

Chen, Z., Zhang, P., & Zhang, Z. (2014). Investigation and analysis of 102 mushroom poisoning cases in Southern China from 1994 to 2012. Fungal Diversity, 64(1), 123–131. https://doi.org/10.1007/s13225-013-0260-7

Chiasson, J.-L., Aris-Jilwan, N., Bélanger, R., Bertrand, S., Beauregard, H., Ekoé, J.-M., … Havrankova, J. (2003). Diagnosis and treatment of diabetic ketoacidosis and the hyperglycaemic hyperosmolar state. Canadian Medical Association Journal, 168(7), 859–866.

Chockkalingam, K., Board, P. G., & Nurse, G. T. (1982). Glucose-6-phosphate dehydrogenase deficiency in Papua New Guinea: The description of 13 new variants. Human Genetics, 60(2), 189–192. https://doi.org/10.1007/BF00569710

Chow, K.-M., Mac-Moune Lai, F., Yee-Moon Wang, A., Chan, Y.-L., Tang, N. L.-S., & Li, P. K.-T. (2001). Reversible renal failure in paroxysmal nocturnal hemoglobinuria. American Journal of Kidney Diseases, 37(2), e17.1–e17.6. https://doi.org/10.1053/ajkd.2001.21361

Chowdhury, F. S., Biswas, J., Siddiqui, M. A. E., Hoque, M. M., & Adnan, S. K. (2008). Transfusion reaction among the blood recipient-A study of 120 cases. Journal of Dhaka Medical College, 17(2), 67-71

Christensen, B., Sackmann-Sala, L., Cruz-Topete, D., Jørgensen, J. O. L., Jessen, N., Lundby, C., & Kopchick, J. J. (2011). Novel serum biomarkers for erythropoietin use in humans: a proteomic approach. Journal of Applied Physiology, 110(1), 149–156. https://doi.org/10.1152/japplphysiol.00665.2010

Chugh, K. S., Singhal, P. C., Sharma, B. K., Mahakur, A. C., Pal, Y., Datta, B. N., & Das, K. C. (1977). Acute renal failure due to intravascular haemolysis in the North Indian patients: The American Journal of the Medical Sciences, 274(2), 139–146. https://doi.org/10.1097/00000441-197709000-00004

Clem, K. J., & Green, S. M. (1996). Emergency medicine expeditions to the developing world: the Loma Linda Iniversity experience in Papua New Guinea. Academic Emergency Medicine, 3(6), 624–633. https://doi.org/10.1111/j.1553-2712.1996.tb03473.x

Cole, J. B. (Ed.). (1988). Anthropology for the nineties: introductory readings. New York : London: Free Press ; Collier Macmillan.

Collinge, J., Whitfield, J., McKintosh, E., Beck, J., Mead, S., Thomas, D. J., & Alpers, M. P. (2006). Kuru in the 21st century—an acquired human prion disease with very long incubation periods. The Lancet, 367(9528), 2068–2074. https://doi.org/10.1016/S0140-6736(06)68930-7

Collinge, J., Whitfield, J., McKintosh, E., Frosh, A., Mead, S., Hill, A. F., … Alpers, M. P. (2008). A clinical study of kuru patients with long incubation periods at the end of the epidemic in Papua New Guinea. Philosophical Transactions of the Royal Society B: Biological Sciences, 363(1510), 3725–3739. https://doi.org/10.1098/rstb.2008.0068

Connell, J. (1997). Health in Papua New Guinea: a decline in development. Australian Geographical Studies, 35(3), 271–293. https://doi.org/10.1111/1467-8470.00027

Connell, J. (2005). Papua New Guinea: the struggle for development. London: Taylor & Francis e-Library. Retrieved from http://public.eblib.com/choice/publicfullrecord.aspx?p=237422

Connell, J. & Hamnett, M. P. (1978). Famine or feast: sago production in Bougainville. Journal of the Polynesian Society, 87(3), 231–241.

Coote, A. (2004). Prevention rather than cure. Making the case for choosing health. London: King's Fund Publications.

Currie, C. S. M., Williams, B. G., Cheng, R. C. H., & Dye, C. (2003). Tuberculosis epidemics driven by HIV: is prevention better than cure? AIDS, 17(17), 2501–2508. https://doi.org/10.1097/00002030-200311210-00013

O'Keefe, J. H., & Curtis, B. M. (2002). Autonomic tone and benefits of cardiac rehabilitation programs: in response. Mayo Clinic Proceedings, 77(4), 399. https://doi.org/10.4065/77.4.399

Day, N. P. J., Phu, N. H., Mai, N. T. H., Chau, T. T. H., Loc, P. P., Van Chuong, L., … White, N. J. (2000). The pathophysiologic and prognostic significance of acidosis in severe adult malaria: Critical Care Medicine, 28(6), 1833–1840. https://doi.org/10.1097/00003246-200006000-00025

Dhaliwal, G., Cornett, P. A., & Tierney, L. M. (2004). Haemolytic anaemia. American Family Physician, 69(11), 2599–2606.

Dierick, K., Van Coillie, E., Swiecicka, I., Meyfroidt, G., Devlieger, H., Meulemans, A., … Mahillon, J. (2005). Fatal family outbreak of bacillus cereus-associated food poisoning. Journal of Clinical Microbiology, 43(8), 4277–4279. https://doi.org/10.1128/JCM.43.8.4277-4279.2005

Diggs, L. W. (1967). Bone and joint lesions in sickle-cell disease. Clinical Orthopaedics and Related Research, 52, 119–144. https://doi.org/10.1097/00003086-196705000-00011

DNPM. (2016). Millennium Development Goals 2015. Summary Report for Papua New Guinea. Port Moresby: Department of National Planning and Monitoring.

Doerner, K., Focke, A., & Gutjahr, W. J. (2007). Multicriteria tour planning for mobile healthcare facilities in a developing country. European Journal of Operational Research, 179(3), 1078–1096. https://doi.org/10.1016/j.ejor.2005.10.067

Donovan, K., Shaw, D., & Amato, D. (1976). Sago and haemolysis. Papua and New Guinea Medical Journal, 19(3), 183–184.

Donovan, K., Shaw, D., & Amato, D. (1977). Sago haemolysis: clinical features and microbiological studies. Papua and New Guinea Medical Journal, 20(4), 167–174.

Dossetor, J. B. (1966). Creatininemia versus uraemia: the relative significance of blood urea nitrogen and serum creatinine concentrations in azotemia. Annals of Internal Medicine, 65(6), 1287–1299. https://doi.org/10.7326/0003-4819-65-6-1287

Duke, T. (1999). Decline in child health in rural Papua New Guinea. The Lancet, 354(9186), 1291–1294. https://doi.org/10.1016/S0140-6736(99)00335-9

Duke, T., Michael, A., Mgone, J., Frank, D., Wal, T., & Sehuko, R. (2002). Etiology of child mortality in Goroka, Papua New Guinea: a prospective two-year study. Bulletin of the World Health Organization, 80(1), 16–25.

Duplain, H., Vollenweider, L., Delabays, A., Nicod, P., Bärtsch, P., & Scherrer, U. (1999). Augmented sympathetic activation during short-term hypoxia and high-altitude exposure in subjects susceptible to high-altitude pulmonary edema. Circulation, 99(13), 1713–1718.

Eckardt, K. U., Boutellier, U., Kurtz, A., Schopen, M., Koller, E. A., & Bauer, C. (1989). Rate of erythropoietin formation in humans in response to acute hypobaric hypoxia. Journal of Applied Physiology, 66(4), 1785–1788. https://doi.org/10.1152/jappl.1989.66.4.1785

Erecińska, M., & Silver, I. A. (2001). Tissue oxygen tension and brain sensitivity to hypoxia. Respiration Physiology, 128(3), 263–276. https://doi.org/10.1016/S0034-5687(01)00306-1

Fasano, M., Curry, S., Terreno, E., Galliano, M., Fanali, G., Narciso, P., … Ascenzi, P. (2005). The extraordinary ligand binding properties of human serum albumin. IUBMB Life (International Union of Biochemistry and Molecular Biology: Life), 57(12), 787–796. https://doi.org/10.1080/15216540500404093

Feachem, R. (1986). Prevention better than cure. World Health, 1986(April), 18–19.

Feeny, S. (2003). The impact of foreign aid on poverty and human well-being in Papua New Guinea. Asia Pacific Development Journal, 10(2), 73–93.

Feest, T. G., Round, A., & Hamad, S. (1993). Incidence of severe acute renal failure in adults: results of a community based study. BMJ, 306(6876), 481–483. https://doi.org/10.1136/bmj.306.6876.481

Feikin, D. R., Nguyen, L. M., Adazu, K., Ombok, M., Audi, A., Slutsker, L., & Lindblade, K. A. (2009). The impact of distance of residence from a peripheral health facility on paediatric health utilisation in rural western Kenya. Tropical Medicine & International Health, 14(1), 54–61. https://doi.org/10.1111/j.1365-3156.2008.02193.x

Fenves, A. Z., & Emmett, M. (2021). Approach to patients with high anion gap metabolic acidosis: core curriculum 2021. American Journal of Kidney Diseases, 78(4), 590-600.

Ferretti, G. (2001). Extreme human breath-hold diving. European Journal of Applied Physiology, 84(4), 254–271. https://doi.org/10.1007/s004210000377

Finch, C. A., & Lenfant, C. (1972). Oxygen transport in man. New England Journal of Medicine, 286(8), 407–415. https://doi.org/10.1056/NEJM197202242860806

Fisher, A. V., & Helps, C. R. (2005). Removal of the spinal cord from carcasses. In J. N. Sofos (Ed.), Improving the safety of fresh meat (pp. 303–317). Cambridge: Woodhead Publishing Limited.

Fishman, A. P. (1976). Hypoxia on the pulmonary circulation. How and where it acts. Circulation Research, 38(4), 221–231. https://doi.org/10.1161/01.RES.38.4.221

Fitz-Clarke, J. R. (2006). Adverse events in competitive breath-hold diving. Undersea & Hyperbaric Medicine, 33(1), 55–62.

Flew, S. (1999). Human health, nutrition and heavy metals. Report of a survey from the Fly River, Western Province, Papua New Guinea, June 1998. Tabubil: Ok Tedi Mining Limited.

Forrester, L. J., Barrett, J. T., & Campbell, B. J. (1978). Red blood cell lysis induced by the venom of the brown recluse spider. Archives of Biochemistry and Biophysics, 187(2), 355–365. https://doi.org/10.1016/0003-9861(78)90046-2

Forse, R., & Shizgal, H. (1980). Serum albumin and nutritional status. Journal of Parenteral and Enteral Nutrition, 4(5), 450–454. https://doi.org/10.1177/0148607180004005450

Foucher CD, Tubben RE. Lactic Acidosis. [Updated 2023 Jul 17]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK470202/

Freedman, J. (2015). Autoimmune haemolysis: a journey through time. Transfusion Medicine and Hemotherapy, 42(5), 278–285. https://doi.org/10.1159/000437195

Frenette, C., MacLean, J. D., & Gyorkos, T. W. (1988). A large common-source outbreak of ciguatera fish poisoning. Journal of Infectious Diseases, 158(5), 1128–1131. https://doi.org/10.1093/infdis/158.5.1128

Gajdusek, D. C., & Zigas, V. (1959). Kuru: Clinical, pathological, and epidemiological study of an acute progressive degenerative disease of the central nervous system among natives of the Eastern Highlands of New Guinea. The American Journal of Medicine, 26(3), 442–469. https://doi.org/10.1016/0002-9343(59)90251-7

Galanello, R., & Origa, R. (2010). Beta-thalassemia. Orphanet Journal of Rare Diseases, 5(1), 11. https://doi.org/10.1186/1750-1172-5-11

Ganczakowski, M., Town, M., Bowden, D. K., Vulliamy, T. J., Kaneko, A., Clegg, J. B., … Luzzatto, L. (1995). Multiple glucose 6-phosphate dehydrogenase-deficient variants correlate with malaria endemicity in the Vanuatu archipelago (Southwestern Pacific). American Journal of Human Genetics, 56(1), 294–301.

Gatchell, V., Forsythe, V., & Thomas, P.-R. (2006). The sustainability of community-based therapeutic care (CTC) in nonemergency contexts. Food and Nutrition Bulletin, 27(3_suppl3), S90–S98. https://doi.org/10.1177/15648265060273S306

Ge, R.-L., Witkowski, S., Zhang, Y., Alfrey, C., Sivieri, M., Karlsen, T., … Levine, B. D. (2002). Determinants of erythropoietin release in response to short-term hypobaric hypoxia. Journal of Applied Physiology, 92(6), 2361–2367. https://doi.org/10.1152/japplphysiol.00684.2001

Gera, T. (2010). Efficacy and safety of therapeutic nutrition products for home based therapeutic nutrition for severe acute malnutrition: A systematic review. Indian Pediatrics, 47(8), 709–718. https://doi.org/10.1007/s13312-010-0095-1

Gerrah, R., Shargal, Y., & Elami, A. (2003). Impaired oxygenation and increased hemolysis after cardiopulmonary bypass in patients with glucose-6-phosphate dehydrogenase deficiency. The Annals of Thoracic Surgery, 76(2), 523–527. https://doi.org/10.1016/S0003-4975(03)00351-5

Gibly, R. L., Walter, F. G., Nowlin, S. W., & Berg, R. A. (1998). Intravascular hemolysis associated with North American crotalid envenomation. Journal of Toxicology: Clinical Toxicology, 36(4), 337–343. https://doi.org/10.3109/15563659809028030

Gibson, J., & Rozelle, S. (2002). Poverty and access to infrastructure in Papua New Guinea. SSRN Electronic Journal. https://doi.org/10.2139/ssrn.334140

Gibson, J., & Rozelle, S. (2003). Poverty and access to roads in Papua New Guinea. Economic Development and Cultural Change, 52(1), 159–185. https://doi.org/10.1086/380424

Gillett, J. E. (1990). The health of women in Papua New Guinea. Goroka: Papua New Guinea Institute of Medical Research.

Gilpin, C. M., Simpson, G., Vincent, S., O'Brien, T. P., Knight, T. A., Globan, M., … Konstantinos, A. (2008). Evidence of primary transmission of multidrug-resistant tuberculosis in the Western Province of Papua New Guinea. The Medical Journal of Australia, 188(3), 148–152.

Gilson, L., Sen, P. D., Mohammed, S., & Mujinja, P. (1994). The potential of health sector non-governmental organizations: policy options. Health Policy and Planning, 9(1), 14–24. https://doi.org/10.1093/heapol/9.1.14

Ginsburg, A. S., Salazar, L. G., True, L. D., & Disis, M. L. (2003). Fatal Bacillus cereus sepsis following resolving neutropenic enterocolitis during the treatment of acute leukemia. American Journal of Hematology, 72(3), 204–208. https://doi.org/10.1002/ajh.10272

Gnaiger, E., Steinlechner-Maran, R., Méndez, G., Eberl, T., & Margreiter, R. (1995). Control of mitochondrial and cellular respiration by oxygen. Journal of Bioenergetics and Biomembranes, 27(6), 583–596. https://doi.org/10.1007/BF02111656

Goetze, O., Schmitt, J., Spliethoff, K., Theurl, I., Weiss, G., Swinkels, D. W., … Geier, A. (2013). Adaptation of iron transport and metabolism to acute high-altitude hypoxia in mountaineers. Hepatology, 58(6), 2153–2162. https://doi.org/10.1002/hep.26581

Goldwater, P. N., & Bettelheim, K. A. (2012). Treatment of enterohemorrhagic Escherichia coli (EHEC) infection and hemolytic uremic syndrome (HUS). BMC medicine, 10, 1-8.

Goodkin, D. A., Krishna, G. G., & Narins, R. G. (1984). The role of the anion gap in detecting and managing mixed metabolic acid-base disorders. Clinics in Endocrinology and Metabolism, 13(2), 333-349.

Goligorsky, M. S. (2001). The concept of cellular “fight-or-flight” reaction to stress. American Journal of Physiology-Renal Physiology, 280(4), F551–F561. https://doi.org/10.1152/ajprenal.2001.280.4.F551

Gomella, L. G., & Haist, S. A. (2007). Clinician’s pocket reference (11th ed.). New York, N.Y.: McGraw-Hill Education LLC.

Gonzalez-Escobedo, G., Marshall, J. M., & Gunn, J. S. (2011). Chronic and acute infection of the gall bladder by Salmonella Typhi: understanding the carrier state. Nature Reviews Microbiology, 9(1), 9–14. https://doi.org/10.1038/nrmicro2490

Greenberg, M. S. (1976). Heinz body hemolytic anemia: ‘bite cells’—a clue to diagnosis. Archives of Internal Medicine, 136(2), 153. https://doi.org/10.1001/archinte.1976.03630020015004

Greenhill, A., Blaney, B., Shipton, W., Pue, A., Fletcher, M., & Amoa, B. (2006). Mycotoxicology of sago haemolytic disease in Papua New Guinea. Presented at the Australia-Europe Symposium on Mycotoxins and Food Safety, 15-17 February 2006, Sydney, NSW.

Greenhill, A. R., Shipton, W. A., Blaney, B. J., Amoa, B., Kopel, E., Pelowa, D., … Warner, J. M. (2010). Hazards and critical control points for traditional sago starch production in Papua New Guinea: Implications for food safety education. Food Control, 21(5), 657–662. https://doi.org/10.1016/j.foodcont.2009.10.003

Greenhill, A. R., Shipton, W. A., Blaney, B. J., Brock, I. J., Kupz, A., & Warner, J. M. (2009). Spontaneous fermentation of traditional sago starch in Papua New Guinea. Food Microbiology, 26(2), 136–141. https://doi.org/10.1016/j.fm.2008.10.004

Greenhill, A. R., Shipton, W. A., Blaney, B. J., & Warner, J. M. (2007). Fungal colonization of sago starch in Papua New Guinea. International Journal of Food Microbiology, 119(3), 284–290. https://doi.org/10.1016/j.ijfoodmicro.2007.08.007

Greenhill, A, Shipton, W, Blaney, B, Warner, J, Pue, A & Amoa, B 2005a, 'Sago Haemolytic Disease-Is it a mycotoxicosis?', in 41st Papua New Guinea Medical Symposium.

Greenhill, A, Shipton, W, Blaney, B, Warner, J, Pue, A & Amoa, B 2005b, 'Sago Haemolytic Disease in Papua New Guinea', in 41st Papua New Guinea Medical Symposium.

Greenhill, A. R., Shipton, W. A., Omoloso, A. D., Amoa, B., & Warner, J. M. (2007). Bacterial contamination of sago starch in Papua New Guinea. Journal of Food Protection, 70(12), 2868–2872. https://doi.org/10.4315/0362-028X-70.12.2868

Greenhill, A. R., Shipton, W. A., Omoloso, A. D., Amoa, B., & Warner, J. M. (2007). Bacterial contamination of sago starch in Papua New Guinea. Journal of Food Protection, 70(12), 2868–2872. https://doi.org/10.4315/0362-028X-70.12.2868

Greenhill, A. R. (2006). Food safety and security of sago starch in rural Papua New Guinea (PhD). James Cook University, Townsville. Retrieved from https://researchonline.jcu.edu.au/2023/

Greenhill, A. R., Blaney, B. J., Shipton, W. A., Pue, A., Fletcher, M. T., & Warner, J. M. (2010). Haemolytic fungi isolated from sago starch in Papua New Guinea. Mycopathologia, 169(2), 107–115.

Grygorczyk, R., & Orlov, S. N. (2017). Effects of hypoxia on erythrocyte membrane properties—Implications for intravascular hemolysis and purinergic control of blood flow. Frontiers in physiology, 8, 1110.

Hadlow, W. J. (1995). Neuropathology and the Scrapie-Kuru connection. Brain Pathology, 5(1), 27–31. https://doi.org/10.1111/j.1750-3639.1995.tb00574.x

Hadlow, W. J. (2008a). Kuru likened to scrapie: The story remembered. Philosophical Transactions of the Royal Society B: Biological Sciences, 363(1510), 3644–3644. https://doi.org/10.1098/rstb.2008.4013

Haidar, R., Musallam, K. M., & Taher, A. T. (2011). Bone disease and skeletal complications in patients with β thalassemia major. Bone, 48(3), 425–432. https://doi.org/10.1016/j.bone.2010.10.173

Hall, J. E., & Guyton, A. C. (2011). Guyton and Hall textbook of medical physiology (Vol. 26). Philadelphia, PA: Saunders Elsevier. Retrieved from http://www.clinicalkey.com/dura/browse/bookChapter/3-s2.0-C20090602506

Haywood, A. M. (1997). Transmissible spongiform encephalopathies. New England Journal of Medicine, 337(25), 1821–1828. https://doi.org/10.1056/NEJM199712183372508

United States (Ed.). (1990). Healthy people 2000: National Health Promotion and Disease Prevention Objectives: Full report, with commentary (Vol. 25). Boston: Jones and Bartlett. Retrieved from https://journals.lww.com/nutritiontodayonline/Abstract/1990/11000/Healthy_People_2000__National_Health_Promotion_and.7.aspx

Hecker, P. A., Lionetti, V., Ribeiro, R. F., Rastogi, S., Brown, B. H., O'Connell, K. A., … Stanley, W. C. (2013). Glucose 6-phosphate dehydrogenase deficiency increases redox stress and moderately accelerates the development of heart failure. Circulation: Heart Failure, 6(1), 118–126. https://doi.org/10.1161/CIRCHEARTFAILURE.112.969576

Henderson, L. N., & Tulloch, J. (2008). Incentives for retaining and motivating health workers in Pacific and Asian countries. Human Resources for Health, 6(1), 18. https://doi.org/10.1186/1478-4491-6-18

Herrmann, F. R., Safran, C., Levkoff, S. E., & Minaker, K. L. (1992). Serum albumin level on admission as a predictor of death, length of stay, and readmission. Archives of Internal Medicine, 152(1), 125–130. https://doi.org/10.1001/archinte.1992.00400130135017

Hii, J., Dyke, T., Dagoro, H., & Sanders, R. C. (1997). Health impact assessments of malaria and Ross River virus infection in the Southern Highlands Province of Papua New Guinea. Papua New Guinea Medical Journal, 40(1), 14–25.

Hii, J. L. K., Smith, T., Vounatsou, P., Alexander, N., Mai, A., Ibam, E., & Alpers, M. P. (2001). Area effects of bednet use in a malaria-endemic area in Papua New Guinea. Transactions of the Royal Society of Tropical Medicine and Hygiene, 95(1), 7–13. https://doi.org/10.1016/S0035-9203(01)90315-3

Hongo, T., Ohtsuka, R., Inaoka, T., Kawabe, T., Akimichi, T., Kuchikura, Y., … Suzuki, T. (1994). Health status comparison by urinalysis (Dipstick test) among four populations in papua new guinea. Asia Pacific Journal of Public Health, 7(3), 165–172. https://doi.org/10.1177/101053959400700304

Hongoro, C., & McPake, B. (2004). How to bridge the gap in human resources for health. The Lancet, 364(9443), 1451–1456. https://doi.org/10.1016/S0140-6736(04)17229-2

Hopp, R. J. (2020). Hypersensitivity reactions: an everyday occurrence in pediatric allergy clinics. Pediatric Allergy, Immunology, and Pulmonology, 33(1), 12-18.

Hornbein, T. F., Townes, B. D., Schoene, R. B., Sutton, J. R., & Houston, C. S. (1989). The cost to the central nervous system of climbing to extremely high altitude. New England Journal of Medicine, 321(25), 1714–1719. https://doi.org/10.1056/NEJM198912213212505

Horwich, T. B., Kalantar-Zadeh, K., MacLellan, R. W., & Fonarow, G. C. (2008). Albumin levels predict survival in patients with systolic heart failure. American Heart Journal, 155(5), 883–889. https://doi.org/10.1016/j.ahj.2007.11.043

Hyndman, D. (1994). A sacred mountain of gold: The creation of a mining resource frontier in Papua New Guinea ∗. The Journal of Pacific History, 29(2), 203–221. https://doi.org/10.1080/00223349408572772

Idro, R., Jenkins, N. E., & Newton, C. R. (2005). Pathogenesis, clinical features, and neurological outcome of cerebral malaria. The Lancet Neurology, 4(12), 827–840. https://doi.org/10.1016/S1474-4422(05)70247-7Igisu, H. (1993). Haemolysis of human

erythrocytes by pentachlorophenol and its suppression by albumin. British journal of industrial medicine, 50(4), 378.

Imbun, B. Y. (2007). 'Cannot manage without the significant other': Mining, corporate social responsibility and local communities in Papua New Guinea. Journal of Business Ethics, 73(2), 177–192. https://doi.org/10.1007/s10551-006-9189-z

Ireland, N 2003. 'Bovine spongiform encephalopathy'.

Jackson, R. (1979). Running down the up-escalator: regional inequality in Papua New Guinea. Australian Geographer, 14(3), 175–184. https://doi.org/10.1080/00049187908702759

Jain, A., & Mondal, R. (2008). Extensively drug-resistant tuberculosis: current challenges and threats. FEMS Immunology & Medical Microbiology, 53(2), 145–150. https://doi.org/10.1111/j.1574-695X.2008.00400.x

Jansen, G. F. A., Kagenaar, D. A., Basnyat, B., & Odoom, J. A. (2002). Basilar artery blood flow velocity and the ventilatory response to acute hypoxia in mountaineers. Respiratory Physiology & Neurobiology, 133(1–2), 65–74. https://doi.org/10.1016/S1569-9048(02)00152-0

Jarolim, P., Palek, J., Amato, D., Hassan, K., Sapak, P., Nurse, G. T., … Liu, S. C. (1991). Deletion in erythrocyte band 3 gene in malaria-resistant Southeast Asian ovalocytosis. Proceedings of the National Academy of Sciences, 88(24), 11022–11026. https://doi.org/10.1073/pnas.88.24.11022

Jelkmann, W., & Metzen, E. (1996). Erythropoietin in the control of red cell production. Annals of Anatomy - Anatomischer Anzeiger, 178(5), 391–403. https://doi.org/10.1016/S0940-9602(96)80124-5

Johnson, D. (1971). Maternal mortality in Papua New Guinea. Papua New Guinea Medical Jounal, 14(4), 133–135.

Johnson, R. T., & Gibbs, C. J. (1998). Creutzfeldt–jakob disease and related transmissible spongiform encephalopathies. New England Journal of Medicine, 339(27), 1994–2004. https://doi.org/10.1056/NEJM199812313392707

Kato, G. J. (2006). Lactate dehydrogenase as a biomarker of hemolysis-associated nitric oxide resistance, priapism, leg ulceration, pulmonary hypertension, and death in patients with sickle cell disease. Blood, 107(6), 2279–2285. https://doi.org/10.1182/blood-2005-06-2373

Kato, G. J., McGovan, V., Machado, R. F., Little, J. A., Morris, C. R., Nichols, J. S., … Morris, S. M. (2006). Lactate dehydrogenase as a biomarker of hemolysis-associated nitric oxide resistance, priapism, leg ulceration, pulmonary hypertension, and death in patients with sickle cell disease. Blood, 107(6), 2279–2285. https://doi.org/10.1182/blood-2005-06-2373

Kato, G. J., & Taylor, J. G. (2010). Pleiotropic effects of intravascular haemolysis on vascular homeostasis. British Journal of Haematology, 148(5), 690–701. https://doi.org/10.1111/j.1365-2141.2009.08004.x

Kelman, G. R. (1969). Cardiac output in shock: International Anesthesiology Clinics, 7(4), 739–758. https://doi.org/10.1097/00004311-196907040-00003

Kim, S., Nguon, C., Guillard, B., Duong, S., Chy, S., Sum, S., … Menard, D. (2011). Performance of the carestartTM g6pd deficiency screening test, a point-of-care diagnostic for primaquine therapy screening. PLoS ONE, 6(12), e28357. https://doi.org/10.1371/journal.pone.0028357

Kim, S., Lee, S., Ahn, S., Park, J., Moon, S., Cho, H., & Choi, S. H. (2024). The prognostic utility of Lactate/Albumin*Age score in septic patient with normal lactate level. Heliyon, 10(17), e37056. https://doi.org/10.1016/j.heliyon.2024.e37056

Kitabchi, A. E., Umpierrez, G. E., Miles, J. M., & Fisher, J. N. (2009). Hyperglycemic crises in adult patients with diabetes. Diabetes Care, 32(7), 1335–1343. https://doi.org/10.2337/dc09-9032

Klahr, S., & Miller, S. B. (1998). Acute oliguria. New England Journal of Medicine, 338(10), 671–675. https://doi.org/10.1056/NEJM199803053381007

Koffler, A., Friedler, R. M., & Massry, S. G. (1976). Acute renal failure due to nontraumatic rhabdomyolysis. Annals of Internal Medicine, 85(1), 23. https://doi.org/10.7326/0003-4819-85-1-23

Riitta-Liisa, & Kolehmainen-Aitken. (1992). The impact of decentralization on health workforce development in Papua New Guinea. Public Administration and Development, 12(2), 175–191. https://doi.org/10.1002/pad.4230120205

Kormoczi, G. F., Saemann, M. D., Buchta, C., Peck-Radosavljevic, M., Mayr, W. R., Schwartz, D. W. M., … Panzer, S. (2006). Influence of clinical factors on the haemolysis marker haptoglobin. European Journal of Clinical Investigation, 36(3), 202–209. https://doi.org/10.1111/j.1365-2362.2006.01617.x

Kratz, A., Lewandrowski, K. B., Siegel, A. J., Chun, K. Y., Flood, J. G., Van Cott, E. M., & Lee-Lewandrowski, E. (2002). Effect of marathon running on hematologic and biochemical laboratory parameters, including cardiac markers. American Journal of Clinical Pathology, 118(6), 856–863. https://doi.org/10.1309/14TY-2TDJ-1X0Y-1V6V

Kraut, J. A., & Madias, N. E. (2010). Metabolic acidosis: pathophysiology, diagnosis and management. Nature Reviews Nephrology, 6(5), 274–285. https://doi.org/10.1038/nrneph.2010.33

Kraut, J. A., & Xing, S. X. (2011). Approach to the evaluation of a patient with an increased serum osmolal gap and high-anion-gap metabolic acidosis. American journal of kidney diseases, 58(3), 480-484.

Kumar, R., Mcgeown, M., & Hill, C. (1973). Acute renal failure in the elderly. The Lancet, 301(7794), 90–91. https://doi.org/10.1016/S0140-6736(73)90480-7

Kupesiz, A., Celmeli, G., Dogan, S., Antmen, B., & Aslan, M. (2012). The effect of hemolysis on plasma oxidation and nitration in patients with sickle cell disease. Free Radical Research, 46(7), 883–890. https://doi.org/10.3109/10715762.2012.686037

Kyle, U., Pirlich, M., Schuetz, T., Lochs, H., & Pichard, C. (2004). Is nutritional depletion by Nutritional Risk Index associated with increased length of hospital stay? A population-based study. Journal of Parenteral and Enteral Nutrition, 28(2), 99–104. https://doi.org/10.1177/014860710402800299

Lalloo, D. G., Trevett, A. J., Black, J., Mapao, J., Saweri, A., Naraqi, S., … Warrell, D. A. (1996). Neurotoxicity, anticoagulant activity and evidence of rhabdomyolysis in patients bitten by death adders (Acanthophis sp.) in southern Papua New Guinea. QJM, 89(1), 25–35. https://doi.org/10.1093/oxfordjournals.qjmed.a030134

Laugier, S., Kuberski, T., & Bagnis, R. (1979). Clinical observations on 3,009 cases of Ciguatera (fish poisoning) in the South Pacific. The American Journal of Tropical Medicine and Hygiene, 28(6), 1067–1073. https://doi.org/10.4269/ajtmh.1979.28.1067

Lawrence, G. (1979). The pathogenesis of pig-bel in Papua New Guinea. PNG Medical Journal, 22(1), 39.

Lawrence, G., & Cooke, R. (1980). Experimental pigbel: the production and pathology of necrotizing enteritis due to Clostridium welchii type C in the guinea-pig. British Journal of Experimental Pathology, 61(3), 261.

Lawrence, G. W., Lehmann, D., Anian, G., Coakley, C. A., Saleu, G., Barker, M. J., & Davis, M. W. (1990). Impact of active immunisation against enteritis necroticans in Papua New Guinea. The Lancet, 336(8724), 1165–1167. https://doi.org/10.1016/0140-6736(90)92776-E

Lawrence, G., & Walker, P. D. (1976). Pathogenesis of enteritis necroticans in papua new guinea. The Lancet, 307(7951), 125–126. https://doi.org/10.1016/S0140-6736(76)93160-3

Leach, R. M. (2002). The pulmonary physician in critical care 2: Oxygen delivery and consumption in the critically ill. Thorax, 57(2), 170–177. https://doi.org/10.1136/thorax.57.2.170

Lee, R. E. J., Golding, J. S. R., & Serjeant, G. R. (1981). The radiological features of avascular necrosis of the femoral head in homozygous sickle cell disease. Clinical Radiology, 32(2), 205–214. https://doi.org/10.1016/S0009-9260(81)80162-6

Levantis, T., & Jowitt, A. (2009). Papua New Guinea: Employment, wages and economic development. Journal of South Pacific Law, 5, 2001.

Levine, M. M., Black, R. E., & Lanata, C. (1982). Precise estimation of the numbers of chronic carriers of salmonella typhi in santiago, chile, an endemic area. The Journal of Infectious Diseases, 146(6), 724–726. https://doi.org/10.1093/infdis/146.6.724

Lim, S. (2007). Metabolic acidosis. Acta Medica Indonesiana, 39(3), 145-150.

Lindenbaum, S. (2008). Understanding kuru: the contribution of anthropology and medicine. Philosophical Transactions of the Royal Society B: Biological Sciences, 363(1510), 3715–3720. https://doi.org/10.1098/rstb.2008.0072

Lindebaum, S. (2009). Cannibalism, kuru and anthropology. Folia Neuropathol, 47(2), 138–144.

Lindholm, P., & Lundgren, C. E. (2009). The physiology and pathophysiology of human breath-hold diving. Journal of Applied Physiology, 106(1), 284–292. https://doi.org/10.1152/japplphysiol.90991.2008

Loeppky, J. A., Luft, U. C., & Fletcher, E. R. (1983). Quantitative description of whole blood CO2 dissociation curve and Haldane effect. Respiration Physiology, 51(2), 167–181. https://doi.org/10.1016/0034-5687(83)90038-5

Lohmann, R. I. (2005). The afterlife of asabano corpses: relationships with the deceased in papua new guinea. Ethnology, 44(2), 189. https://doi.org/10.2307/3773996

Lourie, J. A., Taufa, T., Cattani, J., & Anderson, W. (1986). The Ok Tedi health and nutrition project, Papua New Guinea: Physique, growth and nutritional status of the Wopkaimin of the Star mountains. Annals of Human Biology, 13(6), 517–536. https://doi.org/10.1080/03014468600008701

Maddocks, I., & Rovin, L. (1965). A New Guinea population in which blood pressure appears to fall as age advances. PNG Medical Journal, 48(1–2), 122.

Maegele, M., Gregor, S., Steinhausen, E., Bouillon, B., Heiss, M. M., Perbix, W., … Schwarz, R. (2005). The long-distance tertiary air transfer and care of tsunami victims: Injury pattern and microbiological and psychological aspects*: Critical Care Medicine, 33(5), 1136–1140. https://doi.org/10.1097/01.CCM.0000163269.42524.50

Malone, P. C., & Agutter, P. S. (2008). The aetiology of deep venous thrombosis: a critical, historical and epistemological survey. Dordrecht: Springer.

McLellan, S. A., McClelland, D. B. L., & Walsh, T. S. (2003). Anaemia and red blood cell transfusion in the critically ill patient. Blood Reviews, 17(4), 195–208. https://doi.org/10.1016/S0268-960X(03)00018-3

McLellan, S. A., & Walsh, T. S. (2004). Oxygen delivery and haemoglobin. Continuing Education in Anaesthesia Critical Care & Pain, 4(4), 123–126. https://doi.org/10.1093/bjaceaccp/mkh033

Mehta, A. B. (1994). Glucose-6-phosphate dehydrogenase deficiency. Postgraduate Medical Journal, 70(830), 871.

Meunier, B. C., Camus, C. M., Houssin, D. P., Messner, M. J. M., Gerault, A. M., & Launois, B. G. (1995). Liver transplantation after severe poisoning due to amatoxin-containing lepiota - report of three cases. Journal of Toxicology: Clinical Toxicology, 33(2), 165–171. https://doi.org/10.3109/15563659509000468

Mola, G., & Aitken, I. (1984). Maternal mortality in Papua New Guinea. Papua New Guinea Medical Journal, 27(2), 65.

Morris, C. G., & Low, J. (2008). Metabolic acidosis in the critically ill: Part 2. Causes and treatment. Anaesthesia, 63(4), 396–411. https://doi.org/10.1111/j.1365-2044.2007.05371.x

Moser, C. O. N. (1989). Community participation in urban projects in the Third World. Progress in Planning, 32, 71–133. https://doi.org/10.1016/0305-9006(89)90010-X

Mueller, I., Taime, J., Ivivi, R., Yala, S., Bjorge, S., Riley, I. D., & Reeder, J. C. (2003). The epidemiology of malaria in the Papua New Guinea highlands: 1. Western Highlands Province. PNG Medical Journal, 46(1–2), 16.

Mueller, I., Yala, S., Ousari, M., Kundi, J., Ivivi, R., Sareu, G., … Reeder, J. C. (2007). The epidemiology of malaria in the Papua New Guinea highlands: 6. Simbai and Bundi, Madang Province. PNG Medical Journal, 50(3–4), 123.

Müller, I., Bockarie, M., Alpers, M., & Smith, T. (2003). The epidemiology of malaria in Papua New Guinea. Trends in Parasitology, 19(6), 253–259. https://doi.org/10.1016/S1471-4922(03)00091-6

Muller, I., Smith, T., Mellor, S., Rare, L., & Genton, B. (1998). The effect of distance from home on attendance at a small rural health centre in Papua New Guinea. International Journal of Epidemiology, 27(5), 878–884. https://doi.org/10.1093/ije/27.5.878

Murrell, T. G. (1982). Enteritis necroticans (Pigbel) an unrecognised preventable disease? Chinese Medical Journal, 95(11), 843.

Murrell, T. G. C. (1983). Pigbel in Papua New Guinea: An ancient disease rediscovered. International Journal of Epidemiology, 12(2), 211–214. https://doi.org/10.1093/ije/12.2.211

Murrell, T. G. (2005). Some epidemiological features of pig-bel. 1966. PNG Mecical Journal, 48(1–2), 27.

Murrell, T. G. C., Egerton, J. R., Rampling, A., Samels, J., & Walker, P. D. (1966). The ecology and epidemiology of the pig-bel syndrome in man in New Guinea. Journal of Hygiene, 64(03), 375–396. https://doi.org/10.1017/S0022172400040663

Murrell, T. G. C., & Walker, P. D. (1991). The pigbel story of Papua New Guinea. Transactions of the Royal Society of Tropical Medicine and Hygiene, 85(1), 119–122. https://doi.org/10.1016/0035-9203(91)90183-Y

Nakazawa, M., Yamauchi, T., Tanaka, M., Ishimori, D., Furusawa, T., Midorikawa, T., & Ohtsuka, R. (2002). Community Health Assessment by Urine Dipstick Screening in Relation to the Variety of Lifestyles in the Solomon Islands. People Culture Oceania, 18, 35–44.

Naranjo, M., Denayer, S., Botteldoorn, N., Delbrassinne, L., Veys, J., Waegenaere, J., … Dierick, K. (2011). Sudden death of a young adult associated with bacillus cereus food poisoning. Journal of Clinical Microbiology, 49(12), 4379–4381. https://doi.org/10.1128/JCM.05129-11

Narins, R. G., Rudnick, M. R., & Bastl, C. P. (1980). Lactic acidosis and the elevated anion gap (II). Hospital Practice, 15(6), 91-98.

Nathanson, N., Wilesmith, J., & Griot, C. (1997). Bovine spongiform encephalopathy (Bse): causes and consequences of a common source epidemic. American Journal of Epidemiology, 145(11), 959–969. https://doi.org/10.1093/oxfordjournals.aje.a009064

Neale, F. C., Aber, G. M., & Northam, B. E. (1958). The demonstration of intravascular haemolysis by means of serum paper electrophoresis and a modification of schumm's reaction. Journal of Clinical Pathology, 11(3), 206–219. https://doi.org/10.1136/jcp.11.3.206

Needham, E. (2005). Management of acute renal failure. American Family Physician, 1(72), 7.

Nkhoma, E. T., Poole, C., Vannappagari, V., Hall, S. A., & Beutler, E. (2009). The global prevalence of glucose-6-phosphate dehydrogenase deficiency: A systematic review and meta-analysis. Blood Cells, Molecules, and Diseases, 42(3), 267–278. https://doi.org/10.1016/j.bcmd.2008.12.005

Noor, A. M., Amin, A. A., Gething, P. W., Atkinson, P. M., Hay, S. I., & Snow, R. W. (2006). Modelling distances travelled to government health services in Kenya. Tropical Medicine and International Health, 11(2), 188–196. https://doi.org/10.1111/j.1365-3156.2005.01555.x

Noor, A. M., Zurovac, D., Hay, S. I., Ochola, S. A., & Snow, R. W. (2003). Defining equity in physical access to clinical services using geographical information systems as part of malaria planning and monitoring in Kenya. Tropical Medicine and International Health, 8(10), 917–926. https://doi.org/10.1046/j.1365-3156.2003.01112.x

Noris, M., & Remuzzi, G. (2005). Hemolytic uremic syndrome. Journal of the American Society of Nephrology, 16(4), 1035-1050.

National Statistical Office. (2014). 2011 National Population & Housing Census: Final Figures. Port Moresby.

National Statistical Office. (2015). 2011 National Population and Housing Census: National Report. Port Moresby.

Nwankiti, O. O., Ikeh, E. I., Asala, O., & Seuberlich, T. (2013). A pilot study for targeted surveillance of bovine spongiform encephalopathy in nigeria: bse surveillance in Nigeria. Transboundary and Emerging Diseases, 60(3), 279–283. https://doi.org/10.1111/j.1865-1682.2012.01340.x

O'donnell, Allen, Mgone, Martinson, Clegg, & Weatherall. (1998). Red cell morphology and malaria anaemia in children with Southeast-Asian ovalocytosis band 3 in Papua New Guinea. British Journal of Haematology, 101(3), 407–412. https://doi.org/10.1046/j.1365-2141.1998.00742.x

O'Meara, W. P., Noor, A., Gatakaa, H., Tsofa, B., McKenzie, F. E., & Marsh, K. (2009). The impact of primary health care on malaria morbidity - defining access by disease burden. Tropical Medicine & International Health, 14(1), 29–35. https://doi.org/10.1111/j.1365-3156.2008.02194.x

Ofosu-Amaah, V. (1983). National experience in the use of community health workers: a review of current issues and problems. Geneva: [Albany, N.Y: World Health Organization; Obtain from WHO Publications Centre USA].

Oliva, P. B. (1970). Lactic acidosis. The American Journal of Medicine, 48(2), 209–225. https://doi.org/10.1016/0002-9343(70)90117-8

Olson, K. R. (2010). Activated charcoal for acute poisoning: one toxicologist's journey. Journal of Medical Toxicology, 6(2), 190–198. https://doi.org/10.1007/s13181-010-0046-1

Ongugo, K., Hall, J., & Attia, J. (2011). Implementing tuberculosis control in papua new guinea: a clash of culture and science? Journal of Community Health, 36(3), 423–430. https://doi.org/10.1007/s10900-010-9324-8

Packman, C. H. (2001). The spherocytic haemolytic anaemias. British Journal of Haematology, 112(4), 888–899. https://doi.org/10.1046/j.1365-2141.2001.02440.x

Pearson, T. A., Mensah, G. A., Alexander, R. W., Anderson, J. L., Cannon, R. O., Criqui, M., … Vinicor, F. (2003). Markers of inflammation and cardiovascular disease: application to clinical and public health practice: a statement for healthcare professionals from the centers for disease control and prevention and the american heart association. Circulation, 107(3), 499–511. https://doi.org/10.1161/01.CIR.0000052939.59093.45

Petty, T. L. (1989). Studies of domiciliary oxygen in a common cause. Thorax, 44(7), 588–590. https://doi.org/10.1136/thx.44.7.588

Pineda, A. A., Taswell, H. F., & Brzica Jr, S. M. (1978). Transfusion reaction. An immunologic hazard of blood transfusion. Transfusion, 18(1), 1-7.

National Statistical Office. (2006). 2006 Papua New Guinea Demographic and Health Survey. Port Moresby.

Poka, H., & Duke, T. (2003). In search of pigbel: gone or just forgotten in the highlands of Papua New Guinea. PNG Medical Journal, 46(3–4), 135.

Possemiers, H., Vandermosten, L., & Van den Steen, P. E. (2021). Etiology of lactic acidosis in malaria. PLoS pathogens, 17(1), e1009122. https://doi.org/10.1371/journal.ppat.1009122

Progress towards identification of Haemolytic Agents responsible for Sago Haemolytic Disease in Papua New Guinea. (2008).

Pue, A, Fletcher, M, Greenhill, A, Warner, J, Ng, J, Blaney, B, Atagazli, L & Gena, M 2008. 'Progress Towards Identification of Haemolytic Agents Responsible for Sago Haemolytic Disease in Papua New Guinea', in 44th Papua New Guinea Medical Conference.

Razee, H., Whittaker, M., Jayasuriya, R., Yap, L., & Brentnall, L. (2012). Listening to the rural health workers in Papua New Guinea – The social factors that influence their motivation to work. Social Science & Medicine, 75(5), 828–835. https://doi.org/10.1016/j.socscimed.2012.04.013

Rich, M. W., Keller, A. J., Schechtman, K. B., Marshall, W. G., & Kouchoukos, N. T. (1989). Increased complications and prolonged hospital stay in elderly cardiac surgical patients with low serum albumin. The American Journal of Cardiology, 63(11), 714–718. https://doi.org/10.1016/0002-9149(89)90257-9

Rother, R. P., Bell, L., Hillmen, P., & Gladwin, M. T. (2005). The clinical sequelae of intravascular hemolysis and extracellular plasma hemoglobin: a novel mechanism of human disease. JAMA, 293(13), 1653. https://doi.org/10.1001/jama.293.13.1653

Russell, F. E. (1975). Ciguatera poisoning: A report of 35 cases. Toxicon, 13(5), 383–385. https://doi.org/10.1016/0041-0101(75)90202-0

Rutstein, S. O. (2000b). Factors associated with trends in infant and child mortality in developing countries during the 1990s. Bulletin of the World Health Organization, 78(10), 1256–1270.

Ruwende, C., & Hill, A. (1998). Glucose-6-phosphate dehydrogenase deficiency and malaria. Journal of Molecular Medicine, 76(8), 581–588. https://doi.org/10.1007/s001090050253

Rychetnik, L. (2002). Criteria for evaluating evidence on public health interventions. Journal of Epidemiology & Community Health, 56(2), 119–127. https://doi.org/10.1136/jech.56.2.119

Saikumar, P., Dong, Z., Weinberg, J. M., & Venkatachalam, M. A. (1998). Mechanisms of cell death in hypoxia/reoxygenation injury. Oncogene, 17(25), 3341–3349. https://doi.org/10.1038/sj.onc.1202579

Sanghavi, S. F., & Swenson, E. R. (2023). Arterial Blood Gases and Acid-Base Regulation. Seminars in respiratory and critical care medicine, 44(5), 612–626. https://doi.org/10.1055/s-0043-1770341

Scheiring, J., Andreoli, S. P., & Zimmerhackl, L. B. (2008). Treatment and outcome of Shiga-toxin-associated hemolytic uremic syndrome (HUS). Pediatric nephrology, 23, 1749-1760.

Schneider, J., & Lindenbaum, S. (1987). Frontiers of Christian evangelism: essays in honor of joyce riegelhaupt. American Ethnologist, 14(1), 1–8. https://doi.org/10.1525/ae.1987.14.1.02a00010

Schoeffel, P 1997. 'Myths of community management: sustainability, the state and rural development in Papua New Guinea, Solomon Islands and Vanuatu', Made available in DSpace on 2011-01-05T08: 53: 54Z (GMT).

Schoeps, A., Gabrysch, S., Niamba, L., Sié, A., & Becher, H. (2011). The effect of distance to health-care facilities on childhood mortality in rural Burkina Faso. American Journal of Epidemiology, 173(5), 492–498. https://doi.org/10.1093/aje/kwq386

Schuurkamp, G. J., Kereu , R. K., & Bulungol, P. (1990). Diethylcarbamazine in the control of bancroftian filariasis in the highly endemic Ok Tedi area of Papua New Guinea: phase 1. PNG Medical Journal, 33(2), 89–98.

Schuurkamp, G. J., Kereu, R. K., Bulungol, P. K., Kawereng, A., Popon, W. H., Crane, G. G., … Spicer, P. E. (1992). Diethylcarbamazine in the control of splenomegaly associated with Bancroftian filariasis in the Ok Tedi area of Papua New Guinea. Transactions of the Royal Society of Tropical Medicine and Hygiene, 86(5), 531–536. https://doi.org/10.1016/0035-9203(92)90097-V

Shiota, M., Saitou, K., Mizumoto, H., Matsusaka, M., Agata, N., Nakayama, M., … Hata, D. (2010). Rapid detoxification of cereulide in bacillus cereus food poisoning. PEDIATRICS, 125(4), e951–e955. https://doi.org/10.1542/peds.2009-2319

Simpson, G., Coulter, C., Weston, J., Knight, T., Carter, R., Vincent, S., … Konstantinos, A. (2011). Resistance patterns of multidrug-resistant tuberculosis in Western Province, Papua New Guinea [Notes from the field]. The International Journal of Tuberculosis and Lung Disease, 15(4), 551–552. https://doi.org/10.5588/ijtld.10.0347

Singer, R. B., & Hastings, A. B. (1948). An improved clinical method for the estimation of disturbances of the acid-base balance of human blood: Medicine, 27(2), 223. https://doi.org/10.1097/00005792-194805000-00003

Sinnett, P. F., & Whyte, H. M. (1973). Epidemiological studies in a total highland population, Tukisenta, New Guinea. Journal of Chronic Diseases, 26(5), 265–290. https://doi.org/10.1016/0021-9681(73)90031-3

Sirker, A. A., Rhodes, A., Grounds, R. M., & Bennett, E. D. (2002). Acid− base physiology: the 'traditional'and the 'modern'approaches. Anaesthesia, 57(4), 348–356.

Sjoholm, I., Ekman, B., Kober, A., Ljungstedt-Pahlman, I., Seiving, B., & Sjodin, T. (1979). Binding of drugs to human serum albumin: XI. The specificity of three binding sites as studied with albumin immobilized in microparticles. Molecular Pharmocology, 16(3), 767–777.

Smith, A. (2005). Hypoxia symptoms reported during helicopter operations below 10,000 ft: a retrospective survey. Aviation, Space and Environmental Medicine, 76(8), 794–798.

Smith, A. M. (2008). Hypoxia symptoms in military aircrew: long-term recall vs. Acute experience in training. Aviation, Space, and Environmental Medicine, 79(1), 54–57. https://doi.org/10.3357/ASEM.2013.2008

Smith, B. C. (1997). The decentralization of health care in developing countries: organizational options. Public Administration and Development, 17(4), 399–412. https://doi.org/10.1002/(SICI)1099-162X(199710)17:4<399::AID-PAD976>3.0.CO;2-P

Smith, P. G. (2003). The epidemics of bovine spongiform encephalopathy and variant Creutzfeldt-Jakob disease: current status and future prospects. Bulletin of the World Health Organization, 81(2), 123–130.

Smith, Z. R., Horng, M., & Rech, M. A. (2019). Medication-Induced Hyperlactatemia and Lactic Acidosis: A Systematic Review of the Literature. Pharmacotherapy, 39(9), 946–963. https://doi.org/10.1002/phar.2316

Sreevastava, D. K., & Tarneja, V. K. (2003). Anaphylactic reaction: An overview. Medical Journal Armed Forces India, 59(1), 53-56.

Srivastava, S., & Beutler, E. (1968). Oxidized glutathione levels in erythrocytes of glucose-6-phosphate-dehydrogenase-deficient subjects. The Lancet, 292(7558), 23–24. https://doi.org/10.1016/S0140-6736(68)92892-4

Stacpoole, P. W. (1986). Lactic acidosis: the case against bicarbonate therapy. Annals of Internal Medicine, 105(2), 276. https://doi.org/10.7326/0003-4819-105-2-276

Stewart, P. J., & Strathern, A. (2005). Cosmology, resources, and landscape: agencies of the dead and the living in duna, papua new guinea. Ethnology, 44(1), 35. https://doi.org/10.2307/3773958

Stone, L. (1992). Cultural influences in community participation in health. Social Science & Medicine, 35(4), 409–417. https://doi.org/10.1016/0277-9536(92)90333-L

Stringer, W., Wasserman, K., Casaburi, R., Porszasz, J., Maehara, K., & French, W. (1994). Lactic acidosis as a facilitator of oxyhemoglobin dissociation during exercise. Journal of Applied Physiology, 76(4), 1462–1467. https://doi.org/10.1152/jappl.1994.76.4.1462

Suankratay, Mold, Zhang, Lint, & Gewurz. (1999). Mechanism of complement-dependent haemolysis via the lectin pathway: role of the complement regulatory proteins. Clinical & Experimental Immunology, 117(3), 442-448.

Suetrong, B., & Walley, K. R. (2016). Lactic Acidosis in Sepsis: It's Not All Anaerobic: Implications for Diagnosis and Management. Chest, 149(1), 252–261. https://doi.org/10.1378/chest.15-1703

Symmons, D., & Curry, C. (2007). Rural hospital generalist and emergency medicine training in Papua New Guinea. Emergency Medicine Australasia, 19(2), 151–154. https://doi.org/10.1111/j.1742-6723.2006.00913.x

Tanser, F., Gijsbertsen, B., & Herbst, K. (2006). Modelling and understanding primary health care accessibility and utilization in rural South Africa: An exploration using a geographical information system. Social Science & Medicine, 63(3), 691–705. https://doi.org/10.1016/j.socscimed.2006.01.015

Tanser, F., Hosegood, V., Benzler, J., & Solarsh, G. (2001). New approaches to spatially analyse primary health care usage patterns in rural South Africa. Tropical Medicine and International Health, 6(10), 826–838. https://doi.org/10.1046/j.1365-3156.2001.00794.x

Taufa, T. (1974). Sago haemolytic disease. PNG Medical Journal, 17, 227–228.

Tefferi, A. (2003). Anemia in adults: a contemporary approach to diagnosis. Mayo Clinic Proceedings, 78(10), 1274–1280. https://doi.org/10.4065/78.10.1274

Tilley, L., Nash, G. B., Jones, G. L., & Sawyer, W. H. (1991). Decreased rotational diffusion of band 3 in melanesian ovalocytes from Papua, New Guinea. The Journal of Membrane Biology, 121(1), 59–66. https://doi.org/10.1007/BF01870651

TO, A. (2003). Health for all beyond 2000: the demise of the Alma-Ata Declaration and primary health care in developing countries. Medical Journal of Australia, 178(1), 17–20.

Toikilik, S., Tuges, G., Lagani, J., Wafiware, E., Posanai, E., Coghlan, B., … Clements, C. J. (2010). Are hard-to-reach populations being reached with immunization services? Findings from the 2005 Papua New Guinea national immunization coverage survey. Vaccine, 28(29), 4673–4679. https://doi.org/10.1016/j.vaccine.2010.04.063

Townsend, P & Tan, K 1977. ‘The Cultural Ecology of Sago in New Guinea.’’, in Sago-76: Papers of the First International Sago Symposium, pp. 91-5.

Townsend, P. K. (1974). Sago production in a New Guinea economy. Human Ecology, 2(3), 217–236. https://doi.org/10.1007/BF01531422

Tozoni, S. S., Dias, G. F., Bohnen, G., Grobe, N., Pecoits-Filho, R., Kotanko, P., & Moreno-Amaral, A. N. (2019). Uremia and hypoxia independently induce eryptosis and erythrocyte redox imbalance. Cell Physiol Biochem, 53(5), 794-804.

Trang, T. T. M., Phu, N. H., Vinh, H., Hien, T. T., Cuong, B. M., Chau, T. T. H., … White, N. J. (1992). Acute renal failure in patients with severe falciparum malaria. Clinical Infectious Diseases, 15(5), 874–880. https://doi.org/10.1093/clind/15.5.874

Trevitt, C. R., & Singh, P. N. (2003). Variant Creutzfeldt-Jakob disease: pathology, epidemiology, and public health implications. The American Journal of Clinical Nutrition, 78(3), 651S–656S. https://doi.org/10.1093/ajcn/78.3.651S

Uhr, J. W. (1966). Delayed hypersensitivity. Physiological reviews, 46(3), 359-419.

Valentine, W. N. (1975). Enzyme abnormalities in red cells. British Journal of Haematology, 31(s1), 11–19. https://doi.org/10.1111/j.1365-2141.1975.tb00894.x

Veiga, PA 2005. 'Income-related health inequality in Portugal'.

Vichinsky, E. P. (1998). The morbidity of bone disease in thalassemia. Annals of the New York Academy of Sciences, 850(1 COOLEY'S ANEM), 344–348. https://doi.org/10.1111/j.1749-6632.1998.tb10491.x

Warner, J. M., Pelowa, D. B., Currie, B. J., & Hirst, R. G. (2007). Melioidosis in a rural community of western province, papua new guinea. Transactions of the Royal Society of Tropical Medicine and Hygiene, 101(8), 809–813. https://doi.org/10.1016/j.trstmh.2007.02.024

Weed, R. I., & Reed, C. F. (1966). Membrane alterations leading to red cell destruction. The American Journal of Medicine, 41(5), 681–698. https://doi.org/10.1016/0002-9343(66)90030-1

West, JB 2008. 'JS Haldane and some of his contributions to physiology', in Integration in Respiratory Control, Springer, pp. 9-15.

Wheaton, W. W., & Chandel, N. S. (2011). Hypoxia. 2. Hypoxia regulates cellular metabolism. American Journal of Physiology-Cell Physiology, 300(3), C385–C393. https://doi.org/10.1152/ajpcell.00485.2010

WHO 2014. 'Country Cooperation Strategy', Global Health Observatory.

Williams, S. T., Khare, V. K., Johnston, G. A., & Blackall, D. P. (1995). Severe intravascular hemolysis associated with brown recluse spider envenomation: A report of two cases and review of the literature. American Journal of Clinical Pathology, 104(4), 463–467. https://doi.org/10.1093/ajcp/104.4.463

Winkleman, M., Stangel, W., & Grabensee, B. (1982b). Fatal immunohaemolytic anaemia after eating the mushroom Paxillus involutus. Deutsche Medizinische Wochenschrift, 107(31–32), 1190–1194.

Winkelmann, M., Stangel, W., Schedel, I., & Grabensee, B. (1986). Severe hemolysis caused by antibodies against the mushroom Paxillus involutus and its therapy by plasma exchange. Klinische Wochenschrift, 64(19), 935–938. https://doi.org/10.1007/BF01728620

Woodfield, D., & Biddulph, J. (1975b). Neonatal jaundice and glucose-6-phosphate dehydrogenase deficiency in Papua New Guinea. Medical Journal of Australia, 1(14), 443–446.

Yamada, K., & Nonaka, K. (1996). Diabetic ketoacidosis in young obese Japanese men. Diabetes Care, 19(6), 671–671. https://doi.org/10.2337/diacare.19.6.671a

Yenchitsomanus, P., Summers, K. M., Board, P. G., Bhatia, K. K., Jones, G. L., Johnston, K., & Nurse, G. T. (1986). Alpha-thalassemia in Papua New Guinea. Human Genetics, 74(4), 432–437. https://doi.org/10.1007/BF00280500.

Web references

Downloaded March 7 2012 Figures 2.1, Figure 2.2, Figure 2.3

- Image of oxygen dissociation curve, Figure 2.1
- Berne and LBevy Physiology 6th Edition online image
- http://users.atw.hu/blp6/BLP6/HTML/common/M9780323045827-023-f005.jpg
- , e-safe-anaesthesia.org online image Figure 2.2
- Image of oxygen dissociation curve depict high and low oxygen saturation
- . http://e-safe-anaesthesia.org/sessions/03_09/gif/ana_1_031_5_t3_01_med.gif
- classconnection.s3.amazonnaws.com online image Figure 2.3
- Image of Oxygen dissociation curve with anaemia http://classconnection.s3.amazonaws.com/686/flashcards/955686/png/anemia1335114542348.png.

11 Appendix

Thesis output on the Clinical epidemiology research on sago induced intravascular haemolysis		
No.	Date	The dissemination of results of the study
1.	2009	One health conference, Durban South Africa
2.	2014	Week one September: Papua New Guinea Medical Symposium, Goroka, Eastern Highland Province.
3	2014	Week 2 September Executive Management Ok Tedi Mining Tabubil, North Fly District, Western Province.
4.	2014	Kiunga Government Hospital staff, North Fly District Western Province
5	2014	Department of Community Relation officers, Kiunga based - Ok Tedi Mine.
6	2016	March, Presented to the Papua New Guinea Evaluators Association. Port Moresby
7.	2016	March, Presented to the employees of Department of Community Development. Port Moresby
8.	2016	Epidemiology Division, National Department of Health recommendations of this study to include treatment of sago poisoning into the standard treatment book delivered to the Division of Epidemiology, National Department of Health as the responsible government agency.
9.	2019	Posters presentations during 2019 Papua New Guinea Medical Symposium, Divine Word University, Madang Poster 1. Outbreak investigation of Sago Poisoning. Poster on Pathophysiological changes of sago induced intravascular haemolytic disease
10	2019	Fourth National Environmental Health and Workplace Safety, Divine Word University
11	2013	Papua New Guinea Medical Symposium Papua New Guinea Medical Symposium 2023 in Port Moresby
		Presented to the Papua New Guinea Emergency Physician specialists meeting: 1. Presentation of epidemiological findings

		2. Display of 3 posters: A. Outbreak Investigation of Sago poisoning B. Pathophysiological changes of sago poisoning. C. Graph of bivariate regression analysis- mathematically modelling the dose-response effect.
13.	2023	October: Pre completion seminar via Zoom School of Medicine with the Research committee, James Cook University October 2023.
14.	2024	Presentation at the Grand School of Medicine and Health Science& Port Moresby General Hospital August 2024
15	2008	Radio interview – local adio station from James Cook Univerty
16	2013	Radio interview via National Broad Casting Commision
17	2016	PNG National Newspaper story on Sago poisoning study

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INFORMATION SHEET

Clinical Epidemiology of Sago Haemolytic Disease, Western Province, Papua New Guinea

You are invited to take part in a research project about why some people get sick with Sago Haemolytic Disease and why others do not get it. Though the disease was discovered 34 years ago, the cause remains unknown. The project investigates ways of improving understanding of the disease, find the reasons why some people are unaffected (protected) and others get the disease and die while others survive and find ways to improve investigation, treatment and prevention of the disease. The study is being conducted by **Dr Miila Gena and other investigators, Dr Jeffrey Warner, Professor Richard Speare and Professor Bruce Gummow will** contribute to the **PhD project by Dr Miila Gena** to obtain a Doctor **of Philosophy** degree at James Cook University.

If you agree to be involved in the study, you will be invited to be interviewed. The interview, with your consent, will be a face to face interview, a physical examination which also includes ultrasound examination of the abdomen and a request for you to submit samples of urine, stool and blood and should only take approximately 1 hour of your time. The interview will be conducted in your village.

Taking part in this study is completely voluntary and you can stop taking part in the study at any time without explanation or prejudice. You may also withdraw any unprocessed data from the study.

As some people may become distressed or embarrassed about the physical examination and submission of samples, due care will be taken to arrange specific times for examination for same gender and age to minimise distress to participants. If you do feel upset or distressed in any way, please advise the researcher and you will be referred to health worker to help explain in local language to help you.

(FOR SNOWBALL RECRUITMENT – If you know of others that had illness that was described as Sago Poisoning or that family members had deaths related to Sago Poisoning, can you please pass on this information sheet to them so they may contact me to volunteer for the study.)

Your responses and contact details will be strictly confidential. The data from the study will be used in research publications and reports to the National Department of Health, Western Province Provincial Administration, Office of the Rural Health Service Director, All Health Service Providers in Western Province and communications with Health Professionals in Papua New Guinea and globally). You will not be identified in any way in these publications.

If you have any questions about the study, please contact **(Principal Investigator and Principal Supervisor/Co-Investigator).**

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If you have any concerns regarding the ethical conduct of the study, please contact Tina Langford, Ethics Officer, Research Office, James Cook University, Townsville, Qld, 4811. Phone: 4781 4342, Tina.Langford@jcu.edu.au

Chapter 5 Health status of rural remote communities

Access to health care as reported by gender

Table 5.1 Total number adult evaluated by gender

Access to health care	Male	Female	Total
Yes	197	146	343
No	191	174	365
Total	388	320	708

Table of expected values calculation

Expected number access to health care by gender

Gender	Tengkim	Tarakbits	Ningerum Tamaro	Membok	Ok Tarim	Timoknai	Menumgrupe	Kukuzaba	Total
Male	30.68926554	50.418079	55.35028249	51.51412	59.73446	72.887006	18.08474576	49.32203	**388**
Female	25.31073446	41.581921	45.64971751	42.48588	49.26554	60.112994	14.91525424	40.67797	**320**
	56	**92**	**101**	**94**	**109**	**133**	**33**	**90**	**708**

Chi-square test

	Observed	expected	O - E	$(O-E)^2$	$(O-E)^2/E$	degrees of freedom	Probability 0.05
Male	35	30.68926554	4.3107345	18.58243161	0.605503	7	
Male	49	50.4180791	-1.418079	2.010948323	0.039885		
Male	62	55.35028249	6.6497175	44.21874302	0.798889		
Male	51	51.51412429	-0.514124	0.264323789	0.005131		
Male	57	59.73446328	-2.734463	7.477289412	0.125175		
Male	74	72.88700565	1.1129944	1.238756424	0.016996		
Male	11	18.08474576	-7.084746	50.19362252	2.775467		
Male	49	49.3220339	-0.322034	0.103705832	0.002103		
Female	21	25.31073446	-4.310734	18.58243161	0.734172		
Female	43	41.5819209	1.4180791	2.010948323	0.048361		
Female	39	45.64971751	-6.649718	44.21874302	0.968653		
Female	43	42.48587571	0.5141243	0.264323789	0.006221		
Female	52	49.26553672	2.7344633	7.477289412	0.151775		
Female	59	60.11299435	-1.112994	1.238756424	0.020607		
Female	22	14.91525424	7.0847458	50.19362252	3.365254		
Female	41	40.6779661	0.3220339	0.103705832	0.002549		
						Less than critical	
			Chi-square test statistic		**3.540186**	value	12.02

Results of t-test for equal and unequal variance on mean pre-transfusion haemoglobin levels of male and female SHD cases Chapter 7.

Chapter 8 t-test using excel for

Difference in haemoglobin in SHD and non-SHD anaemia

t-Test: Two-Sample Assuming Unequal Variances

	Non SHD Hb gm/L	*SHD Hb gm/L*
Mean	89.294	49.667
Variance	37.096	270.952
Observations	17	15
Hypothesized Mean Difference	0	
df	17	
t Stat	8.807	
P(T<=t) one-tail	4.81484E-08	
t Critical one-tail	1.740	
P(T<=t) two-tail	9.62968E-08	
t Critical two-tail	2.110	

The two-tail t-test showed a statistically significant difference between the mean haemoglobin between the SHD cases and the non-SHD group that consisted of villagers that had anaemia.

Table 8.9 Difference in red cells counts of SHD and non-SHD anaemia

t-Test: Two-Sample Assuming Unequal Variances

	SHD red cell pop	*Non-SHD red cell pop*
Mean	1469109.273	3529460.176
Variance	1.25697E+12	2.647E+11
Observations	11	17
Hypothesized Mean Difference	0	
df	13	
t Stat	-5.718	
P(T<=t) one-tail	3.53923E-05	
t Critical one-tail	1.771	
P(T<=t) two-tail	7.07847E-05	
t Critical two-tail	2.160	

Chapter 8 Table 8.10

t-Test: Two-Sample Assuming Unequal Variances

	Poor Nutrition	*Good nutrition*
Mean	25.791	66
Variance	576.023	74.667

Observations	11	4
Hypothesized Mean Difference	0	
df	13	
t Stat	-4.771	
P(T<=t) one-tail	0.0001827344	
t Critical one-tail	1.771	
P(T<=t) two-tail	0.000365469	
t Critical two-tail	2.160	

Chapter 7 statistics t-test

	Male age in years	*Female age in years*
Mean	19.71	17.42
Variance	233.38	200.08
Observations	12	12
Hypothesized Mean Difference	0	
df	22	
t Stat	0.381	
P(T<=t) one-tail	0.353	
t Critical one-tail	1.717	
P(T<=t) two-tail	0.707	
t Critical two-tail	2.074	

There was no statistically significant difference in mean age between males and females therefore the study failed to reject the null hypothesis of no difference, and this was attributed to the small sample size.

t-Test: Two-Sample Assuming Unequal Variances
for haemoglobin

	Male Hb gm/L	*Female Hb*
Mean	59.7	51.23
Variance	648.01	680.52
Observations	10	12
Hypothesized Mean Difference	0	
df	19	
t Stat	0.768	
P(T<=t) one-tail	0.226	
t Critical one-tail	1.729	
P(T<=t) two-tail	0.452	
t Critical two-tail	2.093	

There was no statistically significant difference between the mean haemoglobin of males and females therefore the study fails to reject the null hypothesis. Women and men were affected with equal severity by SHD. To obtain significant difference would require pre and post SHD haemoglobin of cases that were likely to remain unresolved among remote communities.

Chapter 7 and chapter 8 use regression analysis to test relationships and predict the pre-blood-transfusion haemoglobin based on the observed pre-transfusion haemoglobin and quantity of a 16cm diameter contaminated sago pancake consumed (estimated as the surface area of a circle). The first regression analysis was with 5 cases of sago poisoning with the reported sized of contaminated sago pancake consumed estimated as 16cm diameter. The second regression analysis was redone for a sample size of 14 cases. The estimated number of pancakes consumed was two each with a diameter of 16cm. This allowed a retest of the relationship between the predictor variable of pre-blood transfusion haemoglobin to the quantity of contaminated sago pancake consumed. The bivariate regression analysis done in excel program confirmed the relationship still existed as shown below with the evidence on tested assumptions of the residuals attached to the appendix section.

Normality

The residuals showed a normal distribution with a linearity pattern and the test for homoscedasticity was evident as residuals spread above and below zero evenly. As it is a bivariate analysis, there was no collinearity.

SUMMARY OUTPUT

Regression Statistics	
Multiple R	0.948081581
R Square	0.898858683
Adjusted R Square	0.865144911
Standard Error	6.847562657
Observations	5

ANOVA

	Degrees of freedom df	Sum of squares SS	MS	F statistic F	Significance F
Regression	1	1250.132657	1250.13266	26.6615	0.014089795
Residual	3	140.667343	46.8891143		
Total	4	1390.8			

	Coefficients	Standard Error	t Stat	P-value	Lower 95%	Upper 95%
Intercept	87.547	8.936005395	9.79709113	0.00226	59.10850184	115.9852165
Size of sago pancake consumed	-0.27	0.052251291	-5.1634745	0.01409	-0.436085135	-0.10351128

RESIDUAL OUTPUT

Observation	Predicted Pre transfusion Haemoglobin gm/L	Residuals	Standard Residuals
1	72.21116297	1.788837033	0.159097983
2	52.31153502	-5.311535019	-0.472404412
3	42.20644183	-14.20644183	-1.263511543
4	42.20644183	0.793558166	0.070578538
5	42.20644183	-13.20644183	-1.174572204
6	42.20644183	-14.20644183	-1.263511543
7	42.20644183	0.793558166	0.070578538
8	42.20644183	-3.206441834	-0.285178816
9	42.20644183	-6.206441834	-0.551996833
10	42.20644183	18.79355817	1.671486636
11	42.20644183	7.793558166	0.69315391
12	42.20644183	15.79355817	1.40466862
13	42.20644183	16.79355817	1.493607958
14	42.20644183	-6.206441834	-0.551996833

PROBABILITY OUTPUT

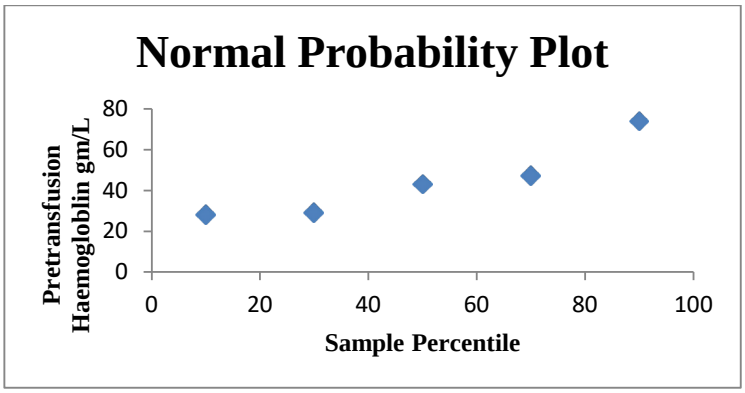
Percentile	Pre transfusion Haemoglobin gm/L
3.571428571	28
10.71428571	28
17.85714286	29
25	36
32.14285714	36
39.28571429	39
46.42857143	43
53.57142857	43
60.71428571	47
67.85714286	50
75	58
82.14285714	59
89.28571429	61
96.42857143	74

RESIDUAL OUTPUT

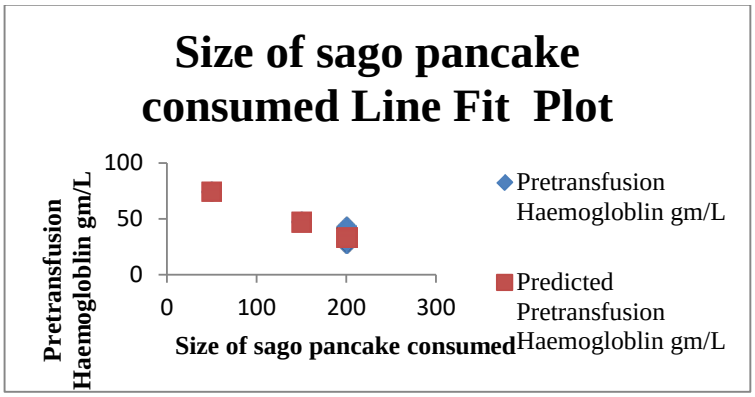
Observation	Predicted Pre transfusion Haemoglobin gm/L	Residuals	Standard Residuals
1	73.992	0.007802748	0.00131577
2	47.023	-0.023168442	-0.0039069
3	33.328	-5.328211435	-0.8984932
4	33.328	9.671788565	1.63094812
5	33.328	-4.328211435	-0.7298638

PROBABILITY OUTPUT

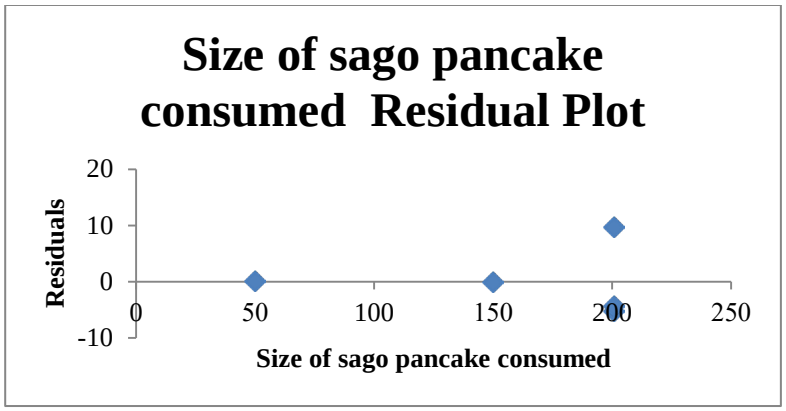
Percentile	Pre transfusion Haemoglobin gm/L
10	28
30	29
50	43
70	47
90	74



The normality plot shows a linear pattern.



The plot of size of contaminated sago consumed
With the predicted pre-blood transfusion haemoglobin.



The residual versus fitted plot near zero.

Regression analysis redone with larger sample size of fourteen cases

The increase in sample size of cases (pre-transfusion haemoglobin) was done by assigning consumption at least 2 sago pancakes (each pancake diameter of 16cms). Analysis yields a lower adjusted R square 0.297 which is associated with a significant p-value for the F statistics in the ANOVA as well as a significant p-value in the t-test for the coefficient. The predicted pre-transfusion haemoglobin reduced by 5 times for every 1cm increase in contaminated sago pancake consumed. The greater variability in the pre-transfusion haemoglobin inflates the magnitude of the risk of intravascular haemolysis compared to the smaller sample size of cases who reported the size of sago pancake that they consumed.

SUMMARY OUTPUT

Regression Statistics	
Multiple R	0.59216108
R Square	0.350654745
Adjusted R Square	0.29654264
Standard Error	11.70272924
Observations	14

ANOVA

	Degrees of freedom	SS	MS	F	Significance F
Regression	1	887.4821125	887.4821125	6.480154	0.025671914
Residual	12	1643.446459	136.9538716		
Total	13	2530.928571			

	Coefficients	Standard Error	t Stat	P-value	Lower 95%	Upper 95%
Intercept	82.21273668	14.92178252	5.509578805	0.000134	49.70096549	114.7245079
Size of sago pancake consumed	-0.19907591	0.078203477	-2.545614566	0.025672	-0.369466649	-0.028685171

RESIDUAL OUTPUT

Observation	Predicted Pre transfusion Haemoglobin gm/L	Residuals	Standard Residuals
1	72.21116297	1.788837033	0.159097983
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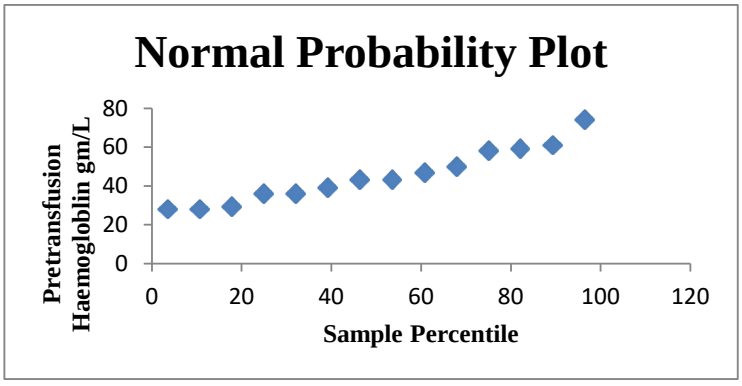
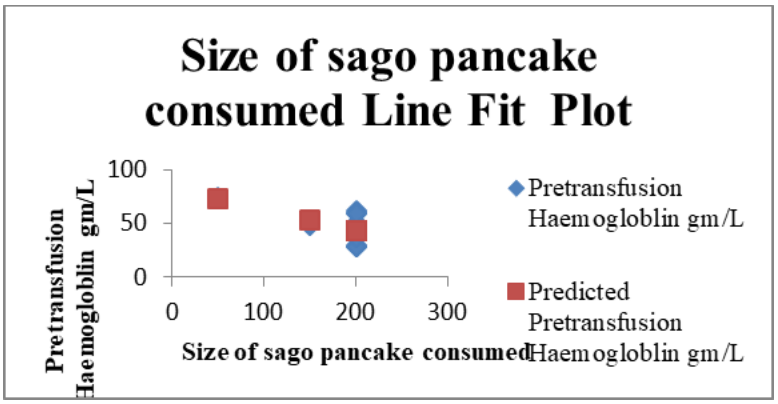
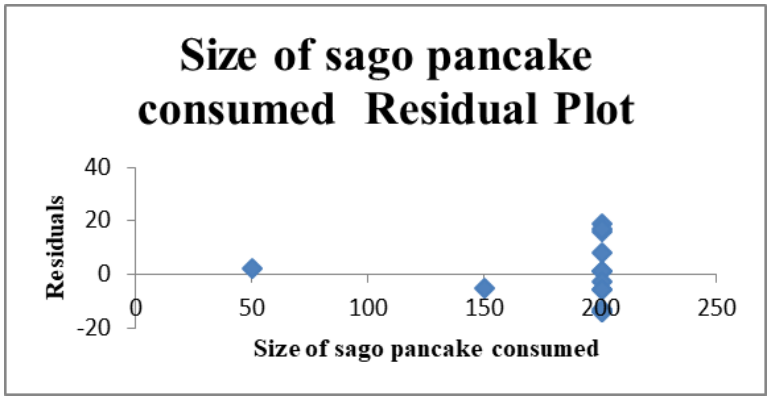
89.28571429	61
96.42857143	74




Size of sago pancake consumed Line Fit Plot
Pretransfusion Haemoglobin gm/L
100
50
0
0
100
200
300
Size of sago pancake consumed
Pretransfusion Haemoglobin gm/L
Predicted Pretransfusion Haemoglobin gm/L


Size of sago pancake consumed Residual Plot
Residuals
40
20
0
-20
0
50
100
150
200
250
Size of sago pancake consumed

Was anaemia of SHD comparable to anaemia of other of other causes found during the health assessment of rural villagers?

H_0 : There haemoglobin levels of SHD cases and non SHD were similar

H_A :. There haemoglobin for SHD cases were different to haemoglobin of Non SHD cases

t-Test: Two-Sample Assuming Unequal Variances

	Non SHD Hb	*SHD Hb*
Mean	89.29411765	49.66666667
Variance	37.09558824	270.952381
Observations	17	15
Hypothesized Mean Difference	0	
df	17	
t Stat	8.807060242	
P(T<=t) one-tail	4.81484E-08	
t Critical one-tail	1.739606726	
P(T<=t) two-tail	9.62968E-08	
t Critical two-tail	2.109815578	

The ttest rejects the null hypothesis of no difference in the mean of haemoglobin between the two groups and accepts that the haemoglobin of the SHD cases was statistical significantly different to the mean haemoglobin of the remote community.

H_0 The prevalence of self reported illness of village with operating aid post was the same as self reported illness by study subjects whose village non operating aid post.

H_a The burden of self reported illness was different between those whose villagers aid post was operating compared to those with.

Calculation for Chi square testing of the observed and expected values for Table 5.4 on the prevalence of self - reported illness.

Observed	**ILL**	**NOT ILL**	**TOTAL**
With Aid Post	10	103	113
Without Aid post	9	45	54
Total	19	148	167

Expected	**ILL**	**NOT ILL**	**TOTAL**
With Aid Post	12.86	100.14	113
Without Aid post	6.14	47.86	54
Total	19	148	167

Hypothesis testing the relationship between the operational aid posts on burden of self-reported illness.

Observed(O)	**Expected(E)**	**O-E**	**$(O-E)^2$**	**$(O-E)^2/E$**
10	12.86	-2.86	8.1796	0.64
103	100.14	2.86	8.1796	0.08
9	6.14	2.86	8.1796	1.33
45	47.86	2.86	8.1796	0.17
			Calculated Chi Square value =	**2.22**
Chi Square Value of α=0.05 is 3.841, failed to reject the null hypothesis of aid post impact on self- reported illness burden				

The prevalence of malaria in Kiunga urban region compared to the most distant rural villages on the Strickland River.

Observed malaria burden	Positive	Negative	Total
Kiunga Urban	17	412	429
Strickland villages	63	102	165
	80	514	594

Expected malaria burden	Positive	Negative	Total
Kiunga Urban	57. 78	371.22	
Strickland villages	22.22	142.78	

Observed	Expected	Observed - Expected	(Observed – Expected)^2	(Observed – Expected)^2 /Expected
17	57.8	40.78	1663.0084	28.80
412	571.22	40.78	1663.0084	4.50
63	22.2	40.78	1663.0084	74.50
102	142.78	40.78	1663.0084	11.65
Chi – square statistic				119.79
With 1 degree of freedom with alpha value of 0.05 the test statistic is > 3.841, the critical value on the Chi –square table				
The burden of malaria was statistically significantly different between the Kiunga urban and the most rural and distant villages away from in the Kiunga urban.				