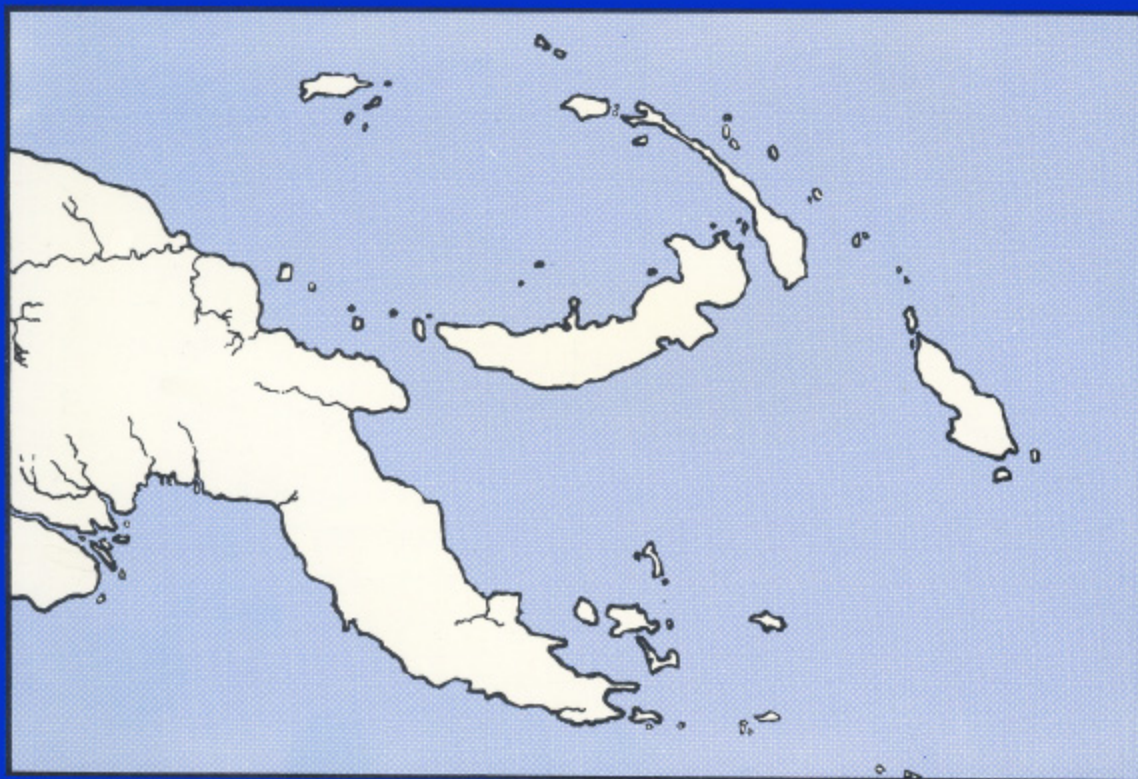


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## EDITORIAL

### Four decades of malaria research in Papua New Guinea

Malaria research in Papua New Guinea (PNG) has a long history dating back more than 100 years to the time of Robert Koch, often considered the father of modern microbiology. Koch led the first malaria expedition to Dutch East Indies (now Indonesia) and German New Guinea (now PNG) (1-3). Some of his theories about malaria related to age of exposure and acquisition of immunity, species-specific immunity, protective immunity and antimalarial vaccine prospects are central to our understanding of malaria and remain important today (4). Over the past 40 years, malaria research led by the Papua New Guinea Institute of Medical Research (PNGIMR) in collaboration with many international partners has included numerous malaria epidemiological studies, entomological studies, parasitological studies, clinical trials and clinicopathological studies (5). Many of these studies have placed PNG on the world map as a setting where high-quality research and data about the burden of malaria, lymphatic filariasis and other vector-borne diseases are generated in order to guide local and global policies. The recent PNGIMR work on the efficacy, safety and effectiveness of a triple-drug therapy (ivermectin, diethylcarbamazine and albendazole) as a mass drug administration tool for lymphatic filariasis eradication efforts has led to the global change of lymphatic filariasis guidelines by the World Health Organization (6). This resulted in Merck expanding its drug donation program by 10 million treatments annually to 2025 for lymphatic filariasis elimination efforts globally and is a classic example of work originating from PNG having a global impact in the area of vector-borne diseases.

The 40th Anniversary Colloquium in Madang in August of 2016 was an occasion on which to reflect upon these achievements and the people and programs that have led to sustained research activities by PNGIMR's Vector-Borne Diseases Unit, enabling the acquisition of a high number of competitive collaborative research grants over the past forty years. This body of research has made outstanding contributions in guiding policies and improving global knowledge on

vector-borne pathogens. This exceptional achievement is special, considering the fact that the research has been conducted to very high standards by hundreds of different people over the past four decades despite many limitations in a logistically challenging environment. The successes of these programs have been grounded on a strong community-based approach, strong collaborative partnerships and committed staff who have a passion to serve in the field of medical research.

Despite this, malaria and other vector-borne diseases remain a major challenge in PNG. Over 90% of the population in PNG remain at risk of being infected by malaria parasites, with the majority of these living in endemic settings where four of the five *Plasmodium* species that infect humans (*P. falciparum*, *P. vivax*, *P. malariae*, *P. ovale*) are found. *Plasmodium vivax* continues to be a serious and under-recognized problem, with challenges in implementing effective radical cure, whilst the effective transmission of malaria by multiple anopheline vectors that are able to adapt and overcome current vector control strategies (7) highlights the realities of the long road PNG is walking towards malaria elimination. In recent years, the initial decline of malaria (2010-2014) followed by a resurgence between 2015 and 2017 that was more pronounced in the Momase and New Guinea Islands regions speaks volumes for the challenges for controlling malaria in PNG. It is clear that a multisectoral approach backed by an appropriate level of resourcing, significant health systems strengthening and political support will be required to reverse this trend and to improve the current status of health in general in PNG.

Despite these challenges, PNG will continue to contribute to local and global knowledge generation and policy development in the field of vector-borne diseases. New opportunities continue to emerge for combining research that will generate critical evidence to guide control and elimination with the capacity and health systems strengthening activities that will be required in order to implement

novel control programs. Examples of these include: i) continued support from the Global Fund to monitor and evaluate the national malaria control program through nationwide household surveys, school surveys and vector monitoring activities; ii) continued support from the United States National Institutes of Health International Centre of Excellence in Malaria Research Program for integrated human, parasite and vector studies to guide the development of improved surveillance strategies; iii) continued support from the Australia-China-Papua New Guinea Trilateral Malaria Project to strengthen malaria diagnosis and operational research in PNG; and iv) new support from Australia's Department of Foreign Affairs and Trade's Indo-Pacific Centre for Health Security to strengthen vector-borne disease surveillance and response through integrated molecular diagnostic and vector monitoring at sentinel sites. These recent large-scale international competitive grants are testaments of the strength and depth of PNGIMR's collaborative programs and the need to continue dovetailing high-quality research with health systems strengthening and program delivery to improve health for all.

This issue of the PNG Medical Journal brings together several historical and scientific perspectives from the past 40 years of malaria research in PNG, as well as several research papers from the next generation of researchers – all of whom are working hard to ensure that the next decade of research continues to generate the novel and program-relevant insights that PNG is renowned for. We hope that together they will bring us closer to achieving the goal of malaria elimination.

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## Personal reflections on malaria after 40 years of the Malaria Research Program at the Papua New Guinea Institute of Medical Research

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### SUMMARY

These reflections on malaria are mostly from the mirror of the past, which have their own intrinsic interest but also, through accounts of success and failure, shine some light on different paths into the future. The rich history of malaria research in New Guinea is briefly alluded to before turning to the work of the Papua New Guinea Institute of Medical Research. The Malaria Research Program of the Institute began in 1976 and celebrated its 40-year anniversary in 2016. Stories about its beginnings and the personalities involved are recounted. Some of the early studies are described, including prophylaxis with antimalarial drugs in children. The many ways used to try and control malaria are outlined as well as the difficulties that were encountered in the face of dogmatic beliefs and colonial attitudes. New ideas included insecticidal mosquito nets used as bednets and a blood-stage malaria vaccine, the travails with which are described in some detail. Further final reflections discount the idea of the eradication of malaria and look to the continued use in places where malaria is hard to control of a creative combination of partially successful measures. Playing with ideas is the basis of good science and, though it is more effective when done with sympathetic colleagues, these personal reflections are offered in the hope that they will not prove entirely narcissistic.

### History of malaria research in New Guinea

There is a distinguished history of research on malaria in New Guinea and associated islands, including significant early work by Robert Koch and others (1-3), which embraced many aspects of malaria. During the Second World War research conducted by the Land Headquarters Medical Research Unit based in Cairns supported the Australian Army's relentless campaign against malaria in New Guinea. The rigorous use of Atebrin reduced the losses due to malaria among Australian troops and was an important factor in the success of their military campaign. After the war the principal medical scientists continued their studies on malaria (4-6) and further research was initiated in Papua New Guinea (PNG) (then the Territory of Papua and New Guinea) by a new team of dedicated scientists (7-9), who established the epidemiology of malaria in both the lowlands and highlands and made comprehensive studies of the anopheline vectors. This

information was then used to strengthen the systematic campaigns using indoor residual spraying of houses with insecticide as part of the Global Eradication Campaign against Malaria, a military-style operation driven by the World Health Organization (WHO) in the 1950s and 1960s. Reading these accounts of malaria is not only enjoyable but also leads to unexpected insights into the disease – and reveals the passions raised around the concept of malaria eradication. Malaria is endemic throughout the tropics and, though most cases and deaths from the disease occur in Africa and Asia, much research has been done and much written about malaria in the Pacific region. Ways into this extensive literature include historical accounts of malaria in Papua New Guinea (10,11), the Bibliography of Medicine and Human Biology of Papua New Guinea (12) and the focus issues of the *Papua New Guinea Medical Journal* devoted to malaria: Vol 16 No 4-Vol 17 No 1, Dec 1973-Mar 1974; Vol 29 No 1, Mar 1986; Vol 35 No 4, Dec 1992; and Vol 57

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### **Papua New Guinea Institute of Medical Research – the beginnings of malaria research and the personalities involved**

The Papua New Guinea Institute of Medical Research (PNGIMR) was founded (as the Institute of Human Biology) in 1968. Greg Crane, a haematologist working for the Department of Public Health in the Territory of Papua and New Guinea, carried out research on malaria, with a special interest in hyperreactive malarious splenomegaly (then called tropical splenomegaly syndrome), and brought this research with him when he became the inaugural Deputy Director of the Institute. However, by the time of PNG Independence in 1975 Greg had left and his project came to an end. The first comprehensive Malaria Research Program at the Institute began to be formulated in 1976 when I was appointed as the second Director of the Institute and was developing ideas for new research programs. The starting point was in fact a conversation that I had with Graham Mitchell. We flew out of Melbourne together and engaged in intense discussion on the plane. This was when our collaboration on malaria began, the point from which new concepts took off and we were fired into action: thus 1976 is the benchmark year for our 40-year celebration.

What Graham and I agreed on was that the time was ripe for a concerted effort to develop a vaccine against malaria. It was possible to grow the falciparum malaria parasite in vitro. Malarial antigens could be studied and immunity to them tested. Through recent advances in recombinant genetic technology it would be possible to make large quantities of relevant malarial antigens and create a subunit malarial vaccine. We knew that the adults who survived growing up in a malaria-endemic area established effective immunity against the disease and it should therefore be possible to develop a vaccine that would protect children from severe disease and dying of malaria. That is about as far as the conversation went, but we became excited and enthusiastic about these ideas. The concepts needed to be refined, and there were massive unknowns – but that was part of the challenge. Research operates at the edge of the unknown: we thought we could identify this interface and ask the right questions to move forward. Also, critically, research is the art of the soluble: we thought that by then

we had the tools to enable us to solve the problems that these questions would raise.

As I threw myself into the process of becoming the new Director of the PNGIMR I began planning strategic research programs that would investigate the principal diseases that affected Papua New Guineans. Malaria was one of these. Graham was in charge of filariasis research at the Walter and Eliza Hall Institute of Medical Research (WEHI) in Melbourne. I started creating a comprehensive research program on malaria and gathering all the collaborative support that I could find in Australia. The support that I received was remarkable. Much of it came from colleagues who were not working on malaria but agreed to apply their skills and the human resources of their institution to study malaria in PNG. They included Chev Kidson, Director of the Queensland Institute of Medical Research, who recruited Allan Saul and others in his Institute to work on malaria, Robert Clancy and his team in the University of Newcastle Medical School, Sue Serjeantson and Ian Clark at the Australian National University in Canberra, and Bill O'Sullivan and Annette Gero at the University of New South Wales. Greg Crane, then back in Sydney at Concord Hospital, was happy to join the program and revive his work in PNG. Meanwhile Graham Mitchell spoke to Sir Gustav Nossal, the Director of WEHI, who was instantly supportive. Graham added malaria to his portfolio and Gus recruited Graham Brown to the program as a clinical scientist and Robin Anders, a biochemist who had spent much of his career working and teaching in PNG, as a laboratory scientist developing appropriate malaria vaccine antigens. This provided a big boost to the incipient program and showed a firm commitment to our collaborative research effort on the part of WEHI. Russell Howard, Lynn Corcoran and Ross Coppel contributed significantly to this early work. When, later, Graham Mitchell left WEHI, Dave Kemp joined and led the team and, when he left, support for the malaria work from WEHI continued unabated.

On my way to Goroka at the beginning of 1977 to take up my appointment I stopped in Sydney to see Professor Robert Black in the School of Public Health and Tropical Medicine. He was the most renowned malariologist in Australia, had undertaken innovative work on malaria (5) and, as a consultant to WHO, became one of the

architects of the Global Eradication Campaign against Malaria. Although by then WHO had formally renounced the Campaign and was promoting enhanced national malaria control programs Professor Black still believed that properly conducted insecticidal campaigns could reduce vector numbers sufficiently to eradicate malaria. He was bitter that the great goal had been prematurely abandoned. He poured scorn on all my ideas for investigating malaria and especially for working towards a malaria vaccine, which was in his opinion 'pure obfuscation'. I did not get much help from that quarter. I would have had a more sympathetic response from Sir Edward Ford (6), Robert Black's predecessor in his University of Sydney chair, whom I knew as a respected friend with a shared passion for old books, but by then he was fully retired.

A few years later, when our malaria research program was well established, Professor Black retired from the University of Sydney. Our collaborative group joined with colleagues in Sydney to organize a Festschrift in his honour, which he attended. It was a great meeting (13), but sadly he did not enjoy it: he complained to the bitter end about the futility of studying the immunology of malaria. It is interesting that malariologists had always paid attention to immunity in malaria infection – it was conceptually an important part of Robert Koch's work in Madang, for example (14) – but they used their own terminology and it was hard, even in the 1980s, to persuade the old guard – or, at least, most of them – that modern concepts of immunology applied equally to malaria as to other infections. Malaria was regarded by malariologists as a special case in every way and they kept it to themselves for a long time: even now, as a relic of the past, we attend international conferences of tropical medicine and malaria, following the amalgamation of the malaria society with the one representing tropical medicine more broadly.

I was sad that not long after our collaborative program had become fully established and was going strong Graham Mitchell left it and moved on to other things. Nevertheless, research on a malaria vaccine and fundamental aspects of malaria expanded at WEHI, with new laboratory facilities and outstanding people such as Dave Kemp and Alan Cowman. When in due course the Hall Institute had plans for a new building the malaria program was used as a key lever for

government funding, based on the claim that the scientists at WEHI were on track to develop a malaria vaccine within 2 years. In their campaign there was a lot of media coverage. At this time we were building our collaborative malaria program in the field in the Wosera, with a base in Maprik, in East Sepik Province, with the expectation of testing the prototype malaria vaccine there. We had explained to the people and community leaders that we were engaged in the development of a malaria vaccine that was designed to protect children from getting severe malaria and dying from it. Though it might be 10 years before the vaccine finally became available we had to start testing it in a population where the characteristics of malaria were well known, which required baseline studies. The people accepted this argument and, because they recognized malaria as a serious disease, and one that was often fatal in children, they were happy to participate in our long-term malaria research program. At that time every village had at least one radio and the national news was listened to every day; in fact we regularly used the local network to send out information to particular villages. The news item from Australia about the new malaria vaccine being developed at WEHI was picked up by the media in PNG and broadcast as relevant and exciting news. The next day we were confronted by our friends in Wosera villages saying, "What's going on here? We want this new malaria vaccine from Australia that will be ready in 2 years. What's the point in taking part in your study of a vaccine that we may not get for another 10 years!" That took a little explaining. In the end we regained our rapport with the community, WEHI got its new building and our collaborative research program went ahead with renewed vigour.

Though Graham Mitchell was no longer involved in the malaria vaccine research program his initiating role was not forgotten. Despite many setbacks and delays a malaria vaccine with three antigens (Combination B) was eventually produced by our commercial partner Biotechnology Australia and formulated with an adjuvant for use in children in a malaria-endemic area. For ethical reasons it first had to be tested for safety and immunogenicity in adults. We took adult volunteers from the Wosera to Goroka, located in a non-endemic area, for the preliminary safety trial. On a day in 1996, 20 years after our high-flying conversation, I injected the first participant with the long-awaited malaria

vaccine and called Graham from Goroka to tell him the good news. For him the call was as much from the past as the present, but he was as happy with the outcome as I was.

## **Papua New Guinea Institute of Medical Research – Malaria Research Program**

### **Establishment of the Program**

To go back again to the beginning, during 1977 the collaborations that I had established to create the PNGIMR's Malaria Research Program were strengthened and specific research projects planned. I made as many new contacts as I could, in the health services, in government departments, national and provincial, in international agencies and in the community. I found that there was a project underway in Madang conducted by John Stace, the paediatrician at Madang Hospital, evaluating chemoprophylaxis with amodiaquine in young children. Funding for this had been provided by the IMR and so I incorporated it into our overall program. One of the early appointments made to the Institute staff was George Nurse as Research Fellow in Genetics and he was encouraged to study human genetics in relation to malaria. To study malaria we obviously needed a site on the coast and Madang was chosen. I started negotiations with the Lutheran Church to use unoccupied buildings at Yagaum Hospital after its post-Independence conversion to a health centre. We reached an agreement that the IMR could take over the buildings in return for any necessary repairs and restoration and their ongoing permanent maintenance. As a first move I needed to secure funding for our proposed work, and two things helped. Firstly, WHO had funds for applied field research through the Special Programme for Research and Training in Tropical Diseases (TDR – Tropical Disease Research). Secondly, the PNG Government had committed budgetary funds for expanded departmental activities to the National Public Expenditure Plan (NPEP) and these funds, which were open to all government departments and statutory bodies, had to be obtained competitively through the National Planning Office. With support from the WHO Regional Office in Manila we were successful in getting an integrated package of proposals funded through TDR, which certainly would not be possible today. These proposed projects are set out in the Seventh Annual Report 1976-1978 of the PNGIMR (15) and include as co-investigators John

Stace, George Nurse, Graham Mitchell, Robert Clancy, Chev Kidson and Greg Crane. The NPEP was advantageous to the IMR, since I had good relations with the National Planning Office and we were experienced in writing proposals. After a successful first round that provided funding for a new building to replace our temporary accommodation in Goroka and a Pneumonia Research Program, we applied for a Malaria Research Program and a Nutrition Research Program, and got everything we asked for. This included funds for refurbishing the buildings in Yagaum and the establishment of parasitological and entomological laboratories, including facilities for in vitro culture and an insectary, offices and accommodation for staff, as well as the necessary staff positions.

We set up our research program in Yagaum and neighbouring communities and in the Madang General Hospital. We wanted, as in all our work, to increase our understanding of infection and disease with appropriate applied research and to reach the point of evaluating interventions (translational research) as quickly as possible. We always kept our mantra in mind – No Research without Service: No Service without Research. We aimed to study parasites, vectors, people – the sick and the well – and villages/hamlets. We needed a range of scientific disciplines and state-of-the-art tools – and collaboration: with scientists, health services, funders and participating communities.

Peter Heywood, who had initially been appointed as Research Fellow in Nutrition, became the Deputy Director of the Institute in his second contract period and was installed as the officer in charge of the Madang branch of the Institute based in Yagaum. We employed new staff and welcomed some extraordinary people to PNG, as well as gaining a cadre of skilled and enthusiastic Papua New Guineans who have continued for decades to contribute loyally to malaria research at the IMR. Establishing rigorous microscopic diagnosis of malaria was fundamental to all our research projects; this was achieved by David Gibson and Arthur Narara, who then supervised the ongoing, endless support that has been provided to all our projects by the microscopists. David had worked with the great names in malaria from the British Colonial Service in Africa. He joined our team somewhat reluctantly because he came from the school that believed that we already knew



all the essential things about malaria and therefore he could see little point in further research. As our program developed David contributed to the conceptual as well as the technical aspects of our malaria work and gradually came to realize that there was an enormous amount that we still had to learn. When he retired he gave me his collection of old malaria classics, books that he had acquired during his time in Africa; they remain treasured possessions in my library. Derek Charlwood was recruited to be our first entomologist and Jackie Cattani to lead our epidemiological studies. Karen Day came first as an immunologist in our lymphatic filariasis research program, but later returned to work on malaria. Helena Vrbova, among other things, established our first longitudinal study of malaria in Gonoa village. Her pioneering work and tragic death shortly before she was about to undertake a course in London are acknowledged in a set of tributes published in the *Papua New Guinea Medical Journal* (16).

### **Prophylaxis with antimalarial drugs in children**

One of the studies that Helena undertook was a rigorous expansion of John Stace's trial of chemoprophylaxis. We were planning to use weekly doses in young children of amodiaquine or Maloprim (a combination of pyrimethamine and dapson), antimalarials that were taken for prophylaxis by expatriates living in PNG. When I took this idea to Geneva, the old guard were horrified since it was part of established malaria dogma that European children needed weekly protection from malaria in the tropics but on no account should this be given to 'native' children since it would prevent them from establishing their own protective immunity. Of course in a malaria-endemic area children did establish protective immunity but in the process many of them died of malaria. This dogma had arisen in the colonial world but there was no evidence for it. Nor did anybody want to look for evidence since if there was value in giving all these children weekly drugs for a few years to protect them from death while they were slowly developing their own immunity, then no doubt it should be done – but who would pay for it? This was not unreasonable but the question had been avoided by reference to a convenient but specious piece of dogma. Helena carried out a placebo-controlled trial of chemoprophylaxis with amodiaquine or Maloprim in semi-immune school children

as a preliminary to more definitive studies in young children. The results showed an effect on parasitaemia and spleen size but neither regimen was completely successful in preventing parasitaemia. The publication of this study did not occur until 10 years after Helena's death, when her draft paper was revised and completed by Katharine Trenholme (17). However, the study in young children was not undertaken. Firstly, we discovered to our dismay that we were facing not only increasing resistance of the malaria parasites to chloroquine and amodiaquine but also to the pyrimethamine-based drugs (Fansidar and Maloprim) used respectively for treatment and prevention (18): it would not be a good time to start using Maloprim for a widespread prophylaxis program. Secondly, this was an intervention which, if successful, would have to be considered for implementation by the Health Department, and they were not enthusiastic about the idea. In keeping with the philosophy that underpinned research at the PNGIMR, the malaria research program engaged in studies that were designed ultimately to lead to an intervention. If such an intervention could not, or would not, be implemented then clearly there was little point in carrying out the research. It is true that we need art as well as science to interpret this rule and doing so is not always straightforward – for example, an independent study on drug resistance might eventually persuade a reluctant Department to change standard treatment. However, in this case we already had another good reason to support our decision. As it turned out, the idea of chemoprophylaxis in the community was at least released from dogma and did not die entirely, since years later successful studies of IPTi and IPTp – intermittent preventive treatment of malaria in infancy and pregnancy, respectively – were carried out in PNG by Ivo Mueller, Stephen Rogerson and their colleagues (19,20).

### **Malaria control**

We chased all kinds of ideas to understand and control malaria: treating children in village communities through volunteer health workers, longitudinal parasitological and immunological studies, the use of insecticide-treated bednets, analysing the behaviour of the mosquito vectors, investigating human genetic polymorphisms conveying resistance to malaria, identifying small-area variation in the epidemiology of malaria and the importance

of local ecologies, developing a blood-stage malaria vaccine, monitoring drug resistance, and so on. We supported the use of indoor residual spraying in certain circumstances, such as in the highlands, but we did not subscribe to its use in highly endemic areas, and we certainly did not believe that we could use it to eradicate malaria. Though the WHO global malaria program had switched from eradication to control in 1969, the dogma of eradication through spraying persisted, even among advisers to the malaria control program in PNG. I had a jubilant message from one such colleague who had gone off to work in the Solomons: "I tell you: spraying works. We have shown it here." For the agnostic, spraying works – for sure, sometimes, in some circumstances. For the religious believer, however, it always works – and if it doesn't, this means that it was not applied properly. We had a meeting in Port Moresby in August 1980 on malaria in the region organized by the WHO Manila Office, with all the interested parties invited, which was attended by the Chief Malaria Adviser from WHO Geneva. All the senior malaria staff from the PNGIMR were there and were each given a place on the program. I was to give the overview of our collaborative research program. Before the meeting the organizer took me aside and said, "We are very interested in the research that you and your team are doing and are proposing to do. Present your ideas as freely as you wish. But please do not make any disparaging remarks about spraying. Though eradication has now been formally dropped, spraying is still sacrosanct among the senior staff in Geneva, and we do not want to cause offence." Dogma was firmly entrenched in malaria, as we have seen, but this was a pillar of their religion. We recognize that there is both an art and a science in malaria control – to add to the example in the previous paragraph, in the face of increasing evidence of drug resistance keen judgement is needed when deciding the best time for making a change in standard treatment and what drugs to use – but we do not also need dogmatic religion to guide our decisions. This fascinating but idiosyncratic and inward-looking aspect to malaria in the past may seem unbelievably remote from the multidisciplinary sweep of the molecular science of today. However, we should still be careful not to overreach the bounds of our scientific knowledge; we can learn a lot from the mistaken grand schemes, entrenched dogmas and false hopes of the past to inform our current global approaches

to controlling malaria.

### **Insecticidal mosquito nets**

One of our ideas was to provide insecticidal mosquito nets to people living in malaria-endemic areas as a way of controlling the disease. This also did not go down well initially in Geneva. The idea was considered a bit of a joke. It was fine for Europeans to sleep under large nets in their houses to stop getting bitten at night, but it was considered somewhat ludicrous to expect this to work for 'natives' in their village huts. Just providing a net would, indeed, probably not have worked but the added insecticide could have a major effect. The feasibility of doing this was brought to our attention by colleagues at Simon Fraser University in Canada, from where Bruce Millen joined us and conducted research for his Masters on insecticide-treated mosquito nets; the results were encouraging. Our team was then augmented by two outstanding entomologists, Patricia Graves and Tom Burkot. Tricia conducted a trial of the impact of permethrin-impregnated nets on falciparum malaria in young children and the positive outcome (21) had a significant influence on WHO policy. Insecticide-treated bednets became not only respectable but a key component of the global effort to control malaria.

### **Dogmatic beliefs and colonial attitudes**

I do not think that I have exaggerated the entrenched attitudes and dogmatic beliefs of the malaria establishment in the past, and the emotional memory of the scornful opposition we encountered is still strong. Nor were the colonial connections far-fetched: they were part of the same wide world of tropical medicine, which in the early days was necessarily a colonial enterprise. The colonial attitudes were not explicit but deeply embedded, as they usually are. Indeed they may still be found in some quarters, and ingrained attitudes emerge in many contexts, often simple ones. For example, the terms 'active' and 'passive' case detection have a long history and are based on the 'active effort' required by the investigators to go out and detect cases of a disease, in contrast to those cases that are detected because they 'passively' turn up. However, if you think of it from the point of view of the patients who constitute the cases in the community the effort goes the other way. If in a community-

based study we are to regard the people and patients as participants in the study and not the subjects of it, there is good reason to choose more neutral and objective terms to describe what we are doing (22).

### **Blood-stage malaria vaccine**

Our malaria research program began with the idea of a malaria vaccine and work towards developing and then testing our vaccine continued for more than 20 years. As development proceeded to the point where the eventual production of a vaccine did look feasible it became essential to establish an appropriate field site for its evaluation. Our program was well set up in Madang, but we began to realize that the population was too urbanized, with good roads, a convenient, well-equipped hospital and ready availability of antimalarial drugs in local stores, and too influenced by our ongoing research activities to be a suitable site for a major field trial of a vaccine in children. So we needed to find somewhere else. We sent Paul Garner and Peter Heywood to investigate the Wosera area near Maprik in East Sepik Province and do some studies there. From what we learned it seemed to be ideal for the purpose. However, how were we going to fund a new branch of the Institute? Then we had a serendipitous offer from the United States Agency for International Development (USAID). There was a sporozoite vaccine under development at New York University (NYU) and USAID had agreed to support the evaluation of this vaccine. They needed a field site in the tropical, malaria-endemic world, and we were encouraged to apply. I wrote the grant proposal in a sleepless week and our application was successful. It was agreed between both parties that we would test a US vaccine as a priority but that the site could also be used to test any other malaria vaccine that became available. USAID agreed, after review, that the study site in Madang was not sufficient for the purpose of the evaluation project and they funded a completely new field site in the Wosera, with a base in Maprik consisting of new buildings for laboratory facilities, offices and staff accommodation and a transit house for the project in Wewak. We bought a house in Wewak, which worked well – even if we were not allowed to use project funds to support the upkeep of the swimming pool! We secured land in Maprik and had the PNGIMR architect design the buildings that we wanted. We had a lot of

support from senior USAID staff and from the US Ambassador in Port Moresby. Getting building contractors to construct the buildings to our requirements in Maprik was a major problem, and the first builder went bankrupt. That is absolutely the worst thing that can happen in a construction project, since you have no redress and are at the mercy of a second contractor, if you can get one. Our second contractor failed and we finished the construction by buying all the materials ourselves and carting them from Wewak to Maprik for a builder who was working on-site. Finally, it was done, and the US Ambassador came from Port Moresby to officially open the building. We had established the Maprik branch of the PNGIMR.

As a sequel to this, we did finally evaluate our vaccine in the Wosera (as I have mentioned earlier) and the NYU vaccine program produced nothing for us to test. However, after its good start the project did not go entirely to plan. Indeed, in 1993 the whole enterprise nearly fell apart, with nothing achieved at all. After the Berlin Wall came down in 1989 and the subsequent unification of Germany, a new market for US aid opened up, and USAID decided to delete its Pacific aid program entirely and put all these resources into Eastern Europe. All contracts were cancelled and we were given 3 months of funding to close down the project. End of story. Well, it could easily have been. I had an emergency meeting with the National Planning Office, who were very supportive. Jointly we approached the Australian Agency for International Development (AusAID). In what I felt was a remarkably generous act, AusAID agreed to take over where USAID had dropped out. They gave us equivalent funding for 18 months to cover a transition period while we were developing a formal proposal to AusAID to continue the project. They wanted the proposal written 'in the AusAID way' and sent advisers from Australia to help me do that. In the end a good outcome was achieved and our malaria vaccine epidemiology and evaluation project was able to continue uninterrupted and fully funded. The extra things that AusAID required were funded separately and since they were not feasible in the context of our work did not actually happen! So it came about that when we eventually tested the Australian malaria vaccine we did so within a project that was supported by Australian aid funding.

To return to the heady days of moving into Maprik, we set up our field studies as planned, which were much more comprehensive than just a vaccine trial (23). We also had support from USAID for the more sophisticated molecular parasitology and immunology investigations being conducted in our Yagaum laboratories, and for entomology, which I had to fight for in a big way against the expert advice being given to USAID. Blaise Genton, a clinician and epidemiologist, Inoni Betuela, a clinician, and Lawrence Rare made a superb team in charge of the field studies, which were conducted in the villages of the South Wosera and Kunjingini Health Centre. In order to strengthen our presence in the Wosera, a project house was later built in Kunjingini. Fadwa Al-Yaman as immunologist and Hans-Peter Beck and Ingrid Felger as molecular parasitologists, with supporting technical staff, carried out their essential studies as part of the overall program. We all spent a lot of time travelling between Wewak and Maprik. We got used to delays in fording the rivers and to making decisions about whether we were brave enough to attempt the first crossing from a long line of waiting cars. However, it was only Blaise who had the experience of facing a plane making an emergency landing on the road he was driving along. The necessary baseline studies were conducted (24,25). Meanwhile the combination vaccine with 3 antigens (MSP-1, MSP-2 and RESA) was being produced by Biotechnology Australia in Sydney. After safety and immunogenicity studies in adults and children the vaccine trial with natural challenge (phase 2b) in children was finally achieved (26). The vaccine had been designed from the beginning to use blood-stage antigens to prevent severe malaria and death in young children. In the trial we used parasite density as a surrogate for severe malaria, and the principle of this vaccine was proved in the trial through a significant reduction in density. The vaccine was never intended to prevent malaria infection. It was designed to be given to children in malaria-endemic areas and was not aimed at tourists or the military to prevent them from getting malaria. Even some of our research team failed to get that point. The trial also showed that MSP-2 was the important component: only one of its two world-wide families was represented in the vaccine, and the first breakthrough infections following vaccination were from the other family (27). Clearly the next thing to do was to formulate a vaccine that contained both families of MSP-

2. Sadly, there was not to be a 'next thing' since our manufacturer ceased operating and we had nowhere to go to find a way forward.

In general, we knew that there was little corporate support for this kind of malaria vaccine since easy money would be made only from putting a vaccine in the market that could be used by non-immune adults to prevent an attack of malaria. Though we had not been able to realize the phase 3 efficacy trial that we and our community participants had anticipated, we had achieved proof of principle for a malaria vaccine, which was a milestone, even though this is rarely acknowledged. I was proud of the outcome and therefore surprised that we had initial difficulty getting our results published. This turned out in part to be our collective fault. Some members of our team were engaged in a project to develop a malaria challenge capability provided through the injection of infective human blood. The other members were not involved and indeed some were strongly opposed to the whole idea. This did not stop the project, however, nor did it prevent our vaccine from being tested in the challenge system (28). To nobody's surprise the vaccine had no effect on the initial growth rate of injected *Plasmodium falciparum* parasites, and we paid little attention to the result. Later, after the trial had been completed, we engaged in the slow process, with all the authors involved, of writing up the phase 2b trial results; we did eventually complete the paper and submitted it to a distinguished journal. The editor sent the manuscript for preliminary review to a malaria 'expert', who recommended that the paper be rejected because "the vaccine has already been shown not to work". This was not peer review since we were given no opportunity for rebuttal. As an editor as well as an investigator and author I was angry with this decision for a range of reasons but we had no choice but to accept it. Of course the paper was eventually published (26), as well as others related to the trial. Robin Anders continued to work on blood-stage antigens...and one day, perhaps, this approach to malaria control may eventually come to fruition.

### Further reflections on malaria

I left the Institute in 2000, long before our celebratory 40-year period ended. Though I was no longer involved, I kept up an interest in the IMR's work and continued my own



compulsive thinking and reading about malaria. In this period there is a wealth of activities and accomplishments to consider but I must restrict my reflections to a few topics.

In recent years we have seen a resurrection of the idea of the global eradication of malaria. Eradication is defined by the World Health Organization as “the permanent reduction to zero of the worldwide incidence of infection caused by a specific pathogen established in a human or animal population, as a result of deliberate efforts, with no more risk of reintroduction”. Malaria is an infection by *Plasmodium* spp. Without considering just how many species might infect humans, to the traditional four (*P. falciparum*, *P. vivax*, *P. malariae* and *P. ovale*) we have now added *P. knowlesi*. *P. knowlesi* causes severe human malaria across South Asia and, moreover, is a zoonosis, with a reservoir of infection in non-human primates. How can we achieve “no more risk of reintroduction”? Only, it seems, by altering the definitions of ‘eradication’ and ‘human malaria’. Certainly, everything has changed: and yet the more it changes the more it is the same thing. We may look to the Malaria Eradication Scientific Alliance (MESA) for answers. Would that our good friend Bob Desowitz, who was part of our team studying malaria in PNG (29) and had a fearless wit (30), were still here to expound for our benefit this Holy Grail and the new adventures of the Knights of the Round Table.

It is striking that malaria in children in PNG, though deadly enough, has a lower case fatality rate than in Africa and malaria in pregnant women has less serious outcomes in PNG than in South-East Asia. The reasons for these differences probably lie in the remarkable number of genetic polymorphisms found in Papua New Guineans that confer resistance to malaria. The PNGIMR program studied them all. In general it was found that there was no effect on levels of infection but a significant reduction in severe disease. This was found with  $\alpha$ -thalassaemia in children (31) – and also, to our surprise, for infections other than malaria – and with South-East Asian ovalocytosis in pregnant women (32). Ovalocytosis also protected children from cerebral malaria (33) and studies of its mechanism of protection (34) provided a likely explanation for its peak of incidence being in slightly older children, after the early ravages of malarial anaemia in infancy. These findings of

natural, sustainable protection were resonant of our strategic approach to a malaria vaccine, and emphasized how mild infection can act as a kind of vaccine (35).

It would be good to know exactly what is going on immunologically in naturally protected adults living in areas of high malarial endemicity. Is it a form of concomitant immunity (tolerating established parasites and rejecting new infections) such as occurs with gut parasites – and, anyway, how does that work? What drives the dramatic transition in protection among pregnant women from their first to their second, or sometimes third, pregnancy? To reflect is good, no doubt, but in reflections so often all that we descry is a deep pool of uncertainties!

In recent years the Malaria Control Program has been intensified by the national roll-out of long-lasting insecticidal nets (LLINs), with 2.4 million free LLINs distributed to households in communities throughout PNG. The evaluation of this program undertaken by Manuel Hetzel and his team at the PNGIMR was a massive undertaking in itself (36). There is no doubt that the LLINs contributed to a very successful intervention, which has also been achieved globally, but sustaining the effect is difficult. The nets need to be continually used and eventually will need replacing. While insecticide resistance has threatened this program in many places it has not been a problem in PNG. Furthermore, though the mosquitoes have adapted their behaviour by biting people earlier when they are not protected by nets and this has reduced the level of protection against malaria exposure (37), mosquito behaviour is not fixed and so the nets are still partially successful. A similar situation is found with host selection; most species of *Anopheles* are opportunistic and show plasticity of host selection, which adds to the complexity of control but does not negate it (38). Thus the current norm for malaria control is a combination of a range of measures appropriate for the location that are each expected in the long term to be partially successful. Prompt treatment with effective antimalarial drugs remains an important mainstay; this requires boosting of general health services, accurate diagnosis, more community engagement and monitoring of drug resistance. Community engagement might also contribute to a creative use of humanized insecticidal screens. Taking endectocides, such as ivermectin, well-known

as a vital drug in the campaign against filariasis, which will poison the mosquitoes when they bite, may well be popular – and also good for scabies. To bring these reflections to an end, and return to basics, in contemplating any malaria control program in PNG we cannot forget that we have *Plasmodium vivax*, with its relapses from hypnozoites in the liver, as a major cause of malaria. That is a problem enough, by itself.

Elimination is the natural outcome of good control, but it has to be followed by rigorous surveillance and vigilance, and therefore is not a conclusion to a malaria control program. Political support and funding remain essential but I do not think we can achieve sustainable levels of good control without much more emphasis on engaging the support of communities in a determined active collaborative effort to control 'their malaria'. The health services must also be involved, and malaria will not be the only health problem that they need to consider. Finally, in what we do and plan we have to contend, as in all aspects of life now and in the future, with the effects of global warming and climate change.

#### ACKNOWLEDGEMENTS

This paper is based on a presentation at the Colloquium to celebrate 40 years of the PNGIMR's Malaria Research Program, which was organized by Moses Laman, Leanne Robinson and Livingstone Tavul in Madang on 24-26 August 2016 (39). In thanking them I take the opportunity to recognize many others for their support over decades of research. I also honour the memory of those colleagues who have died and note those for whom we have created a written memorial (16,40-42). Some acknowledgements of colleagues occur in the text and other names appear in the references. For a more complete list one could consult the malaria papers in the PL (the PNGIMR Publication List), which do represent, by any criterion, an impressive collection of biomedical and translational research findings. Outcomes and achievements are undeniably important but what I remember most is the spirit of good humour and collegiality that imbued all our hard work. As well as those who became authors I thank the IMR support staff of many kinds, and also members of the Health Department, National Planning Office, World Health Organization and funding agencies who provided needed assistance to the staff, especially me, and the scientific

work of the Institute over many years. We also had support from the Medical Faculty and I am happy to pay tribute to my friend Sirus Naraqi, who was Professor of Medicine at the University of Papua New Guinea and studied malaria in Port Moresby. I acknowledge the Institute Council, from which I gained much through the influence and support of Adolf Saweri (43), and the Buttressing Coalition (44). I thank Raymond Paru, Manasseh Baea, Andrew Raiko, Lawrence Rare, Benson Kiniboro, Kenny Rupa and others who have had the unenviable task of being in charge of a branch of the Institute, Dawn Parsons, who mothered us all, and our architect John Proctor. We have enjoyed valuable input from clinical scientists, such as Steve Allen, David Mokela and Laurens Manning in Madang and Jim Kazura and Tim Davis as senior collaborators. Jim and his colleagues, in particular Pete Zimmerman and Chris King, from Case Western Reserve University collaborated with us first on filariasis and later made major contributions to our malaria work and training programs. Tim and his group from the University of Western Australia were equally committed colleagues who added pharmacokinetics to the Institute's portfolio. Our malaria vaccine team included Blaise Genton, Ingrid Felger, Hans-Peter Beck and, as statistician, Tom Smith. They all ended up in the Swiss Tropical and Public Health Institute, whose Director, Marcel Tanner, was another great supporter of the IMR's collaborative programs of research and training. Of course the malaria research program goes way beyond me, and was continued by John Reeder, Ivo Mueller, Manuel Hetzel and many others until we reached our 40-year mark, held high by Leanne Robinson, Livingstone Tavul and Moses Laman. They can do so because of their own stature but also because they represent, respectively, the continuous, ongoing commitment from the Walter and Eliza Hall Institute to our collaborative malaria research program, the decades of competent and loyal service contributed by our long-serving technical and scientific staff, and the bright future for sustained programs of research being created by the growing Papua New Guinean college of qualified, innovative medical scientists. It was entirely appropriate that the award of Livingstone's PhD was announced during the Colloquium. Finally, I thank the members of every community that contributed to our research work. Many I came to know well; their astute questions about the rationale of our studies led to many

lively discussions and their willingness to participate faithfully over many years was exemplary. Though we managed to ease the community burden of malaria I am sorry that we were unable to deliver more sustainable outcomes, to match the great expectations, from our studies.

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## **Responding to change – current perspectives on four decades of malaria research at the Papua New Guinea Institute of Medical Research**

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### **SUMMARY**

**These perspectives relate principally to the most recent of the four decades of research on malaria conducted by the Papua New Guinea Institute of Medical Research. The achievements of the Institute, in both research and training, over this period have been impressive. Innovative leadership, dedicated staff at all levels, collaborative international partnerships and success in obtaining major grant funding have enabled these achievements. The quality and commitment of the Papua New Guinean scientists in training or trained to Masters and PhD levels through malaria research bodes well for the future of medical research and its implementation in Papua New Guinea. The Institute has established close working relationships with institutions such as national and provincial departments of health, the Central Public Health Laboratory, health facilities at different levels, the World Health Organization, international research and training institutions and all the communities engaged in its research. The active involvement of participating communities in the research is an outstanding aspect that upholds a long-standing tradition at the Papua New Guinea Institute of Medical Research.**

These perspectives are modified and updated from those I presented at the Colloquium to celebrate 40 years of malaria research at the Papua New Guinea Institute of Medical Research (PNGIMR) (1). Any perspectives on the history of the malaria and vector-borne diseases research program at the PNGIMR over the last 40 years are perhaps best observed through the experiences of the inspirational individuals that have preceded my own time at PNGIMR. There is a truly fascinating mix of chance encounters between like-minded individuals as well as strategically planned studies. As I have reflected on this, it seems to me that the capacity – indeed, the necessity – to grab hold of opportunities and respond to changing circumstances, not only in funding and resource priorities but also scientifically, has underpinned much of the historical vector-borne disease (VBD) research strategy. And so it continues to unfold in this manner today.

A visit to the mainstay of malaria research at the sites in Yagaum and Maprik would have you think that perhaps not too much has changed over the past few decades. We were certainly privileged to have quite a few long-term staff from the early days still working as part of the IMR family as we celebrated the 40-year milestone (1). We owe a great deal to their dedicated service and the consistency and commitment they have maintained in the face of real change and the occasional great challenge.

Sadly, the tired old office and laboratory buildings at Yagaum still sit relatively unchanged whilst the very hard work of a committed few – namely Dr Moses Laman and Professor William Pomat – continues to generate the necessary investment for the development of the new site in Madang town. By the time we celebrate 50 years it is my sincere hope that the highly anticipated

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development and transition of IMR Madang to town will be complete. However, these constant aspects of our infrastructure mask what has certainly been a period of great change and great achievement.

In the past decade alone there has been a radical shift in the malaria situation, in Papua New Guinea (PNG) as well as globally. The priority focus has shifted from one of sustained malaria control to that of global malaria eradication, through a country by country, region by region strategy of malaria elimination. This has necessitated an overall shift in the way malaria research questions are prioritized, funded and implemented.

In PNG, with support from the Global Fund to fight AIDS (acquired immune deficiency syndrome), tuberculosis (TB) and malaria, and evidence generated from the PNGIMR's own research program, the country embarked upon an intensified program of malaria control in 2008 with the nation-wide distribution of long-lasting insecticidal nets (LLINs), alongside changes to diagnosis and treatment protocols. Since then, the prevalence of malaria has declined by more than 80% across the country.

The PNGIMR has been a key partner in this National Malaria Control Program, monitoring the effectiveness via the establishment of a highly multidisciplinary 'MalCon' operational research team, based within the Population Health and Demography Unit at Goroka IMR headquarters but effectively working in every corner of Papua New Guinea. Initially established under the direction of Dr Manuel Hetzel and Dr Justin Pulford, this team continues to closely support the program under the guidance of Prof. William Pomat and Dr Moses Laman. Through serial malaria indicator surveys, sentinel site surveillance and health facility surveys, as well as vector and insecticide resistance surveys, this program continues to deliver evidence to inform the broader national program (2-4). This program has also provided many opportunities for PNG researchers to take leading roles and gain valuable experience as independent researchers. Dr Livingstone Tavul completed his PhD on one such study, monitoring the therapeutic efficacy of artemether-lumefantrine in Milne Bay Province and East Sepik Province and, in doing so, provided key evidence to the National Department of Health Malaria

Program and the World Health Organization (WHO) that our first-line antimalarials remain highly efficacious in PNG (5). Tragically, five highly skilled members of the MalCon team went missing whilst they were conducting surveys in West New Britain Province in 2011 – an immeasurable loss for their families, the MalCon team, PNGIMR and their country. They will always be remembered.

One of the first field trials that I took a leading role on after joining the IMR in a full-time capacity in early 2009 was with Prof. Ivo Mueller and Dr Inoni Betuela on the Albinama treatment to reinfection study. I am not sure any of us expected it to be quite as tedious, all-consuming or, indeed, as satisfying as it turned out to be. It was certainly worthwhile in the end – not only providing clear evidence that hypnozoites are responsible for 80% of *Plasmodium vivax* infections in PNG children (6), but also laying the ground work for an extremely solid, ongoing working relationship that continues today. I remain highly indebted to both Ivo and Inoni for their professional support, encouragement and guidance, not to mention some culinary insights and life lessons during shared times in the Sepik. Inoni was Head of the Vector-Borne Diseases Unit (VBDU) from 2010 to 2012, whilst simultaneously completing his PhD at the University of Barcelona. Despite officially moving on from PNGIMR in 2010, Ivo has remained closely involved in the programs he had set up, providing enormous support and opportunity to many – something that I will certainly always be grateful for. Both the form and function of the current VBDU owes a great deal to Ivo's personal and professional input.

A major program of the VBDU over the past decade has been to develop a more detailed understanding of the impact that reduced transmission is having on the epidemiology of malaria – in particular interaction between hosts, parasites and vectors, the acquisition of natural immunity, parasite diversity and the abundance and behaviour of major anopheline vectors. These coordinated epidemiological, entomological and host immunity studies have been conducted as part of two large international programs: the National Institutes of Health (NIH) International Centre of Excellence in Malaria Research (ICEMR) Program, led by Prof. James Kazura, and the Bill and Melinda Gates Foundation Epidemiology of Malaria

Transmission (TransEPI) Consortium, led by Prof. Ivo Mueller. On the ground, I have shared all the joy and pain of executing these large and intensive epidemiological field studies with a really experienced and tremendously enthusiastic team, without whom the work would truly not have been possible. Most especially, the contribution of Dr Maria Ome-Kaius has been immense, but so many people (Mary Salib, Daisy Mantila, Dulcie Lautu-Ninda, Bethuel Kotty, Henson Dima, Benson Kiniboro, Matthew Philip – just to name a few) have poured so much of themselves into this work.

These highly collaborative programs are not only yielding extremely valuable insights into the impact of intensified malaria control on the epidemiology of malaria in PNG (7), but have also allowed us to develop considerable capacity here in PNG that, in turn, is allowing us to do the kind of research that reduced transmission demands. In particular, the infrastructure and capacity to perform high-throughput DNA (deoxyribonucleic acid) extraction, RNA (ribonucleic acid) extraction and real-time quantitative polymerase chain reaction (PCR) diagnosis of malaria infections (asexual and sexual stages) is now well established within the VBDU. The past efforts of Dr Anna Rosanas-Urgell and Dr Eline Kattenberg (with steady support and encouragement from Prof. Ingrid Felger) to implement systems of quality control, and to up-skill and cross-skill everyone in the group, has ensured that molecular epidemiology will remain a strength of the program into the future. There has also been continued support and capacity development under these programs for the strong program of immunoepidemiological studies that Dr Danielle Stanic initiated during her years in Madang. In particular we have had strong collaborations with Prof. Chris King (Case Western Reserve University) investigating i) the impact of in utero exposure to malaria on the development of infant immune responses and the risk of all-cause morbidity in the first year of life, and ii) immunoregulatory networks elicited by an episode of clinical malaria, both in the acute and convalescent phase; and with Prof. James Beeson (Burnet Institute) investigating antibody responses to *P. falciparum* and *P. vivax* merozoite surface proteins and developing the capacity to conduct functional assays (eg, complement fixation). In addition to developing considerable 'on-the-job' capacity, the NIH ICEMR program

is providing research support to Dr Moses Laman to conduct surveillance for severe malaria and paediatric illness at Modilon General Hospital; to John Bosco Keven in his PhD studies investigating the non-random feeding preferences of anopheline vectors in PNG; and to Dr Maria Ome-Kaius, a key component of whose PhD project is a child cohort study from the ICEMR program.

With continued ICEMR funding and new TDR (Special Programme for Research and Training in Tropical Diseases) funding (Principal Investigator: Dr Moses Laman), we have commenced a multidisciplinary but highly integrated project on the north coast of Madang, investigating the magnitude and drivers of residual malaria transmission after the roll-out of standard interventions to determine which human, vector and/or parasite behaviour/characteristics are the most important obstacles to elimination. A first-of-its-kind trilateral partnership, the China-Papua New Guinea-Australia Pilot Cooperation on Strengthening Malaria Diagnosis in PNG, is also providing support for operational malaria research at the sentinel sites, and offering up the potential for new relationships with the National Institute of Parasitic Diseases, unique training opportunities and stronger partnerships with in-country organizations including the National Department of Health (NDoH), Central Public Health Laboratory (CPHL) and School of Medicine and Health Sciences (SMHS). In addition, in 2016 Dr Moses Laman, Prof. Ivo Mueller, Dr Stephan Karl and myself were able to secure a new NIH ICEMR proposal – Understanding, tracking and eliminating malaria transmission in the Asia-Pacific region – that will provide support for continued malaria epidemiological field work in PNG from 2017 to 2024.

In recent years, several highly challenging areas of laboratory research, membrane-feeding transmission studies and *Plasmodium vivax* invasion assays have all been re-established in the VBDU. Investigating human-to-mosquito transmission of malaria and vector competence was an important component of work conducted by Prof. Patricia Graves and Prof. Tom Burkot during their years at IMR and Dr Lisa Reimer and the team re-established a colony of *Anopheles farauti* 1 and membrane-feeding assays in 2009-2013, allowing this work to proceed once again. Under the TransEPI project and in collaboration with Prof. Jetsumon

Sattabongkot Prachumsri and her team at Mahidol University in Thailand, and more recently under the guidance of Dr Stephan Karl and due to the dedication of Mr Lincoln Timinao, we have been able to strengthen our capacity to conduct this work. We were also able to establish short-term *P. vivax* culture in the molecular lab in the context of an ongoing South-east Asian ovalocytosis (SAO) and *P. vivax* invasion collaboration with Dr Anna Rosanas-Urgell and her team at the Institute of Tropical Medicine in Antwerp. Together with the aforementioned membrane-feeding assays, this line of research is extremely challenging but represents a great opportunity for the VBDU going forward, as the demand to assess the efficacy of potential transmission-blocking antibodies continues to escalate.

Clinical trials have once again been a major feature of our program, as well as an area of substantial capacity development and a clear strength for the future. The implementation of two major randomized trials of intermittent preventive treatment with antimalarials for the prevention of malaria and anaemia in infants (IPTi) (8) and pregnant mothers (IPTp) (9) were a highlight for the Unit. These two very large clinical trials (IPTi: 1100 children in Madang plus 500 in Maprik) were the first studies to prove that these interventions were able to prevent both *P. falciparum* and *P. vivax* malaria in children and prevent placental malaria and improve birthweights outside Africa and in areas with *P. vivax* malaria. These results have important public health implications and IPTp is now part of the PNG National Standard Treatment guidelines. Importantly, these trials not only facilitated on-the-ground input from international clinicians and scientists such as Prof. Stephen Rogerson, Prof. Ivo Mueller, Prof. James Beeson, Dr Nicolas Senn, Dr Danielle Stanisic, Dr Sarah Hanieh, Dr Alex Umbers and Dr Holger Unger but also provided opportunity for talented young PNG clinicians such as Dr Patricia Rarau, Dr Maria Ome-Kaius and Dr Regina Wangnapi to join PNGIMR, complete their Masters degrees and develop into experienced and independent clinical researchers. I had the privilege of directly working alongside Dr Patricia Rarau to complete the IPTi trial during my first two years at the IMR. She not only introduced me to IMR Madang, the trial team and all the intricacies of the trial itself, but has been a good friend ever since.

Sadly in early 2016, we mourned the tragic

loss of our colleague and sister, the late Dr Regina Wangnapi, a woman who had achieved so much in her 35 years: a medical doctor, a Masters level clinical researcher forging her career, a wife and a mother. Her legacy will continue to shine brightly, enlightening and inspiring us to be a better version of ourselves, everyday (10).

This period has also seen the continuation of a highly productive collaboration on drug efficacy and pharmacokinetic studies with Prof. Tim Davis and Dr Brioni Moore at the University of Western Australia, producing high-quality data that are continuing to inform policy decisions in PNG (11-14). Dr Moses Laman completed a highly successful PhD as part of this collaboration in 2014, demonstrating that artemisinin-naphthoquine is non-inferior to artemether-lumefantrine in PNG children with falciparum malaria and has greater efficacy against vivax malaria.

Beyond the scope of malaria, we have also expanded into large public health intervention trials, investigating alternative mass drug administration (MDA) regimens for the elimination of lymphatic filariasis. This work has largely been conducted by the Maprik team, in particular Nelly Sanuku, Samson Satofan and Barth Lombore, with long-term collaborators Prof. Jim Kazura, Prof. Chris King and Dr Daniel Tisch, developing considerable capacity in this area and highlighting the great potential that the triple drug therapy (ivermectin, diethylcarbamazine and albendazole [IDA]) has for eliminating lymphatic filariasis (LF) in settings such as PNG. With additional Bill and Melinda Gates Foundation support, we embarked upon an expanded community safety, efficacy and acceptability trial of this triple drug regimen in Bogia in late 2016. Data from this multicountry cluster-randomized trial showed that IDA was safe and acceptable at the community level, with more than 20,000 participants treated, prompting the World Health Organization to change the global guidelines for LF MDA. Programmatic implementation of IDA could make a very significant difference in the global effort to eliminate LF by accelerating elimination and reducing the number of rounds of mass drug administration required for elimination. The greatest impact of this new treatment may be in areas with high infection rates where MDA has not yet been introduced, but it also could be very useful for areas where LF infection persists despite several years of



annual MDA with current 2-drug regimens. In PNG, both areas exist and continue to present a challenge to LF elimination efforts.

It is important to note that with declining prevalence of malaria and an increasing proportion of infections exhibiting no clinical symptoms, our malaria studies have become increasingly challenging – requiring larger sample sizes, innovative methods, increased funding and even stronger relationships with communities than ever before. This causes me to reflect on my first experiences in PNG during my PhD studies back in 2006-2007. I was in awe of the way the PNGIMR teams worked with communities and the genuine enthusiasm that communities had for being involved in the study we were doing. By effectively involving communities in the research, not only through participation but also as community reporters, village health volunteers or mosquito collectors, we were not only making the research possible and successful, but also allowing communities access to health promotion information and a greater understanding of the infections most commonly affecting them and their children. This was the kind of research I wanted to be involved with and I am grateful and proud of being able to do so. Equally, everyone involved with the PNGIMR should be really proud of having established such a community-based participatory health research model so early on and ensuring that we continue to uphold these high standards decades later, despite new challenges.

Personally I have had the pleasure and privilege of working alongside these teams since 2006 and I feel like we are constantly teaching each other new things as we progress our research. In addition, I have derived a great deal of pleasure from being part of the IMR family during a time when we have prioritized – perhaps above all else – the development of technical, scientific and research capacity, in particular through the formal Honours, Masters and PhD training of Papua New Guinean researchers. For the VBDU, this previously culminated in 2014-2015 when Dr Inoni Betuela and Dr Moses Laman had their PhDs conferred, and during the 40th anniversary event we celebrated Dr Livingstone Tavul being awarded his PhD. In addition, Mr John Bosco Keven and Dr Maria Ome-Kaius continue to undertake their own PhD research. In 2016 the IMR congratulated Dr Janet Gare from our Goroka headquarters

for obtaining her PhD in HIV research, the first Papua New Guinean woman at the IMR to be awarded a PhD. Less than two years on in 2018, Celestine Aho was finishing her PhD and we know that there are many talented women who will follow in their footsteps. In 2015 we celebrated the vast achievements of Dr Moses Laman when he was awarded the inaugural Prime Minister's Excellence Award – Papua New Guinean of the Year – on Independence Day. This was a richly deserved award for a colleague who is greatly admired by many, an outstanding and much-needed role model for aspiring researchers and health professionals in PNG and globally.

It is this group of highly dedicated, self-sacrificing individuals, who often need to leave their families behind in order to pursue their postgraduate studies abroad, that truly take the work of the PNGIMR to new levels: rising to the challenge of changing circumstances, embracing new tools and technologies, and forging tight relationships with health centres, hospitals, and provincial and national departments of health, to ensure that the research being done is directly relevant to the health problems of PNG and can be translated into new tools and new policies for implementation. It is for this reason I am not only most hopeful, but also confident, that, by continuing to work together, another 40 years of malaria research will not be needed!

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## **In vitro susceptibility of *Plasmodium falciparum* isolates from East New Britain Province to antimalarial drugs using a colorimetric lactate dehydrogenase assay**

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### **SUMMARY**

The in vitro susceptibility of *Plasmodium falciparum* to chloroquine (CQ), amodiaquine (AQ), monodesethylamodiaquine (mAQ) and piperazine (PQP) antimalarial drugs was evaluated in 13 isolates from East New Britain Province of Papua New Guinea (PNG) using a colorimetric *Plasmodium* lactate dehydrogenase (LDH) assay. Of the 13 isolates assessed, 9 (69%) showed in vitro resistance to CQ with the concentration required to inhibit growth by 50% (IC<sub>50</sub>) ranging from 25 to 188.8 nM (geometric mean 118.7 nM). All parasites exhibited in vitro susceptibility to AQ, mAQ and PQP with their mean IC<sub>50</sub>s well below reported threshold values. Significant rank order positive correlations were observed between PQP and CQ ( $r_s = 0.67$ ,  $p < 0.005$ ) suggestive of potential in vitro cross-resistance between these two 4-aminoquinoline drugs. These results demonstrate the suitability of the enzyme-based LDH assay for assessing in vitro *P. falciparum* susceptibility and highlight the importance of in vitro assessment of antimalarial drugs in PNG in tandem with local therapeutic efficacy studies.

### **Introduction**

Malaria is a public health problem in Papua New Guinea (PNG). In 2017 PNG's malaria incidences represented over 80% of all cases reported in the Western Pacific Region (1). Long-lasting insecticidal nets (LLINs) and artemisinin combination therapy (ACT) are the main strategies for malaria control in the country (2,3). While both methods have proven useful for malaria control, the emergence of *Plasmodium falciparum* resistance to available antimalarial drugs is a concern (4,5).

Antimalarial drug resistance with *P. falciparum* resistance to chloroquine (CQ) emerged in PNG in the early 1970s (6). Soon after, the development of multidrug-resistant strains further compromised the effectiveness of conventional combination treatment regimens in PNG (7). Since the mid-1990s, a prime focus of assessment of antimalarial efficacy has been through in vivo therapeutic efficacy studies. Consequently, in vitro parasite drug resistance data were scarce. While Hombhanje had reported the in vitro susceptibility of *P. falciparum* from Central Province (8), it was not until 10 or more years later that another in vitro study of *P. falciparum*

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susceptibility to a range of antimalarial drugs using field isolates was conducted, by Wong et al. in Madang Province (9).

Since 2008, clinical drug trials and studies conducted in Madang Province by the PNG Institute of Medical Research (PNGIMR) (9-12) and the Global Fund Malaria Control Program in Milne Bay and East Sepik Provinces (13) have assessed the in vitro susceptibility of *P. falciparum*. With increasing data being generated and localized to a particular region, there is a need for data from other parts of the country, particularly the New Guinea Islands, which could be used to help formulate national treatment guidelines that are applicable to all provinces where malaria transmission occurs.

The aim of this study was to evaluate the in vitro susceptibility of *P. falciparum* isolates from East New Britain (ENB) Province using a *Plasmodium* lactate dehydrogenase (pLDH) assay and, more broadly, to assess its appropriateness as an in vitro tool for monitoring parasite resistance in a regional PNG setting.

### Materials and Methods

We selected a panel of antimalarial drugs that encompasses conventional as well as novel treatments and used a non-isotopic colorimetric *Plasmodium* lactate dehydrogenase assay (14). The pLDH assay in antimalarial drug susceptibility tests is based on the biochemical processes that take place during parasite glycolysis (Embden-Meyeroff pathway). Malaria parasites rely principally on the Embden-Meyeroff pathway to produce energy in the form of adenosine triphosphate (ATP). In addition to ATP, glycolysis produces pyruvate (further used for cell biosynthesis) through consumption of glucose and reduction of nicotinamide adenine dinucleotide (NAD) to nicotinamide adenine dinucleotide hydride (NADH). During parasite metabolism, pyruvate is converted into lactate by the lactate dehydrogenase (pLDH) enzyme. The underlying principle of this assay relies on the detection of the pLDH activity during *Plasmodium* culture as evidence of parasite survival in vitro.

### Study site and approval

Two study sites, Butuwin and Kerevat Health Centres, were chosen based on the intensity of malaria transmission and the lack of data

on local parasite antimalarial resistance. The study took place between May and December 2008 and was approved by the PNG Institute of Medical Research Institutional Review Board (IRB) and the Medical Research Advisory Committee (MRAC), while approval for engaging in medical research in ENB Province was granted by the ENB Provincial Health Department.

### Samples

Patients  $\geq 5$  years of age with no prior exposure to antimalarial drugs and a positive blood smear for *P. falciparum* mono-infection  $>0.6\%$  (determined microscopically by counting the number of infected cells in a total of 1000 erythrocytes) were identified through outpatient screening. After each participant, or their parent/guardian, had given informed consent to study procedures, venous blood (4-5 ml) was collected into ethylenediamine-tetra acetic acid (EDTA)-coated tubes using sterile techniques.

### Drugs

Amodiaquine (AQ) was obtained from Sigma-Aldrich (Australia), and chloroquine (CQ), piperaquine (PQP) and monodesethylamodiaquine (mAQ) were kindly donated by Professor Ken Ilett of the School of Medicine and Pharmacology, University of Western Australia. Stock solutions of AQ, mAQ and CQ were prepared in sterile distilled water. PQP was dissolved in 0.5% lactic acid (Sigma-Aldrich) and then a stock solution prepared in sterile distilled water. The concentration ranges for each drug were adapted from similar studies. Two-fold serial dilutions for each drug were prepared in culture-complete media (15,16) to give the following final concentrations: 6.25-400 nM for PQP, 5-320 nM for AQ and mAQ and 25-1600 nM for CQ (17-19).

### In vitro assay

The plasma and buffy-coat layer of the blood sample were removed and retained while the packed erythrocytes were washed three times with RPMI 1640 culture media after further centrifugation at 1700 rpm for 5 minutes on each occasion. If the sample parasitaemia (infected erythrocytes per 1000 counted) was  $>1\%$ , uninfected erythrocytes were added to achieve a final parasite density  $\leq 1\%$ . A 100  $\mu$ l aliquot of culture

media suspension containing a 3% volume of infected erythrocytes was inoculated into 96-well U-bottom plates (Becton Dickinson, Australia) already containing 100 µl per well of antimalarial drug in various concentrations to give a final erythrocyte content (haematocrit) of 1.5%. Control wells void of drugs were also included to monitor parasite growth. The inoculated drug plates were then incubated for 48 hours using the 'candle-jar method' inside a 37°C incubator (20). After incubation, the plates were placed in a -20°C freezer to terminate parasite growth. The frozen drug plates were then transported back to the PNGIMR Vector-Borne Diseases Unit in Yagaum, Madang Province for subsequent pLDH measurement and data analysis.

At the Yagaum Laboratories, the plates were subjected to 4 repeated freeze/thaw cycles to enable total cell haemolysis prior to pLDH assay. The colorimetric enzyme assay was performed using a modification of the technique described previously (14). Briefly, 10 µl of the haemolyzed sample was added to 200 µl of Malstat solution – Trisma base 1.21 g in 90 ml deionized water with pH adjusted to 9.1, 200 µl Triton X-100 (Sigma, Australia), 2 g lithium-L-lactate and 62 mg 3-acetyl pyridine adenine dinucleotide (Sigma) – plus 10 µl nitro blue tetrazolium (10 mg/ml) (Sigma-Aldrich) and 10 µl diaphorase (10 mg/ml) (Sigma). Colour intensity was developed at room temperature for 45 minutes to 2 hours and absorbance was measured spectrophotometrically at 650 nm using an Emax/Molecular Devices microplate reader facilitated by SoftMax Pro 5 software.

Absorbance readings were expressed as optical densities.

The in vitro activity of the compounds was expressed as a 50% inhibitory concentration ( $IC_{50}$ ), defined as the drug concentration at which 50% of parasite growth was inhibited compared to the drug-free wells, using HN-NonLIN (V1.1). Optical densities (ODs) were plotted against the logarithm of drug concentrations to generate a fitted sigmoidal (polynomial) concentration-effect curve, from which the  $IC_{50}$  was determined. Based on previously published values (17,18,21), the threshold  $IC_{50}$  values for in vitro resistance to CQ, AQ, mAQ and PQP were taken as  $\geq 100$  nM,  $\geq 60$  nM (AQ and mAQ) and  $\geq 80$  nM respectively.

### Statistical analysis

Data were analysed using STATA version 8.1 (Stata Corporation, College Station, Texas, USA) and expressed as geometric mean, median, range and 95% confidence interval (CI) for each drug tested. Spearman's rank-order correlation was used to test associations between the  $IC_{50}$  values of the drugs tested.

### Results

A total of 27 *P. falciparum* isolates were collected from patients aged 5 to 61 years but, due to logistical problems during transportation, only 13 were fully assessed for in vitro susceptibility. The  $IC_{50}$  values for the drugs tested are summarized in Table 1. For CQ, 9/13 isolates (69%) showed in

TABLE 1

IN VITRO SUSCEPTIBILITY OF ISOLATES OF *P. FALCIPARUM* FROM EAST NEW BRITAIN PROVINCE TO SELECTED ANTIMALARIAL DRUGS

Drug	n	Median (nM)	Geometric mean (nM)	95% CI	Range (nM)
Piperaquine	13	9.6	22.2	6.4-37.9	6.25-80.5
Monodesethylamodiaquine	13	13.2	13.6	8.6-17.6	5-29.4
Amodiaquine	12	11.3	13.1	7.6-19.8	5-34.3
Chloroquine	13	146.3	118.7	85.6-151.6	25-188.8

CI = confidence interval  
nM = nanomolar



vitro resistance. The four CQ-susceptible isolates had  $IC_{50}$ s below 80 nM. All isolates were susceptible to both AQ and its active metabolite mAQ, with  $IC_{50}$ s well below the suggested in vitro thresholds of 60 nM. For PQP, 12/13 of isolates were susceptible (median, 9.6 nM; range, 6.25-80.5 nM).

Rank-order correlations between  $IC_{50}$  values are shown in Table 2. There was a highly significant correlation between PQP and CQ ( $p < 0.005$ ). Weak correlations ( $0.10 > p > 0.05$ ) were observed for PQP and mAQ and for AQ and mAQ.

There were no significant differences between the  $IC_{50}$ s of AQ and its metabolite mAQ; however, observations show that 75% of the isolates (9/12) had lower  $IC_{50}$  values for mAQ than AQ.

## Discussion

At the time this study was conducted, almost four decades had elapsed since the first reports of *P. falciparum* resistance to CQ emerging in PNG. Despite this, CQ was still used as first-line treatment (in adults) in combination with sulfadoxine-pyrimethamine (SP) in many health facilities throughout PNG (22). This was primarily because of its low cost and ready availability. The high levels of in vitro CQ resistance observed in this study are consistent with previous in vitro studies from Madang and Central Provinces (8,23). The

most likely reason for this is the past systematic use of 4-aminoquinolines for all fever cases. As in most endemic countries, presumptive antimalarial treatment was prescribed in the presence of fever up until 2011-2012. Although this is clinically justified where microscopy is unavailable, it increases drug pressure on malaria parasite populations. Subtherapeutic blood concentrations of antimalarial drugs, especially compounds with a long half-life like CQ, permit the survival of tolerant strains of *P. falciparum* and the consequent development of drug-resistant infections (24). Since the implementation of artemisinin combination therapy in 2011 in PNG, there has been a dramatic reduction in 4-aminoquinoline drug pressure on *P. falciparum*. Indeed, Koleala et al. have shown increased susceptibility of *P. falciparum* isolates to CQ in Madang Province after ACT implementation (12).

In none of the *P. falciparum* isolates was there evidence for AQ resistance. Although there is no information on the in vitro profile of antimalarials in the New Guinea Islands Region of PNG, AQ in vitro resistance has been reported on the north of mainland PNG with much higher  $IC_{50}$ s (23). This disparity likely reflects methodological differences since microscopic enumeration of schizonts produces  $IC_{50}$  values several times higher than isotopic methods of determining parasite susceptibility (25) and, by implication, the pLDH assay used in this study. However, a study from East Sepik Province conducted

TABLE 2

RANK CORRELATION COEFFICIENT ( $r_s$ ) FOR PAIRED  $IC_{50}$  VALUES

Drug pairs	$r_s$	p value
Piperaquine-monodesethylamodiaquine	0.5041	0.079
Piperaquine-amodiaquine	-0.0667	0.8369
Piperaquine-chloroquine	0.6749	<0.005
Monodesethylamodiaquine-amodiaquine	0.514	0.0873
Monodesethylamodiaquine-chloroquine	0.3567	0.2315
Monodesethylamodiaquine-dihydroartemisinin	0.5368	0.0719
Amodiaquine-chloroquine	0.0033	0.9914

later reported a lower prevalence of AQ in vitro resistance (10 of 36 isolates), which is consistent with our findings (26). Despite observations of in vitro susceptibility of these isolates to AQ, clinical studies in PNG have reported high AQ-SP treatment failure rates (7,27,28). This apparent discrepancy is not unexpected since, at the time of the this study, AQ in combination with sulfadoxine-pyrimethamine was administered as first-line treatment for infants and young children (<19 kg body weight) under the PNG National Treatment Guidelines (22). Due to this young age, a relative lack of immunity may counterbalance any benefits from parasite susceptibility to AQ (29). While host immunity and pharmacokinetic factors may contribute to the poor correlations between these in vitro results and clinical outcomes observed in previous studies, it is important to note there is widespread prevalence of the SVMNT allele for the chloroquine-resistant transporter gene (*crt*) in PNG parasites (27,30,31). Although the SVMNT allele confers resistance to CQ, it also provides resistance to AQ. Therefore, further molecular assessments will need to be employed to explain such discrepancies.

Parasite-drug interactions may influence the different susceptibilities between the 4-aminoquinolines CQ and AQ. The study by Hawley et al. (32) observed that AQ accumulation in the parasite was 2- to 3-fold greater than that of CQ and suggested that this resulted from the drug's higher affinity for intraparasitic binding sites. This may account for the greater inherent activity of AQ against *P. falciparum* compared to CQ and explain the lower  $IC_{50}$ s for AQ in our study.

Although there were no significant differences between the mean  $IC_{50}$ s for AQ and mAQ, the majority of the isolates (9/12) recorded lower  $IC_{50}$  values for mAQ than for AQ; this is indicative of the greater in vitro activity of the metabolite against the parasite. Pharmacokinetic studies have shown that, after oral administration, AQ is rapidly metabolized to desethylamodiaquine, which accounts for 75% of the drug's antimalarial activity (33-35). Similar observations have been recorded in PNG children treated with AQ, where blood levels of the metabolite were relatively high and still detectable 3-14 days after administration (36). Thus the in vitro susceptibility of local parasite strains to mAQ is more important in predicting the in vivo response than is the susceptibility to AQ itself.

Unlike other malaria-endemic countries with extensive prior use of PQP, in vitro resistance levels to this drug in PNG is expected to be low. As such our findings and other in vitro data at that time show that PNG isolates are susceptible to PQP. Here, PQP was effective against both CQ-susceptible and CQ-resistant isolates, as has been previously reported (9,10,37,38). Nevertheless, the threshold for resistance to PQP is not well defined and potential cross-resistance between these 4-aminoquinolines remains a concern. With continuous exposure and accumulated drug pressure, a decrease in susceptibility may be expected in the future. However, recent assessments have shown that despite 5 years into its implementation, the in vitro susceptibility to PQP continues to remain below the suggested thresholds of resistance (12). This is not unexpected as dihydroartemisinin (DHA)-PQP as the second-line treatment for uncomplicated malaria is administered infrequently, which results in minimal drug pressure insufficient to induce resistance.

Nevertheless, we found a significant correlation between CQ and PQP  $IC_{50}$ s, which is consistent with previous in vitro data from PNG. Indeed, potential PQP-CQ cross-resistance may have contributed to the unexpectedly high DHA-PQP treatment failure rates observed in a trial in Madang and East Sepik Provinces (9,10,13).

The present study, albeit limited by the sample size, adds to the available data characterizing *P. falciparum* drug susceptibility in PNG. Our findings suggest that, despite geographical separation, the susceptibilities of parasite isolates from ENB Province and their inter-relationships were similar to those from studies on the north coast of PNG. This provides reassurance that treatment guidelines developed on the basis of extensive in vitro and in vivo studies in Madang and the East Sepik are widely applicable within PNG.

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## **Molecular evidence of asymptomatic and multispecies malaria infections in a small community on the north coast of Madang Province, Papua New Guinea**

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### **SUMMARY**

Asymptomatic malaria is prevalent in highly endemic areas of Papua New Guinea and is a challenge for malaria prevention and control strategies. We used nested polymerase chain reaction (PCR) to determine the prevalence of asymptomatic malaria and parasite species distribution in a small community on the north coast of Madang, Papua New Guinea. A population household study was conducted in October, 2015. A pretested questionnaire was used to collect demographic data. Giemsa-stained thin and thick blood films were examined for detection, identification and quantification of malaria parasites. Due to wide discrepancies in malaria microscopy results, only molecular analysis data are presented here. The prevalence of asymptomatic malaria was 62.5% (40/64) with mixed multispecies infections accounting for 20% (13/64). The prevalence of malaria parasite carriers observed here in the small community is higher than previously reported for the same region. Asymptomatic malaria remains a challenge for malaria elimination and PCR testing should be considered in areas where malaria transmission is low.

### **Introduction**

Malaria will continue to be a major public health issue in Papua New Guinea (PNG) for some years to come (1-3). While country-wide distribution and use of long-lasting insecticide-treated nets (ITNs) has led to declining transmission (4,5), complete interruption of malaria parasite transmission cannot be achieved by this intervention alone. Early diagnosis and effective treatment are additional measures that must be applied alongside ITN distribution to have any impact on malaria transmission. Although malaria transmission has markedly declined in areas where intervention has been intensified, the question of how to deal with asymptomatic

(persons having malaria infections without clinical symptoms) and submicroscopic (below the level microscopy can detect) infections still remains a challenge (6,7). Asymptomatic and submicroscopic infections have been shown to carry gametocytes that are infective to mosquitoes (7-11): a situation where a human *Plasmodium* reservoir is maintained to continue onward transmission.

Successful targeting of malaria transmission can only be achieved if asymptomatic parasitaemia is accurately detected and effectively managed. Rapid diagnostic tests (RDTs), light microscopy (LM) and polymerase chain reaction (PCR) are the diagnostic tools currently being used for the assessment of

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parasite prevalence in communities (12). LM and RDTs have their limitations in accurately detecting lower parasitaemia in asymptomatic and submicroscopic malaria (13-15), and the PCR technology, despite being operationally expensive, remains the only highly sensitive diagnostic tool. Moreover, the PCR methodologies are improving and are able to detect progressively lower-density asymptomatic and submicroscopic parasitaemias (16,17). In this study we employed nested PCR, after failure of light microscopy examination, to assess malaria prevalence and to understand the parasite species distribution in a small village community along the north coast of Madang Province, Papua New Guinea. We report the results of the nested PCR carried out on blood stored on filter paper and discuss the implications of the findings.

## Methods

### Ethical statement

Ethical clearance for the study was obtained from the Divine Word University Ethics Committee. For the molecular analysis, ethical approval was obtained from the Juntendo Medical University Ethics Committee, Japan. Signed consent was obtained from the head of the community and from all participants, including children from their parents/guardians.

### Study design and study area

This was a population-based household study conducted in October 2015. Before the study commenced a population census based on households was undertaken and each house was identified with a unique number. The names of the occupants of each household were recorded. The site (Jog hamlet community) in which the study was conducted is a typical coastal community located about 10 km northwest of Madang township in the Sumkar District, Madang Province. A pre-designed questionnaire was used to record demographic data including ownership and use of insecticide-treated bed nets.

### Study procedures

All individuals (adults and children) of each household in the study area were selected (convenience sampling) to participate in the

study. On the day of the study, individual names from each house were called for blood sampling by finger-prick by a trained laboratory technician for microscopy and for PCR. Each participant had their axillary temperature taken, and a history of fever or any other malaria symptoms within the last week was recorded. A finger-prick blood sample was collected for microscopy (thin and thick blood smears) and 100 µl of blood, collected in a sterile micropipette, was spotted on to filter paper (ET31CHR; Whatman Limited, Kent, UK) for nested PCR. Filter papers were dried in the field and taken to the laboratory and stored at 4°C until processed. No RDTs were performed because of their unavailability.

## Laboratory procedures

### Microscopy

In the laboratory the thick and thin blood smears were stained with 5% Giemsa stain. Stained blood smears/films were examined according to the World Health Organization (WHO) guidelines (18). Two microscopists, with more than 10 years of microscopy experience between them, were assigned to examine blood smears independent of each other. Where smears were positive, identification of parasite species and density calculation were done. Parasite density was calculated by counting the number of asexual parasites for 500 white blood cells (for asymptomatic individuals) in the thick smear, assuming a concentration of 800 white blood cells/µl of blood. A slide was declared negative if no parasites were found after examining 100 fields.

### Nested PCR

The nested PCR was conducted on 64 blood-spotted filter papers collected from all ages in the study area. Briefly, parasite DNA (deoxyribonucleic acid) was purified from a quarter of each blood spot filter paper using the QIAamp DNA Blood Mini Kit (QIAGEN, Hilden, Germany) according to a modified version of the manufacturer's instructions (19). We performed species-specific PCR with controls to confirm *Plasmodium* spp. infection as previously described (20). This method is based on the amplification of 18S small subunit ribosomal RNA (ribonucleic acid) with a semi-nested, multiplex PCR. The first PCR amplification detects the genus *Plasmodium* infection and the second

amplification differentiates all human *Plasmodium* species. For ovale malaria, two closely related subspecies, *Plasmodium ovale curtisi* (classical) and *Plasmodium ovale wallikeri* (variant), were differentiated by nested PCR (21).

## Results

A total of 64 individuals, whose age ranged from 6 months to 61 years, from 10 households were surveyed for malaria parasitaemia in the study. According to the survey form records, all households (n = 10) had at least one ITN. The head of each household reported that children mainly used the nets. Because of the wide disagreement and/or discrepancies with the microscopy results, the presentation of

results here is solely based on the molecular analysis using nested PCR. These results are presented in Table 1.

All four malaria parasite species were detected in the study area, comprising *Plasmodium vivax* (Pv) 44%, *Plasmodium falciparum* (Pf) 27%, *Plasmodium ovale* (Po) 11% and *Plasmodium malariae* (Pm) 9%. The clear majority of *Plasmodium vivax* and *Plasmodium falciparum* infections were not accompanied by any febrile symptoms. Of the 64 blood-spotted filter paper samples analysed, 40 were positive for a malaria parasite, giving a malaria parasite carrier prevalence of 62.5%. The mixed species infections accounted for 20%, of which there were more double species infections than

**TABLE 1**

PREVALENCE OF MALARIA INFECTIONS AND PARASITE SPECIES

<b>Sample size</b>	N = 64	Positive for malaria 62.5% (n = 40)
		Mixed infections 20.3% (n = 13)
<b>Species prevalence</b>	Pf 26.6% (n = 17)	
	Pv 43.8% (n = 28)	
	Pm 9.4% (n = 6)	
	Po 10.9% (n = 7)	
<b>Mono-infections</b>	Pf 12.5% (n = 8)	
	Pv 28.1% (n = 18)	
	Pm 0% (n = 0)	
	Po 1.6% (n = 1)	
<b>Mixed infections</b>	<b>Double (n = 8)</b>	<b>Triple (n = 5)</b>
	Pf+Pv 4.7% (n = 3)	Pf+Pv+Pm 4.7% (n = 3)
	Pf+Pm 1.6% (n = 1)	Pf+Pm+Po 1.6% (n = 1)
	Pf+Po 1.6% (n = 1)	Pv+Pm+Po 1.6% (n = 1)
	Pv+Po 4.7% (n = 3)	

Pf = *Plasmodium falciparum*  
Pv = *Plasmodium vivax*  
Pm = *Plasmodium malariae*  
Po = *Plasmodium ovale*

triple species infections (8 double versus 5 triple infections). Only the *Plasmodium ovale curtisi* subspecies was positive when tested for the two *Plasmodium ovale* subspecies, *Plasmodium ovale curtisi* and *Plasmodium ovale wallikeri*, in the study area.

### Discussion and conclusion

The molecular analysis (nested PCR) of the blood-spotted filter papers shows the presence of asymptomatic and mixed multispecies infections in the study area. Asymptomatic infections have serious implications for malaria elimination campaigns (2,6,7). Since asymptomatic malaria parasite carriers do not seek treatment for their infection and may carry gametocytes in their blood, they undoubtedly contribute to the persistence of malaria transmission in a community population. For a small population, the prevalence rate of 62.5% is high and may be influenced by site-specific sociodemographic household characteristics and ecological conditions in the study area. The prevalence observed in this study is higher than was found some 30 years ago (22), and also in a more recent study (2). The reasons for the higher prevalence remain to be determined; the use of the PCR as the diagnostic tool is most relevant but the age of the population, the transmission intensity and temporal factors may have had some influence.

The proportion of *Plasmodium vivax* parasite carriers in the study community is higher than for other species, suggesting the possibility of a silent vivax reservoir. Unless necessary measures are taken to interrupt transmission, vivax transmission will continue in the local community. The use of antimalarial drugs that include primaquine would be appropriate in this particular setting, and such strategic interventions have previously been shown to be successful in interrupting *P. vivax* transmission (23,24).

We are mindful of the limitations of this study, which include small sample size and a small area from which we generated the data. Therefore the findings do not necessarily provide generalizable information beyond the study site. Nonetheless, the study findings underline some important considerations: detection of asymptomatic malaria depends on the sensitivity of the diagnostic tool used, and PCR testing may be considered in settings where malaria transmission is low or

seems negligible.

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# Investigation of polymorphisms in *Plasmodium falciparum* *hrp2*, *hrp3*, *aldolase* and *pldh* genes and their impact on the performance of malaria rapid diagnostic tests in Papua New Guinea

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## SUMMARY

The World Health Organization (WHO) recommends that parasitological confirmation of clinical malaria diagnosis be performed before antimalarial treatment is administered. Malaria rapid diagnostic tests (RDTs) represent a valuable tool for prompt and efficient diagnosis of malaria in settings where microscopic diagnosis is unavailable or unreliable. Concerns remain, however, that *Plasmodium falciparum* polymorphisms in the genes coding the antigens detected by RDT could impact on RDT performance. Using field isolates of *Plasmodium falciparum*, we aimed to characterize genetic variability in histidine-rich proteins 2 and 3 (PfHRP-2 and PfHRP-3), aldolase (ALD) and *Plasmodium* lactate dehydrogenase (pLDH) genes and to evaluate their impact on the performance of RDT. *Pfhrp-2*, *Pfhrp-3*, *aldolase* and *pldh* were amplified using polymerase chain reaction (PCR) and sequenced. Genetic variation was observed in *pfhrp-2* and *pfhrp-3* genes while *aldolase* and *pldh* showed high levels of conservation. These findings suggest that RDTs based on pLDH and ALD are reliable in the study settings where there is intense diversity or polymorphisms of histidine-rich protein (HRP). Nevertheless, there is no evidence from this study to suggest that RDTs based on the detection of PfHRP-2 and PfHRP-3 have lower sensitivity in Papua New Guinea (PNG). The results observed in this study will be used to inform the PNG National Department of Health on the continued usage of pLDH/HRP-2 RDT for malaria diagnosis in PNG.

## Introduction

Malaria is responsible for approximately 435,000 deaths annually (1). Since the 1950s, Papua New Guinea (PNG) has had numerous national malaria programs that have gradually

contributed to the decline of malaria cases in the country (2). In the years 2001-2013, a steady decline of malaria cases per 1000 people was noted (3). However, despite this, malaria is still prevalent in the lowlands and coastal regions of PNG (2).

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Traditionally, health workers and communities have been taught that 'fever equals malaria unless proven otherwise' (4,5). In areas where resources are limited, individuals presenting to health clinics with any febrile illness are prescribed antimalarial drugs without a confirmed diagnosis of malaria (5). The misuse of antimalarial drugs contributes to the selection of drug-resistant parasites.

With the adoption of artemether-lumefantrine (AL) as first-line therapy for uncomplicated malaria in PNG, it is important to ensure that selection of drug-resistant parasites is prevented or at least slowed substantially (6-9). As a result, the PNG National Department of Health (NDoH), in accordance with the World Health Organization (WHO) guidelines, has recommended that a confirmed parasitological diagnosis of malaria infection be performed before any malaria treatment is administered (10).

Rapid diagnostic test (RDT) cassettes contain antibodies to parasite proteins embedded in a nitrocellulose strip that captures the parasite proteins as the tested blood migrates along the cassette. Most RDTs can detect *Plasmodium falciparum* (Pf) histidine-rich protein 2 (PfHRP2), *Plasmodium* lactate dehydrogenase (pLDH) and *Plasmodium* aldolase (ALD) encoded by *pfhrp2*, *pldh* and *aldolase* (*pfald*) genes. There is also cross-reactivity between PfHRP2 and Pf histidine-rich protein 3 (PfHRP3). While PfHRP2-based RDTs are considered to be more sensitive (11) than pLDH-based RDTs for detecting *P. falciparum* (12), PfHRP2 can persist in the circulation for up to 4 weeks following antimalarial treatment (13). This persistence could prove to be a liability, especially in areas of high malaria transmission, resulting in the potential misdiagnosis of patients recently successfully treated for malaria. pLDH-based RDTs can detect four species of malaria and are more specific of ongoing infections because lactate dehydrogenase (LDH) is cleared from the blood circulation as soon as the parasites are cleared (12).

RDTs have a limit of detection of ~100 parasites/ $\mu$ l (14-16). However, storage conditions (17), the ability of the user to correctly interpret the results (18,19) and parasite density (ie, the number of parasites present in a blood sample) (20) can influence RDT sensitivity.

Previous studies have also shown that RDT sensitivity is impacted by deletion (21) or polymorphisms in the genes coding the proteins that are targeted by the RDT (22). Genetic polymorphisms inducing modifications in PfHRP2 can alter the affinity of the parasite proteins to the antibodies on the test strip (22,23). PfHRP2 and HRP3 are known to be rich in repeated sequences of the amino acids alanine and histidine that vary in motifs and number of repeats. Baker et al. reported 18 repeat sequence types in PfHRP2 and HRP3 of *P. falciparum* isolates from 19 different countries (22). Repeat sequences AHHAHHVAD (A = alanine; H = histidine; V = valine; and D = aspartic acid), AHHAHHAAD, AHH and AHHAAD (type numbers 1, 2, 4 and 7 respectively) occurred in both PfHRP3 and PfHRP2 (22). A binary logistic regression model was developed to predict how the occurrence of certain repeat types and parasite density levels could impact on *P. falciparum* RDT detection (22). According to this model, 16% of studied isolates from the Asia-Pacific Region would be undetectable by RDT at parasitaemias  $\leq 250$  parasites/ $\mu$ l.

Rapid diagnostic tests for malaria have been in use in PNG since 2011 (24,25). However, there is a lack of data in PNG regarding genetic polymorphisms and RDT performance. This study was undertaken following the observation that 11 children presenting with severe malaria showed low or undetectable PfHRP2 plasma concentrations ( $<5.0$  ng/ml) despite parasite densities above the RDT limit of detection (26). All 11 children had positive RDT results that could be attributed to cross-reactivity with PfHRP3 (26).

In this study we therefore aimed to i) characterize polymorphisms or deletions of *pfhrp2* and *hrp3* that could support these observations; and ii) investigate the presence and prevalence of polymorphisms in *pfhrp2*, *pfhrp3*, *pldh* and *pfald* in PNG *P. falciparum* isolates and evaluate their impact on the performance of malaria RDTs in two malaria-endemic regions of PNG.

## Materials and Methods

### Study area and design

Two available sample sets were used. The first set included 62 samples from children who had presented with severe malaria in

Madang Province (26). From these samples, 29 had low concentrations of PfHRP2 (0 to 30 ng/ml) and 33 high concentrations (484 to 11373 ng/ml). All had parasite density >1000 parasites/μl by microscopy.

The second set included 130 archival samples from cross-sectional population surveys of malaria-positive asymptomatic adults and children in 2005 and 2006 from Mugil in Madang Province and Wosera in East Sepik Province.

This study was approved by the Medical Research Advisory Committee (MRAC) of the PNG NDoH (approval #10.41) and the PNG Institute of Medical Research (PNGIMR) Internal Review Board (IRB) (approval #1014).

### Isolation of genomic DNA and species differentiation

DNA was isolated from frozen blood using a QIAamp 96 DNA Blood Kit (Qiagen). Sample selection was based upon the following criteria being met: i) Pf positivity confirmed with a post-PCR ligase detection reaction-fluorescent microsphere assay (LDR-FMA) (27) or a TaqMan real-time PCR assay (28); and ii) Pf infection was monoclonal.

### Polymerase chain reaction (PCR) for *pfhrp2*, *pfhrp3*, *ald* and *pldh*

*Pfhrp2* and *pfhrp3* and *ald* and *pldh* were amplified in two distinct multiplex reactions in a primary PCR (Table 1). Specific secondary PCRs were then run for each gene.

2 μl of genomic DNA was used as template in a total reaction volume of 15 μl in the primary PCR reaction. The PCR1 reaction mix contained a final concentration of 1x HotMaster™ Taq Buffer 10x, 3 mM of MgCl<sub>2</sub>, 0.12 μM of each forward and reverse primer and HotMaster™ Taq DNA polymerase (5 U/μl). PCR1 conditions had an initial DNA denaturation phase at 94°C for 5 minutes followed by 35 cycles of denaturation for *pfhrp2/pfhrp3* and 25 cycles for *ald/pldh* at 94°C for 20 secs, annealing at 57°C for *hrp2/hrp3* and 55°C for *ald/pldh* for 20 secs and extension at 72°C for 1 min, including a final extension phase at 72°C for 5 minutes.

3 μl of PCR1 product for *hrp2/hrp3* and *ald/pldh* was used as template for the secondary nested PCR reaction mix, which had a total

reaction volume of 50 μl containing a final concentration of 1x HotMaster™ Taq Buffer 10x, 3 mM of MgCl<sub>2</sub>, 0.12 μM of each primer and HotMaster™ Taq DNA polymerase (5 U/μl). PCR2 conditions for *hrp2* and *hrp3* were similar to that of PCR1 with the number of cycles increased to 45 and an annealing temperature of 60°C for 20 seconds. PCR2 conditions for *ald* and *pldh* also remained similar to that of PCR1 with the number of cycles increased to 35.

### Gel electrophoresis

5 μl of all PCR products for *pfhrp2*, *pfhrp3*, *pldh* and *ald* was loaded on to a 1.5% agarose gel and separated via electrophoresis. A 0.1-10 kp DNA molecular ladder was used to estimate the molecular size of each DNA fragment.

### Sequencing of PCR products

All PCR products were sent to Macrogen in South Korea for purification and sequencing. Sequences were analysed using Geneious Pro (version 5.1.6) (29).

### Statistical analysis

PfHRP2 and PfHRP3 repeat motifs observed were compared to those described by Baker et al., 2005 and 2010 (22,30). Isolates were predicted to be sensitive (ie, detectable at parasite densities ≤250 parasites/μl) or not sensitive (ie, detectable at parasite densities >250 parasites/μl) to RDT using a binary logistic regression model developed by Baker et al. (22). An isolate was predicted to be detected if the score (product of the number of type 2 and type 7 repeats) of HRP2 was >43 (22).

## Results

### Severe malaria sample set: Investigation of *pfhrp2* and *pfhrp3* polymorphisms

From a total sample set of 62, only the 29 samples that showed low HRP2 concentrations (by ELISA measurement) were run for *pfhrp2* PCR. 24 samples were PCR positive (83%). 5 samples (17%) remained negative. There was no association between *pfhrp2* PCR outcome and HRP2 levels detected previously by ELISA (Mann-Whitney U-test,  $p = 0.36$ ). There was also no association between *pfhrp2* PCR outcome

TABLE 1

POLYMERASE CHAIN REACTION (PCR) PRIMERS USED FOR THE SINGLE PCR STRATEGY AND FOR THE NESTED PCR

PCR primers	Primer sequence 5'-3'	Target gene	PCR product size (bp)	Usage
Pfhrp2 PF	TTCCGCATTTAATAATAACTTGT	<i>P. falciparum</i> histidine-rich protein 2	988	Pfhrp2/Pfhrp3 primary PCR
Pfhrp2 PR	TTTTGTAATTTCTGTGTTATGTTT			
Pfhrp2 F	TGTGTAGCAAAAATGCAAAAGG		905	Pfhrp2 secondary PCR
Pfhrp2 R	AATAAATTTAATGCGTAGGCA			
Pfhrp3 PF	CTCCGAATTTAACAATAACTTG	<i>P. falciparum</i> histidine-rich protein 3	867	Pfhrp3/Pfhrp2 primary PCR
Pfhrp3 PR	GATTCATCATTCTATATTTACATGG			
Pfhrp3 F	TGTTTAGCAAAAATGCAAAAGG		565	Pfhrp3 secondary PCR
Pfhrp3 R	TGCGTAGTGGCATTATGGTG			
Pfldh PF	TATTTCAATTTTATTTTCATCATGG	<i>P. falciparum</i> lactate dehydrogenase	1169	Pfldh/Pfald primary PCR
Pfldh PR	TAATTTGTACTTGGTACATGAAAG			
Pfldh F	GCACCAAAAAGCAAAAATCGT		922	Pfldh secondary PCR
Pfldh R	TTTCAGCTATGGCTTCATCAAA			
Pfald PF	GAATATATGAATGCCCCAAA	<i>P. falciparum</i> aldolase		Pfald/Pfldh



1006	primary PCR
	Pfald
924	secondary PCR

Pfald PR	TGGCTTCAGCTCTTTGTAAT
Pfald F	AGCAGATGTTGCCGAAGAAT
Pfald R	TTTCCTTGCCCATGTGTTCAA

bp = base pairs

and parasitaemia levels ( $p = 0.18$ ).

No *pfhrp2* sequencing results are available for this sample set due to the poor quality of the 24 sequences retrieved.

From the 62 samples, no strong association was observed between the levels of HRP2 (0-11373.2 ng/ml) previously measured via ELISA and the levels of parasitaemia (Spearman's rank correlation  $\rho = 0.23$ ,  $p = 0.06$ ).

From the total sample set of 62 samples, 53 (85%) were *pfhrp3* PCR positive. From those, 17 (32%) provided sequences of sufficient quality and length to be analysed. Of the 17 sequences obtained, 15 (88%) were unique. 13 of them were found once and 2 were found to occur twice for a ratio of [number of sequences] / [number of isolates] of 0.9. Corresponding protein sequences ranged from 121 to 172 amino acids (Figure 1). *Pfhrp3* motifs noted were similar to those by Baker et al. (30). Motifs found were types 1 (AHHAHHVAD), 4 (AHH), 7 (AHHAAD), 15 (AHHAHHAAN), 16 (AHHAAN), 17 (AHHDG), 18 (AHHDD) and 20 (SHHDD) repeats (N = asparagine; G = glycine; S = serine). The type 2 motif (AHHAHHAAD) was absent. All 17 sequences began with a type 1 repeat and finished with a type 4 repeat (Figure 1).

### Cross-sectional malaria population surveys (Wosera and Mugil) sample set

The PCR outcomes of 130 samples analysed from the cross-sectional malaria population surveys in Wosera and Mugil are displayed in Table 2.

### Polymorphisms in *pfhrp2*

DNA sequencing of the 16 *pfhrp2* PCR products from the Mugil samples was not successful. The sequences obtained were too short and displayed high background signal.

DNA sequencing was successful for 10 out of 41 *pfhrp2* PCR products (24%) from the Wosera samples. Corresponding protein sequences ranged from 227 to 255 amino acids in length (Figure 2).

9 unique PfHRP2 sequences were identified (Figure 2) for a ratio of [number of sequences] / [number of isolates] of 0.9. Motifs found were types 1 (AHHAHHVAD), 2 (AHHAHHAAD), 3 (AHHAHHAAY), 4 (AHH), 5 (AHHAHHASD), 6 (AHHATD), 7 (AHHAAD), 8 (AHHAAY), 10 (AHHAHHATD) and 12 (AHHAHHHEAATH) (Y = glutamine; T = threonine; E = glutamic acid). The number of type 2 (AHHAHHAAD) repeats observed ranged from 8 to 13 per sequence. The

**TABLE 2**

*PLASMODIUM FALCIPARUM* HRP2, HRP3, ALD AND PLDH PCR OUTCOMES FOR 93 SAMPLES FROM WOSERA AND 37 SAMPLES FROM MUGIL

PCR outcome	Wosera samples (%)	Mugil samples (%)
Genes amplified:		
<i>hrp2</i>	41 (44)	16 (43)
<i>hrp3</i>	56 (60)	29 (78)
<i>ald</i>	54 (58)	21 (57)
<i>pldh</i>	50 (54)	18 (49)
No amplification	20 (22)	5 (14)

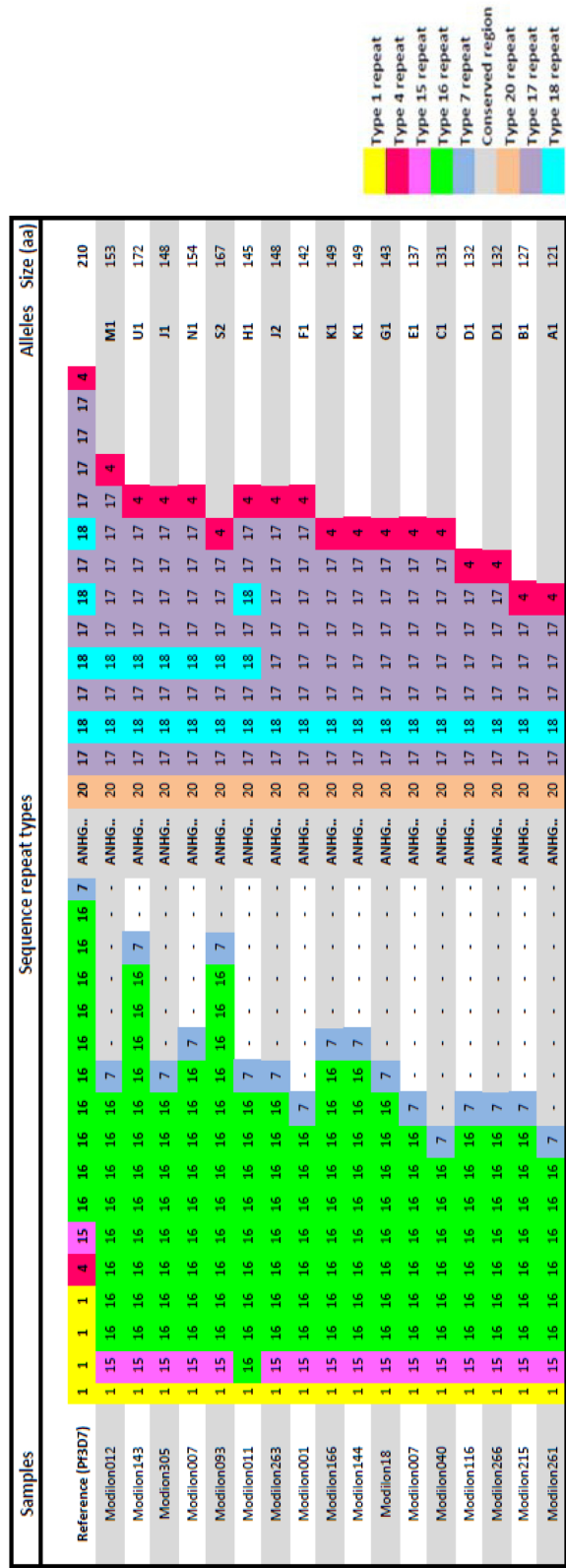


Figure 1. PfHRP3 sequence types identified from the severe malaria sample set. Sequences were differentiated according to their length and their amino acid composition (the type of repeats and their number). Repeat types are highlighted in different colours and numbered according to the nomenclature proposed by Baker et al., 2005 and 2010 (22,30). aa = amino acids

Samples	Sequence repeat types																				Size (aa)
	1	4	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	
Reference (Pf3D7)	1	4	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	272
Wosera15	1	1	2	2	6	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	248
Wosera22	1	1	2	2	3	2	6	7	7	7	7	7	7	7	7	7	7	7	7	7	255
Wosera4	1	1	2	2	3	2	6	7	7	6	2	2	2	2	2	2	2	2	2	2	254
Wosera17	1	1	2	2	3	2	6	7	7	6	2	2	2	2	2	2	2	2	2	2	254
Wosera44	1	1	2	2	3	2	6	7	7	6	2	2	2	2	2	2	2	2	2	2	230
Wosera45	1	1	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	227
Wosera10	1	1	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	233
Wosera21	1	1	1	2	3	2	7	7	7	7	2	2	2	2	2	2	2	2	2	2	242
Wosera28	1	1	1	1	2	3	2	6	7	6	7	2	2	2	2	2	2	2	2	2	240
Wosera30	1	1	1	1	2	3	2	6	7	6	7	2	2	2	2	2	2	2	2	2	240

Type 1 repeat

Type 4 repeat

Type 2 repeat

Type 3 repeat

Type 5 repeat

Type 7 repeat

Type 8 repeat

Type 6 repeat

Type 10 repeat

Type 12 repeat

Figure 2. PfHRP2 sequences identified in samples from the Wosera region. Sequences were differentiated according to their length and their amino acid composition (the type of repeats and their number). Repeat types are highlighted in different colours and numbered according to the nomenclature proposed by Baker et al., 2005 and 2010 (22,30). aa = amino acids

number of type 7 repeats ranged from 4 to 10 repeats per sequence. The score obtained ([number of type 2 repeats] x [number of type 7 repeats]) ranged from 44 to 108 (Table 3). All 9 unique sequences began with a type 1 repeat and finished with a type 12 repeat (Figure 2).

### Polymorphisms in *pfhrp3*

DNA sequencing was successful for 13 out of 29 *pfhrp3* PCR products (45%) from the Mugil samples (Table 4). Corresponding protein sequences ranged from 147 to 187 amino acids in length. 10 unique PfHRP3 sequences were identified for a ratio of [number of sequences] / [number of isolates] of 0.8. Motif types 1 (AHHAHHVAD), 4 (AHH), 7 (AHHAAD), 15 (AHHAHHAAN), 16 (AHHAAN), 17 (AHHDG), 18 (AHHDD) and 20 (SHHDD) were found.

DNA sequencing was successful for 47 out

of 56 *pfhrp3* PCR products (84%) from the Wosera samples (Table 4). Corresponding protein sequences ranged from 152 to 205 amino acids in length. 20 unique PfHRP3 sequences were identified for a ratio of [number of sequences] / [number of isolates] of 0.4. Motif types 1 (AHHAHHVAD), 4 (AHH), 7 (AHHAAD), 15 (AHHAHHAAN), 16 (AHHAAN), 17 (AHHDG), 18 (AHHDD) and 20 (SHHDD) were found.

Overall there were 39 *pfhrp3* unique sequences identified in East Sepik (Wosera) and Madang (Mugil and severe malaria sample set) regions (Table 4). Motif types 1 (AHHAHHVAD), 4 (AHH), 7 (AHHAAD), 15 (AHHAHHAAN), 16 (AHHAAN), 17 (AHHDG), 18 (AHHDD) and 20 (SHHDD) were found in both regions.

6 of the 39 unique sequences (15%) were found in isolates from both Madang and East Sepik Provinces. There were geographical

**TABLE 3**

PREDICTED RAPID DIAGNOSTIC TEST (RDT) RESULTS BASED ON *PFHRP2* SEQUENCES OF ISOLATES COLLECTED IN THE WOSERA REGION

Sequence type	Score*	Predicted RDT result
A	65	Sensitive
B	108	Sensitive
C	60	Sensitive
D	72	Sensitive
E	55	Sensitive
F	44	Sensitive
G	44	Sensitive
H	90	Sensitive
I	63	Sensitive

\*Score = [number of type 2 repeats] x [number of type 7 repeats]



differences noted between the Wosera and Madang regions in the repeat sequences observed for PfHRP3 (Table 4).

### Polymorphisms in *pfald* and *pldh*

From Mugil, 21 of 37 samples (57%) were *pfald* PCR positive (Table 2). 20 (95%) were successfully sequenced. For *pldh*, 18 samples (49%) were PCR positive. All were successfully sequenced.

From the Wosera, 54 of 93 samples (58%) were *pfald* PCR positive (Table 2). 53 (98%) were successfully sequenced. For *pldh*, 50 samples (54%) were PCR positive. All were successfully sequenced.

*Pfald* sequences displayed only one nucleotide change A → T at nucleotide 836, resulting in the change from an asparagine (N) to an isoleucine (I). This polymorphism was present in all the samples analysed

**TABLE 4**

PfHRP3 SEQUENCE TYPES IDENTIFIED FROM THE WOSERA AND MADANG SAMPLES

Size (aa)	Sequence types	Number of isolates	Origin		
			Madang		East Sepik
			Mugil (n = 13)	Severe malaria (n = 17)	Wosera (n = 47)
121	A1	1	-	1	-
127	B1	1	-	1	-
131	C1	1	-	1	-
132	D1	2	-	2	-
137	E1	1	-	1	-
142	F1	1	-	1	-
143	G1	1	-	1	-
145	H1	1	-	1	-
147	I1	2	2	-	-
148	J1	1	-	1	-
148	J2	1	-	1	-
149	K1	2	-	2	-
152	L1	2	-	-	2
153	M1	1	-	1	-
153	M2	7	1	-	6
154	N1	1	-	1	-
158	O1	4	-	-	4
159	P1	1	1	-	-
163	Q1	2	-	-	2

164	R1	5	3	-	2
167	S1	1	-	-	1
167	S2	1	-	1	-
169	T1	4	1	-	3
172	U1	1	-	1	-
173	V1	1	1	-	-
174	W1	1	-	-	1
174	W2	1	-	-	1
175	X1	2	-	-	2
176	Y1	8	1	-	7
18-	Z1	3	-	-	3
18-	Z2	1	-	-	1
181	a1	2	1	-	1
182	b1	3	1	-	2
186	c1	3	-	-	3
187	d1	1	1	-	-
193	e1	1	-	-	1
199	f1	3	-	-	3
205	g1	1	-	-	1
205	g2	1	-	-	1

aa = amino acids

from Wosera and Mugil. No nucleotide polymorphism was observed in *pldh*.

### Discussion

This study was undertaken from archival *P. falciparum* samples. The primers and PCR conditions used gave optimal results for *hrp3*, *ald* and *pldh*, but amplification of *hrp2* was less optimal leading to weak PCR products and poor sequencing results.

Samples collected in a previous study (severe malaria, Madang Province) showed low levels of PfHRP2 (as measured by ELISA) (26) while still being positive by malaria RDT, suggesting that RDT positivity may be due to cross-reactivity with PfHRP3. We hypothesized that these samples displayed polymorphisms in PfHRP2 or a gene deletion. If these polymorphisms were common in

PNG, this could have an impact on RDT performance in malaria-endemic regions of the country. Out of the 29 samples available from this sample set, we could only amplify *pfhrp2* in 24 samples. As we were not able to obtain sequences of sufficient quality for analysis, we cannot exclude that genetic polymorphisms were responsible for the low level of HRP2 previously detected by ELISA in this sample set. Another factor that could have contributed to the measured low levels of HRP2 is variation in the mRNA transcription of *pfhrp2* and *hrp3* between different parasite strains as was observed by Baker et al. (31). Levels of transcription of *pfhrp2* and *hrp3* were reported to vary between the parasite isolates observed at different time points in the malaria life cycle stages. Because of the small amount of blood available for testing, it was not possible to repeat DNA extraction and PCR in the remaining 5 samples that

showed no amplification of *pfhrp2*. Neither was it possible to amplify flanking regions of the *pfhrp2* region targeted in order to confirm a hypothetical deletion of *pfhrp2*. Additionally, 26 of these samples with low HRP2 levels showed positive *hrp3* amplification. As was observed by Baker et al. and from the sequencing results obtained for *pfhrp2* and *hrp3*, each gene has repeat sequences which occur independently but are partly shared. It has been suggested that these shared repeats may form the basis for the cross-reactivity observed between PfHRP2 and PfHRP3 by monoclonal antibodies directed against PfHRP2 (30).

Sequencing of *pfhrp2* and *hrp3* from isolates collected in two provinces of PNG provided information on the diversity of these genes in PNG. While our sample size is limited, most PfHRP2 sequences were unique within the sample set (ratio [number of sequences] / [number of isolates] of 0.9). Sequences were shorter (227 to 255 amino acids) than those previously reported by Baker et al. (30) (194 to 306 amino acids) but in terms of quantity more unique sequences were identified in this sample set. This could possibly be explained by the geographical origin of isolates.

Based on the PfHRP2 sequences, all 10 samples were predicted to be detectable by RDT (22). The scores obtained (Table 3) were similar to those reported for PNG PfHRP2 sequences by Willie et al. (32).

Similar results to Baker et al. (30) were observed in PfHRP3 sequences with consistent repeat types of 1, 15, 16, 7, 20, 17, 18 and 4, in each sample. HRP3 sequences appear less diverse in East Sepik than in Madang Province, with ratios [number of sequences] / [number of isolates] of 0.4 and 0.8, respectively. Interestingly, within Madang Province, there were no shared sequences between our two sample sets, highlighting the diversity of HRP3 sequences.

High levels of conservation in PfALD and PfLDH sequences in the samples obtained from the two populations studied were observed. This finding signifies that LDH- and ALD-based RDT tests are reliable in a setting where there is intense diversity or polymorphisms of HRP. However, other factors such as storage and transporting of RDTs and asymptomatic infections could still have an impact on the sensitivity and

specificity of these RDTs.

## Conclusion

This study did not find evidence for the deletion of *pfhrp2* in *P. falciparum* PNG isolates that would possibly result in false negative RDT results. The study highlighted the high level of PfHRP2 and HRP3 diversity in PNG but there was no evidence that the polymorphisms observed impacted on RDT sensitivity. There is an absence of polymorphisms in *pldh* and *ald* genes in PNG isolates from two regions (Madang and Wosera). Evidence from this study confirms that RDTs based on the detection of pLDH or aldolase, combined with PfHRP2, can continue to be used for malaria diagnosis in PNG.

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## **Tobacco control in Papua New Guinea – the need for a renewed commitment**

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### **SUMMARY**

**The tobacco epidemic is one of the biggest public health threats the world has ever faced. Low- and middle-income countries like Papua New Guinea (PNG) have the highest burden of illness and death from tobacco use because they lack political commitment, are plagued with inadequate resources and funding, and comply poorly with tobacco laws and regulations. These factors contribute to the high prevalence of tobacco smoking in these countries where 80% of the 1.1 billion smokers world-wide live. In PNG the tobacco epidemic has had detrimental effects on the health and economy of its people. Even though tobacco laws were enacted over 30 years ago and regulatory frameworks have been officially adopted, yet it suffices to say, given the present scenario, that tobacco control in PNG remains poor and is ineffective. The government, the health ministry and other relevant stakeholders must renew their commitment to control the growing tobacco epidemic. It is now time to act.**

The seemingly glamorous but deadly addiction of the 21st century is tobacco smoking. It has become a lifestyle like wearing your jeans, combing your hair, or putting on a lipstick. Tobacco smoking is now unfortunately a national pastime in Papua New Guinea (PNG). It brings a false sense of self-esteem and belongingness to peer groups while it moves tardily, eventually sending its users to an early death.

The tobacco epidemic is one of the biggest public health threats the world has ever faced, with the heaviest burden from illness and death due to tobacco use in low- and middle-income countries, where 80% of the 1.1 billion smokers world-wide live (1). Tobacco use is the leading global cause of preventable deaths (2-5). It is the only risk factor common to all four of the main non-communicable diseases (NCDs) – cancer, cardiovascular disease, diabetes and respiratory disease – and is also the single greatest preventable cause of NCDs (2). The World Health Organization (WHO) estimates that smoking kills more than 7 million people around the world, including 890,000 passive smokers, every year (1).

In PNG, while research is scanty, it is

estimated that 12,800 people die every year from diseases related to tobacco use (6) – that is, 35 people dying every day. Yet about 44% of adult men and 17% of adult women continue to use tobacco daily (6). What is even more alarming is that 6% of children between the ages of 10 and 14 years use tobacco daily (6). Using current population figures (7,8) and data from the Tobacco Atlas (6), over 1.6 million males and 741,000 females over the age of 10 years use tobacco daily in PNG. These statistics mean that approximately 30% of the population of PNG over the age of 10 years use tobacco daily. This should raise concern for the future outlook of tobacco use and its impacts in PNG.

There is no safe level of tobacco use, including exposure to passive smoking (1,2). One cigarette smoke contains over 4000 toxic chemicals (9,10). When it is set alight, the burning process results in over 7000 toxic chemicals being produced (11). 69 of these chemicals are known to cause cancer (11). These toxic chemicals include acetone, acetic acid, ammonia, arsenic, benzene, cadmium, carbon monoxide, naphthalene, nicotine (used in insecticides such as gramoxone), toluene, tar, cyanide and formaldehyde (9-11),

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which enter the lungs and bodies of tobacco users at a steady rate every day.

As a result, tobacco smoking has been associated with over 20 diseases (12). It is the number one cause of lung cancer and a significant risk factor for other cancers of the body including cancers of the stomach, lip, mouth, throat, liver, colon, rectum, bladder, cervix and others (2,6,9,11-13). It is also a significant risk factor for cardiovascular diseases, including heart attack, stroke and peripheral vascular disease, and chronic lung diseases such as emphysema and bronchitis (2,6,9,11-13). Smoking increases the risk of developing diabetes (14). People from Central Province (especially those from Wanigela) (15-17), New Britain (17,18) and Bougainville (17,19) have a genetic predisposition to diabetes and smoking tobacco further increases that risk. Smoking increases the risk of developing eye disease, rheumatoid arthritis, tuberculosis, hearing loss and heartburn, and reduces sperm counts and eggs for males and females respectively (20,21). Smoking in pregnancy can result in low infant birthweights, premature labour, fetal death in the uterus, fetal deformities and other complications (21). It also reduces youthful appearances, making smokers look older and haggard, with poor dental health, poor sleep times and an offensive smell.

For parents who smoke, it is highly likely that their children will smoke and they will smoke at an earlier age than the parents, and if they continue they will die earlier. The old Biblical adage in the book of Ezekiel, "...as is the mother, so is her daughter" (22) still holds true. Children will follow after their parents and the vicious cycle will continue, killing each generation at an earlier age than the last.

The British Doctors Study in the 1950s revealed that smokers lose ten years of their lives and are twenty times more likely to die than non-smokers (12). The current average life expectancy of Papua New Guineans is 66 years (7). Melanesians in Vanuatu and Solomon Islands have an average life expectancy of 72 years (23,24). They live about 6 years more than Papua New Guineans. It is likely that smoking is contributing to the observed low life expectancy in PNG. The benefits therefore of not smoking in this regard can be quite startling, but remain to be seen.

The socioeconomic consequences of

smoking, apart from its health effects, have been well established. Individuals who smoke have higher health costs, undergo complicated treatments and impose huge costs on industries through absenteeism (2). Tobacco use raises government health systems' costs and increases social and financial inequity by disproportionately harming the poor, especially in developing countries like PNG (2,25). In 2012, the amount of global health expenditure due to smoking-attributable diseases totalled purchasing power parity (PPP) US\$422 billion, which equates to 5.7% of the global health expenditure (26). The total economic cost of smoking (from health expenditures and productivity loss) totalled PPP US\$ 1436 billion, and 40% of this cost occurred in developing countries (26). In PNG, \$370,000 was spent in treating tobacco-related illnesses in 1981, and an associated 30% time loss from work was reported (13). Furthermore, another study in PNG showed that tobacco use accounted for 7% of the total household expenditure and about 23% of food expenditure among families in the poor quartile compared to 4.9% and 15.3% respectively for the entire sample (2). This is detrimental to the socioeconomic and health state of the average family in PNG because tobacco use eats away a huge chunk of the family income and leaves them deprived of necessities. The current economic burdens of tobacco smoking in PNG, given rising health and living costs, are conceivably high, but remain undocumented.

Tobacco use has no long-term benefit, but constitutes everything to lose. In PNG, apart from its health and economic costs, unrestrained smoking in public places including restaurants, shops and vehicles has become a source of social irritant to the non-smoking public. The carelessly discarded butts conspicuously litter the streets and like discarded betelnut husks and spittle are a public eye-sore. The human behaviour of smoking is a paradox. Its toxic effects have been known for over 30 years and yet the prevalence of smoking is increasing at an alarming rate, especially in low- and middle-income countries like PNG (1) – this rise has been proportional to the strength and force of the tobacco industries, who do not fear the action of developing nation states because their resources are often much greater (6).

Given its health and socioeconomic costs, the government and other organizations

concerned about PNG's health have an obligation to control tobacco smoking. Leaving citizens to an uncontrolled use of tobacco is akin to leaving children beside a pool of chocolate – they will drown in it. Developed countries like Britain and Australia have imposed a high excise tax on tobacco, developed legislation to control or curb cigarette smoking and have implemented it rigorously (4,5,27,28). As required by law cigarettes are sold only in packets by licensed vendors and children below 18 years of age are prohibited from purchasing tobacco products (2,4,5,27). Smoking is banned in public places like government offices, universities, health care facilities, pubs and bars, public transport and indoors in public buildings (4,5,27,28). It is also required by law that all cigarette packets must have graphic warning labels (5,27,28). These efforts are enforced further by anti-tobacco campaigns (5,28).

So have any of these measures been implemented in PNG? In 2015, the government of PNG through the National Department of Health developed a comprehensive policy to reduce and control demand for tobacco use, including a ban on local production of tobacco on a commercial scale (29). A technical unit was set up to implement this policy at the Health Department but very little has been done to date to curb tobacco smoking (30). It is reported that the unit has only one full-time staff member and the government spends only about K50,000 every year on tobacco control. Compliance with regulatory regimes recommended by the WHO framework, which PNG is party to, remains low (28,30). The WHO framework recommends measures relating to the reduction of demand for and supply of tobacco products. In order for the WHO framework to be successful in PNG, it requires strong political commitment, international cooperation, comprehensive measures, financial assistance and the participation of relevant stakeholders (28). Measures directed towards reducing the demand for tobacco include increasing tobacco excise taxes and raising the cost of tobacco sales (28). PNG imposes only 27.8% of retail price as excise tax when the WHO recommends a minimum of 70% of retail price as excise tax (6). Research has shown that a 10% increase in tobacco price can result in a 2-8% drop in tobacco consumption (6). A ban on tobacco advertisement, promotion, sponsorship and tobacco use in public facilities and implementing laws mandating

adequate labelling and warnings on tobacco products are also part of this approach (28,30). WHO recommends labels containing graphic warnings on tobacco products, but this is confined to text only in PNG (30). In addition, increasing anti-tobacco mass campaigns on radio, television, billboards and print media and enhancing the monitoring and policing of tobacco laws and regulations will reduce the demand for tobacco (28,30). Furthermore, health services to treat tobacco dependence and cessation need to be considered (28,30). Measures directed towards reducing the supply of tobacco include banning sales of tobacco to and by minors, providing alternative means of income generation for tobacco growers and eliminating the illicit trade of tobacco products (28,30).

PNG has a Tobacco Act, the Tobacco Products (Health Control) Act 1987 (31), and has ratified the WHO Framework Convention on Tobacco Control on the 25th of May 2006 (30). Yet it suffices to say, given the present scenario, that tobacco control in PNG remains poor and is ineffective. This is regretful considering the devastating effects tobacco use is having on PNG. It will leave behind a diseased population resulting in economic loss and adding health costs to an already saturated system. Premature deaths from tobacco use will worsen PNG's health indicators, reduce life expectancy, reduce literacy rates, suppress the economy and worsen poverty.

The government, the health ministry, donor agencies and non-governmental organizations must act now to develop, implement and monitor tobacco control policies – it is one of the best investments any country can do for its people. All these small investments will reap enormous dividends in health and prosperity for PNG. The time for a renewed focus and commitment to curb the growing epidemic of tobacco use in PNG is now at hand and we must act.

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# **The role of surgery and oral methotrexate treatment on lower lip squamous cell carcinoma in Milne Bay Province and National Capital District, Papua New Guinea**

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## **SUMMARY**

This cohort study was undertaken over 54 months to observe the effectiveness of primary surgery and long-term oral methotrexate (MXT) treatment on lower lip squamous cell carcinoma (SCC) in Milne Bay Province and National Capital District, Papua New Guinea (PNG). The current standard treatment for lower lip SCC depends on the stage of the disease: stage 1 is treated with either surgery or radiotherapy only, while stages 2 and 3 are treated with surgery followed by chemotherapy and radiotherapy; stage 4 is metastatic disease and is treated with palliative chemotherapy and radiotherapy. Due to limited treatment options available in Papua New Guinea for cancer patients, this study was conducted with the primary aim of finding an alternative, affordable and effective treatment option for lower lip SCC in our setting. There were 20 patients recruited in the study with histologically confirmed SCC of the lower lip. They had primary surgeries which included selective neck dissection (SND) for positive neck involvement (stages 2, 3 and 4) (8; 40%) and tumour resection and reconstruction (20; 100%), and, once the wounds had healed well, they were commenced on long-term oral MXT treatment for 24 months. The follow-up period was approximately 54 months and the results of the primary outcomes measured were: no local recurrence, no neck metastasis, no distant metastasis and no mortality. In conclusion, even though we acknowledge the small number of subjects recruited, this cohort study does give some hope to health care practitioners, including surgeons, in PNG that lower lip SCC can be alternatively treated with surgery and methotrexate when there are no other treatment modalities available in their health facility.

## **Introduction**

Globally, there has been an increase in mortality associated with oral cancer, with 124,000 deaths in 2010 compared to 82,000 in 1990 (1).

In 2011, close to 37,000 Americans were projected to be diagnosed with oral or pharyngeal cancer. 66% of these were to be found as late stage 3 or 4 disease. It was predicted to account for over 8000 deaths. Of those 37,000 newly diagnosed individuals, only slightly more than half would have a 5-year survival rate (1).

Approximately 75% of risk factors for oral

cancers and lower lip cancers are modifiable. These include chewing areca nut concoctions (betelnut with lime), smoking cigars, consuming alcohol, human papillomavirus (HPV16, HPV24), herpes simplex virus (HSV1 and HSV2), prolonged sunlight exposure and poor oral hygiene (1). In many Asian cultures chewing betel, paan and areca has been shown to be a strong risk factor for developing oral cancer. In India, where such practices are common, oral cancer represents up to 40% of all cancers, compared to just 4% in the United Kingdom (UK) (1).

While the incidence of lip cancers is low (1-2%), it accounts for approximately 25%

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of oral cancers globally. They are extremely important from a clinical and surgical point of view because of the morphological and functional changes involved. Over 90% of these tumours consist of squamous cell carcinomas (SCCs) and, in lesser numbers, basal cell tumours (BCCs), adenocarcinomas and, more rarely, melanomas, sarcomas and lymphomas (2). Despite advanced treatments available in developed countries, SCC of the lip still has a mortality of 50% (3).

In 1974 a more comprehensive review of the Tumour Registry was completed in Papua New Guinea (PNG). The preponderance of oral cancer was noted, with a ten times lower frequency in the highlands (0.3/100,000) than on the north coast and in Papua (excluding Western Province) (3.2 and 3.3/100,000 respectively) (4).

Thomas and co-workers conducted longitudinal population-based studies in New Ireland Province throughout 1985-1987 and established that chewing of betelnut produced a threshold and dose-related increased risk of oral cancer. The addition of smoking enhanced this risk considerably and in a dose-dependent manner, with an odds ratio of up to 4.85 for chewers of betelnut who were also heavy smokers (5).

A Master of Medicine (MMed) thesis done by Mesol in 1997 on oral cancers in Angau Memorial Hospital and Port Moresby General Hospital in Papua New Guinea revealed that out of 90 patients recruited, lower lip SCC was found in only 3%. The cheek and tongue are the commonest sites with 49% and 27% respectively (6).

Another audit done by Seta between 1992 and 1999 on oral cancers in Milne Bay Province also revealed that lower lip SCC represented only 3.4% while palate and buccal mucosa each accounted for 12% and gingiva 13% (7).

The current standard treatment for lower lip SCC depends on the stage of the disease. It is managed as follows: stage 1 is treated with either surgery or radiotherapy only, while stages 2 and 3 are treated with surgery followed by chemotherapy and radiotherapy; stage 4 is metastatic disease and is treated with palliative chemotherapy and radiotherapy (8).

Due to the limited supply of chemotherapy drugs and non-availability of radiotherapy, the above standard treatment is not practical in developing nations like Papua New Guinea. Therefore the primary aim of the study was to evaluate the outcome of surgery and oral methotrexate (MXT) treatment on lower lip SCC over a 54-month period after the patients were exposed to the two treatment modalities. This monitoring included as primary outcomes local recurrence, neck metastasis, distant metastasis and mortality. The secondary outcomes measured included immediate, short-term and long-term post-surgical complications.

## Methodology

### Study design

The study was a prospective cohort study looking at 20 patients with lower lip SCC undergoing surgery and MXT treatment who were followed up over 54 months and the outcomes observed. The patients who presented to the hospital with chronic lower lip lesions and were clinically diagnosed as tumours consented and had biopsies done. Those that had confirmed SCC were recruited and had major surgeries, ie, neck dissection for positive neck SCC, tumour resection and lower lip reconstruction. After the wounds had healed well, the patients were commenced on oral methotrexate treatment one month after surgery, which was continued for 24 months, and they were followed up for 54 months.

A patient information sheet was used for each individual patient. The sheet contained identification information, history, examination, investigation results, biopsy results, and surgery and follow-up information. During the follow-up period, the patients' full blood counts were reviewed on a monthly basis and patients were assessed for local recurrences, neck metastases, distant metastases and mortality. The secondary outcomes were taken into account during the follow-up.

### Study site

The study was conducted between 1 January 2013 and 31 May 2017. The initial study site was at Alotau Provincial Hospital, Papua New Guinea, and then was continued at Port Moresby General Hospital, Papua New Guinea.



## Study criteria

### *Inclusion criteria:*

- patients with lower lip SCC confirmed by histology,
- patients who presented with stages 1-4 disease but with resectable tumours,
- patients who consented for the study, and
- patients who were compliant to treatment.

### *Exclusion criteria:*

- patients with non-SCC lower lip lesions by histology,
- patients with stage 4 disease with non-resectable tumours,
- patients who had comorbidities,
- patients who did not consent for the study, and
- patients who were non-compliant to treatment or lost to follow-up.

## Data analysis

The Statistical Package for Social Sciences (SPSS version 20.0) and Excel MS 2010 software package were used for information storage and graphical presentations.

## Ethical clearance

Approval for this study was obtained from the Milne Bay Provincial Health Authority Research Committee and Research Committee, School of Medicine and Health Sciences, University of Papua New Guinea. The patients consented for the usage of their photographs in this publication.

## Results

The age range of the 20 patients was 45-76 years, with a mean age of 59.8 years and median age of 60 years. There were 11 (55%) females and 9 (45%) males. Lower lip lesions presented between 3 and 36 months to the hospital. All 20 patients admitted chewing betelnut with mustard fruits and lime for more than 20 years. 5 (25%) of the patients

consumed both betelnut and alcohol, 8 (40%) took both betelnut and cigarettes, and 7 (35%) consumed betelnut, alcohol and cigarettes.

The TNM (tumour, nodes and metastases) classification of the 20 subjects is as follows: 5 T3N0M0, 4 T4N0M0, 3 T4N2M0, 2 T4N1M1, 1 T4N2M1, 4 T2N0M0 and 1 T3N1M0. 2 patients who had T4N1M1 had tracheostomies and hemi-mandibulectomies. The other with left submandibular gland involvement had submandibular gland resection and selective neck dissection (SND). All 20 patients had histologies done with 19 (95%) squamous cell carcinoma and 1 (5%) verrucous carcinoma, which is a prerequisite for SCC.

Figure 1 shows the relationship between age of the patients and the stage of the tumour. All of these patients were above 40 years of age and with 4 exceptions presented with tumours of stage 3 or 4 (late stage of the disease).

Figure 2 shows the haemoglobin (Hb) levels of the patients. Most patients' haemoglobin levels were within the normal range before surgery. There were a few outliers but these were due to anaemia and were covered with iron tablets to improve the Hb levels.

Figure 3 shows that the patients had a white cell count (WCC) within the normal range, with the exception of one outlier due to super-infection of the tumour. The patient was covered with an antibiotic.

Figure 4 shows the nutritional status of the patients. The majority of the patients had a normal albumin level and body mass index (BMI) before surgery. This is one of the factors which contributed to the good surgical outcomes.

Figure 5 shows the treatment outcomes of the patients. In the 54-month period of follow-up, there was no local recurrence, no neck metastasis, no distant metastasis and no mortality observed.

The types of primary reconstructions and flaps done included: Esthlander flaps 5 (25%), Karapandzic flaps 4 (20%), submantle-local tissue flaps 3 (15%), nasolabial flaps 2 (10%), wedge resection 2 (10%), combined nasolabial-Karapandzic flap 1 (5%), combined nasolabial-Karapandzic-stair case flap 1 (5%), a combined submantle and Karapandzic flap

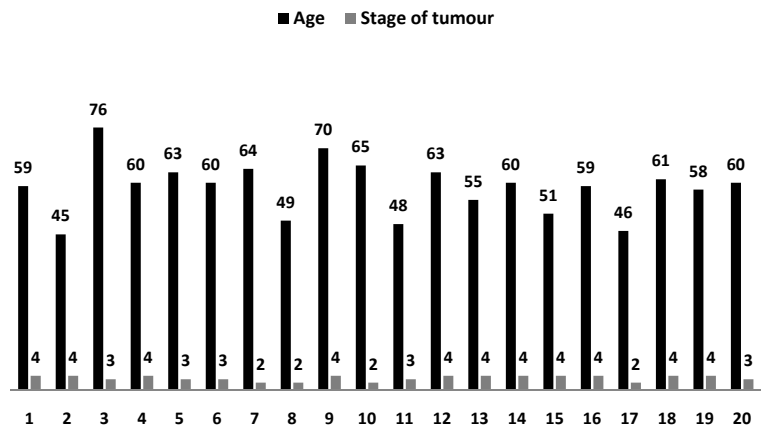


Figure 1. Age of patient and stage of tumour in the 20 study patients.

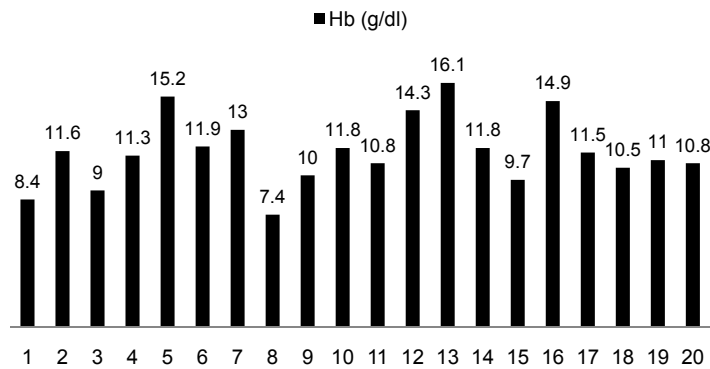


Figure 2. Haemoglobin (Hb) level of the 20 patients.

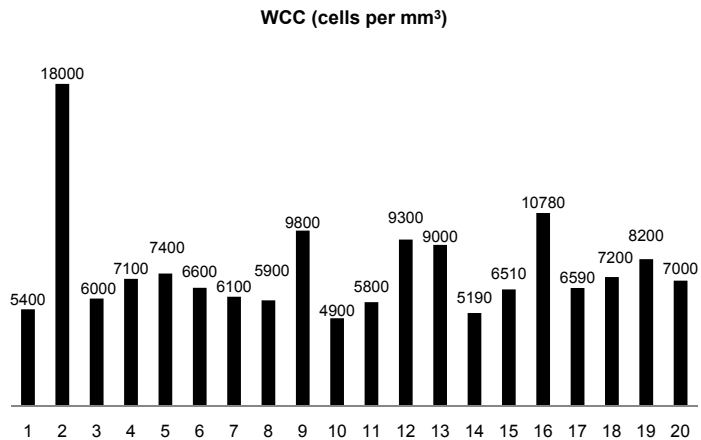


Figure 3. White cell count (WCC) of the 20 patients.

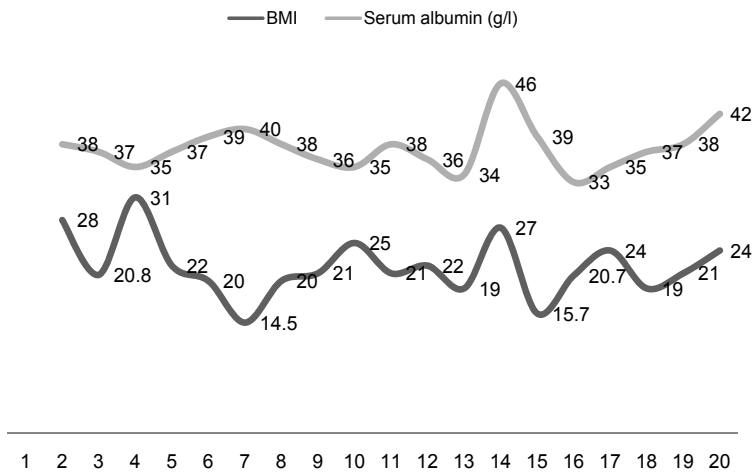


Figure 4. Body mass index (BMI) and serum albumin level of 19 patients.

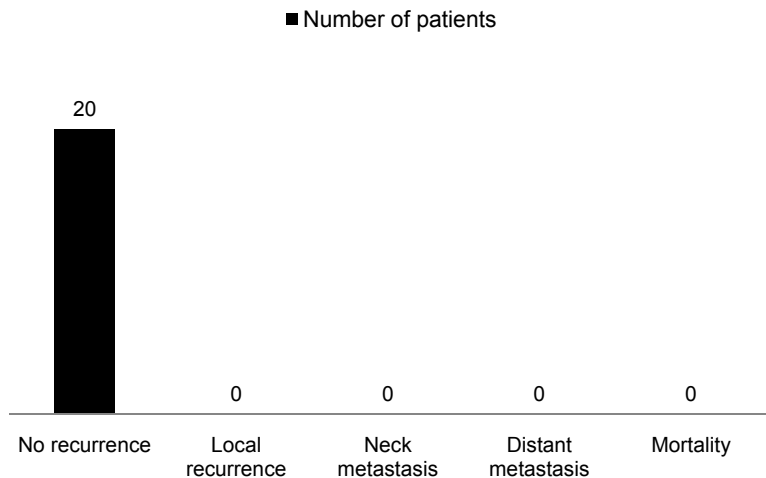


Figure 5. The outcome of the patients over the 54-month follow-up.

1 (5%), and a combined Esthlander and stair case flap 1 (5%). Elective neck dissection was done on only 8 patients (40%) with clinically enlarged level 1-2 cervical lymph nodes.

Figure 6a shows Patient F.P. who had stage 4 SCC disease; she had tracheostomy, SND, left hemi-mandibulectomy, tumour resection and lower lip reconstruction (Figure 6b). She had two additional revisions of her lower lip and has been disease free for the past 4 years (Figure 6c and 6d).

Figure 7a shows Patient K.T. who had stage 3 SCC disease of the lower lip; he had SND,

bilateral Karapandzic flaps and reconstruction done (Figure 7b); he had wound break-down and a V-defect with oral incompetence (Figure 7c); he had revision done using a left nasolabial flap (Figure 7d); and, finally, he has near normal lower lip function and has been disease free for the past 4 years (Figure 7e).

Complications observed after primary reconstructions were immediate, short-term or long-term. *Immediate complications* noted were swelling/oedema 20 (100%), bleeding 1 (5%), deformity 20 (100%), loss of lower lip 20 (100%), change in voice 16 (80%) and tracheostomy 2 (10%). *Short-term*

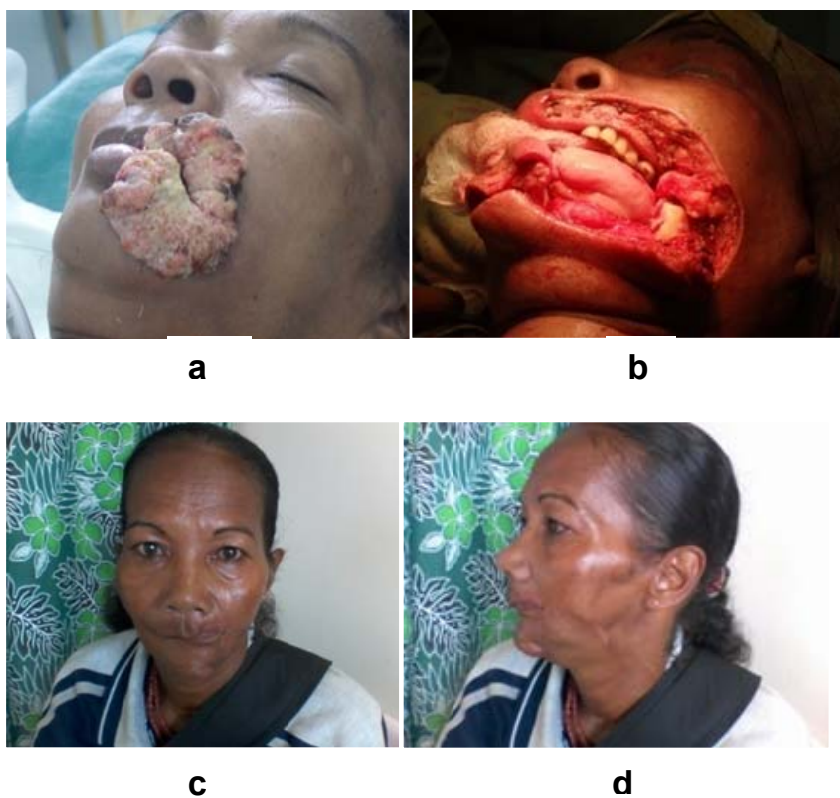


Figure 6. Patient F.P. with advanced disease. Images published with the patient's consent.

*complications* noted were wound infection 5 (25%), wound break-down 4 (20%), loss of lower lip 6 (30%), oral incompetence 6 (30%), V-deformity 3 (15%), trismus 4 (20%) and taking only a soft diet 2 (10%). The *long-term complications* noted were loss of lower lip 1 (5%), change in voice 1 (5%) and trismus 1 (5%). 4 cases (20%) had revisions and 5 (25%) are still awaiting revisions. 9 patients (45%) did not require further revisions as there was patient satisfaction. 19 patients (95%) were compliant to the methotrexate treatment while 1 (5%) was non-compliant due to chronic right ear infection (chronic suppurative otitis media).

During the initial stages of the study, all 20 patients were educated on the radiotherapy service in Angau Memorial Hospital in Lae (the only hospital in PNG with radiotherapy) and treatments abroad. This was done on the basis of ethics and standard cancer treatment guidelines. However, for various reasons none of the patients were able to seek those treatments: 13 (65%) had accommodation

problems, 6 (30%) had financial difficulties, and 1 (5%) did not travel because the team's efforts to contact the Angau Oncology Unit were unsuccessful.

### Discussion

Lower lip cancers are quite common in PNG but there is no published literature on their incidence and management in PNG and in the Pacific region. However, the two hospital audits done by Mesol and Seta confirmed that lower lip SCC accounted for 3-4% of the oral cancers in Angau Hospital, Port Moresby General Hospital and Alotau Hospital in Papua New Guinea (6,7).

From these audits they confirmed that chewing betelnut with mustard and lime is strongly associated with SCC of the oral cavity (6,7). The present study also revealed that chewing of betelnut with mustard and lime represented a high risk of developing SCC. The two audits also showed that late presentation was common among all patients



Figure 7. Patient K.T. with stage 3 disease. Images published with the patient's consent.

for various reasons (6,7). Our study found that the patients presented with between 3 and 36 months of illness before seeking medical treatment.

Small lesions had fewer complications postoperatively, as compared to larger lesions. Large lesions had larger areas of resection and greater defects, which had more complications and eventually had 1-3 revisions to regain near normal lower lip functions.

Three other similar studies were done in

China, Netherlands and Serbia (9-11). They were all retrospective studies over 10, 9 and 13 years respectively. The Chinese study used surgery and radiotherapy for stages 1-4 disease; the Netherlands study used only surgery for stage 1 disease; and the Serbian study used surgery and radiotherapy for stages 1-4 disease (9-11). The results are shown in Table 1. There are differences in their local recurrences, neck metastases, distant metastases, and mortality rates during their follow-up periods.

When the 3 studies are compared to



**TABLE 1**

COMPARISON OF RESULTS FROM 4 STUDIES OF SQUAMOUS CELL CARCINOMA OF THE LIP

	<b>PNG current study</b>	<b>Chinese study (9)</b>	<b>Netherlands study (10)</b>	<b>Serbian study (11)</b>
<b>Study type</b>	Prospective (4 years)	Retrospective (10 years)	Retrospective (13 years)	Retrospective (9 years)
<b>Patient number</b>	20	109	184	223
<b>Tumour site</b>	Lower lip	Lower lip	Lower lip	Lip
<b>Treatments</b>	Surgery + ND and oral MXT (stages 1-4)	Surgery + ND and radiotherapy (stages 1-4)	Surgery only (no ND) (stage 1 only)	Surgery + ND and radiotherapy (stages 1-4)
<b>Follow-up period</b>	54 months	38 months	24 months	56 months
<b>Outcomes:</b>				
<b>Local recurrence</b>	0 patients	5 patients	9 patients	22 patients
<b>Neck metastasis</b>	0 patients	3 patients	10 patients	10 patients
<b>Distant metastasis</b>	0 patients	1 patient	1 patient	0 patients
<b>Mortality</b>	0 patients	5 patients	40 patients (5 years)	5 patients

PNG = Papua New Guinea  
 ND = neck dissection  
 MXT = methotrexate

this current study, our study's results are promising. The early tumour resection and elective neck dissection for positive neck nodes with the use of oral methotrexate is an alternative, affordable and effective approach to managing lower lip SCC. So far it is very encouraging that in the 54-month follow-up period there were no local recurrences, no neck metastases, no distant metastases and no recorded deaths in this cohort study.

### Conclusion

In conclusion, though we acknowledge the small number of subjects recruited and the exclusion of those lost to follow-up, this cohort study does give some hope to health care practitioners, including surgeons, in PNG that lower lip SCC can be alternatively treated to achieve remission with surgery

and methotrexate when there are no other treatment modalities available in their health facility.

### ACKNOWLEDGEMENT

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# Ligation of the internal iliac arteries: personal experience over 36 years

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## SUMMARY

**My experience with ligation of the internal iliac arteries (IIA) over a period of 36 years is described. Internal iliac artery ligation (IIAL) was performed to control postpartum haemorrhage, bleeding after prostatectomy and after a stab wound. Only once, during an abdominoperineal resection of the rectum, did I perform it prophylactically.**

## Introduction

The internal iliac arteries (IIA), also called the inferior epigastric arteries, arise at the bifurcation of the common iliac arteries, anterior to the lumbosacral articulation, at the level of the pelvic brim. They are large vessels, their branches supply the walls and viscera of the pelvis, the gluteal muscles and the medial compartment of the thigh. There are several anastomoses between their branches and other somatic and visceral arteries (1).

The IIA can, if facilities are available, be obliterated radiologically. Internal iliac artery ligation (IIAL) is usually performed through a transperitoneal approach, but can be done extraperitoneally. IIAL may be done to control pelvic haemorrhage, or prophylactically at the beginning of an operation if significant bleeding is anticipated.

Ligating them through a transperitoneal approach involves packing the intestines away from the pelvic brim, identifying the origin of the IIA, which is close to the ureter, and freeing the artery from the vein. When ligating the IIA the external iliac, or femoral artery, is palpated to confirm that the correct vessel is being ligated. The IIA do not need to be divided.

I presented the first person whose IIA I had divided at the Papua New Guinea (PNG) Surgical Society meeting in 1978. I did not have access to any literature on IIAL

during the 15 years I was working full-time in PNG and, with no knowledge of possible complications that could arise after doing it, only considered doing it in a situation where there was continuous pelvic bleeding, and a shortage of blood for transfusion.

## Patients

### Patient with postpartum haemorrhage

I first ligated the IIA, with the assistance of an obstetrician, for a woman with postpartum haemorrhage in 1978, when I was surgeon at Nonga Base Hospital in Rabaul.

She was a febrile 22-year-old woman from a remote area who at the time of admission had been in obstructed labour, with ruptured membranes, for three days. Her dead baby was delivered by caesarian section on the day of her admission.

Postoperatively she was treated with broad spectrum antibiotics for puerperal sepsis, but she remained febrile with foul-smelling vaginal discharge. Four days after operation she started bleeding. At operation the following day she had a subtotal hysterectomy. The obstetrician had hoped that she might be able to do a total hysterectomy, but gross swelling and inflammation around the cervix had made removing it too difficult.

Two days later I was asked by the obstetrician if I could ligate the IIA while she

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assisted. By then the woman had had 12 units of blood and was still bleeding. I had not at that stage of my career heard of ligation of those vessels, but the obstetrician was enthusiastic, she had seen it done before, the indications seemed reasonable, and without drastic measures the patient would probably not survive. I revised the anatomy of the vessels, but could not find anything about ligating them in the hospital library.

At operation later that day the large inflammatory mass around her pelvis was left undisturbed. Her IIA were identified and ligated. Postoperatively her bleeding was much less, and stopped five days later, by which time she had had 20 units of blood. We thought that IIAL had probably saved her life.

I presented her at the PNG Surgical Society meeting that year. None of the surgeons at the meeting were familiar with the operation.

### **Patients undergoing prostatectomy**

During the 1970s and 1980s I did 10-15 prostatectomies a year on men who had presented with retention of urine from benign prostatic hypertrophy. Obtaining enough blood to cover blood loss at operation, and possible continuing blood loss after surgery, was always difficult.

I used a retropubic approach for a prostatectomy initially, but changed to Hryntschak's modification of a transvesical prostatectomy after reading Macky's experience with 300 consecutive cases (2), and hearing Dr Ken Clezy present his experience at a PNG Surgical Society meeting.

Hryntschak's modification is done after the prostate has been removed through a transvesical approach and the operation has proceeded to the point where the dome of the bladder is ready to be closed.

His modification involves closing the bladder neck off, with two or three deep transverse plain catgut sutures which are tied tight on each side of the catheter and cut short.

The theory behind Hryntschak's modification is that the prostate bed will be contained by the sutures and the catheter, and the tympanic effect of any continuing bleeding will be haemostatic. Plain catgut

sutures are used, tied tight, and cut short, because they will not be strong enough to last more than a few days, and will come undone before stricture of the bladder neck becomes a problem.

My experience with this technique was that postoperative bleeding was usually well controlled and I was not aware of any long-term urethral strictures in any of the men I operated on.

Occasionally a postoperative prostatectomy had frank haematuria and signs of hypovolaemic shock soon after operation, suggesting that the plain catgut sutures had not held. I aimed to reoperate before shortage of blood became a problem. At the second operation I evacuated clots from the prostatic bed, packed it tight with gauze packing, opened the abdominal cavity, and ligated the internal iliac arteries. The packing was in the prostatic bed for at least half an hour while I ligated the vessels. There was minimal bleeding after it was removed.

I have no records of the number of times I ligated the IIA after prostatectomy, but estimate that I did it at least once a year for 12 years. I changed from doing a lower transverse Pfannensteil incision for a prostatectomy to a lower midline incision so that if I wanted to ligate the IIA access would be easier. I had no problems with bleeding after IIAL, and was not aware of any postoperative ischaemic problems.

### **Patient with stab wounds**

A woman who had recently become a second wife was lying asleep on her right side at a market near Rabaul when she was stabbed in the buttock with a bush knife by the first wife. When I saw her an hour after the assault she was lying on her left side on a trolley in the operating theatre. She had a blood pressure of 70/50 and was being vigorously resuscitated by the anaesthetic staff.

She had two wounds. There was a longitudinal wound 5 cm in length just below her umbilicus from which omentum was protruding. From her left buttock wound a large portion of her small intestine was protruding. Her left sciatic nerve was not damaged, and peripheral pulses were present in her warm left leg.

At operation, a midline incision was made with her lying on her left side. After her intestines were drawn back into her abdominal cavity, she was rolled on to her back. There was torrential haemorrhage from her pelvis, which was firmly packed. Her small intestine had not been perforated. This may have saved her life as her intestines were dilated, and possibly had some tympanic effect on the bleeding vessels.

Her small intestine was viable, but she had a large cut in its mesentery and several vessels in it were bleeding vigorously. These were clamped and ligated. The packing remained in her pelvis while her left internal iliac artery was ligated and the hole in the mesentery repaired.

After the packing was removed the bleeding was significantly reduced and bleeding vessels in the pelvis were able to be ligated before the pelvic peritoneum and abdominal wall were closed. She was then turned on her side again and the buttock wound closed.

Her postoperative course was uneventful.

### **Patient having an abdominoperineal resection of the rectum**

In 2014 when I was working in Dili, East Timor, I prophylactically ligated the IIA in a man who was having an abdominoperineal resection for rectal cancer. After IIAL bleeding was minimal, but the pelvic tissues were obviously still well perfused. Blood transfusion was not required and his postoperative course was uneventful.

### **Discussion**

Kelly, who described IIAL in 1894, thought that ligating these vessels entirely cut off all pelvic circulation (3).

Burchell, in an article in 1968 on the physiology of the IIA, showed that pelvic circulation was not cut off after IIAL (1). He made observations on 51 women who had gynaecological surgery; 45 had IIAL as part of the operative procedure and 6 were controls. He observed that blood flowed freely from a severed uterine artery after bilateral IIAL. This bleeding was able to be controlled by compression alone.

He made direct measurement of various

pelvic arterial pressures at operation. These showed that with bilateral ligation the drop in pulse pressure was 85%; it was greatly dampened, and the pelvic arterial system seemed to transform into a venous-like system.

In 21 patients who had had IIAL, he observed the flow of radio-opaque material injected into their lower aortas. 3 had this done at operation by direct injection into the aorta and the others via femoral artery cannulation up to three years after operation.

His aortograms demonstrated three principal collateral circulations, all involving vessels of small diameter. The diameter of these collateral anastomoses did not increase with time. He concluded that the pelvic blood supply is so abundant that no compensatory growth in the collateral vessels was necessary. None of his patients had tissue necrosis.

Das and Biswas, in Calcutta, reviewed 46 women who had had IIAL over a five-year period (4): 15 were for postpartum haemorrhage (PPH), 4 for secondary bleeding after hysterectomy, and 27 were done prophylactically before gynaecological cancer surgery. PPH was controlled in 14 women: 1 with atonia also required hysterectomy. Secondary haemorrhage was arrested in all, and IIAL almost entirely avoided blood transfusion during operations for gynaecological cancers. Others have reported similar findings (5-8).

Forty years ago, open prostatectomy in a Base or Provincial Hospital in Papua New Guinea, where there was limited blood available for transfusion, no equipment for transurethral resection of the prostate and no specialist urologist, was a hazardous procedure for me, a general surgeon with very limited urological experience. This still is the situation in some regional hospitals in PNG.

I forget what near disaster made me first ligate the IIA for someone who had continuous bleeding after prostatectomy. But after I had stopped the bleeding without complications by performing IIAL at reoperation, I felt much more comfortable doing open prostatectomy.

Prostates were removed early on my morning lists. The patients were kept in the resuscitation room in the operating theatre for at least an hour after operation, and I reviewed



them regularly during the day. Most of them did not have significant bleeding. But if they did I had plan B. They returned to theatre for IIAL within a few hours of their first operation. I had no problems with bleeding after that.

Bao, in China, documented 110 patients who had significantly less bleeding, and no complications, after internal iliac artery ligation during open prostatectomy (9).

The internal iliac arteries are very close to the rectum, but before reviewing the literature I had never considered IIAL during an abdominoperineal resection of the rectum. Retrospectively, when I had problems with persistent bleeding after an abdominoperineal resection I could have ligated the IIA instead of packing the pelvis and waiting 48 hours before removing the packing under general anaesthesia.

My experience with one patient in 2014 was that prophylactic IIAL early in an abdominoperineal resection made the operation much easier, and significantly reduced blood loss, without complications.

Some surgeons may be reluctant to ligate vessels as large as the IIAL for fear of ischaemic necrosis. The only reports of ischaemic necrosis I found in the literature were in patients who were having far more radical surgery than I did.

Kaisary and Smith report a case of spinal cord ischaemia after IIAL during radical cystoprostatectomy (10).

Andriole and Sugarbaker reported that if they were doing pelvic sidewall dissection for treatment of a bulky primary or locally recurrent rectal neoplasm, they usually ligated the internal iliac arteries and veins early in the course of the procedure to reduce intraoperative blood loss (11). They reported a case of profound vesical and perineal necrosis after bilateral internal iliac artery ligation in a female patient operated on for recurrent rectal cancer. They noted that no complications related to bilateral internal iliac artery ligation in this setting had been described previously.

The main proponents for IIAL are obstetricians and gynaecologists. Das and Biswas, in Calcutta, comment that while the value of IIAL to control pelvic haemorrhage

was highlighted long ago, it has never been uniformly accepted (4).

Reich and Nechtow feel that the biggest pitfall with IIAL is waiting too long to perform it (7).

Van Gelderen makes a plea for more frequent use of this simple operation and for its routine teaching during the training of pelvic surgeons (5).

Bellad regards IIAL as a procedure that every obstetrician must be able to perform, and that every trainee should be exposed to (6).

From my experience I think it is important that general surgeons in PNG should be able to ligate the IIA in an emergency. If there is a shortage of blood available for transfusion, or isotonic saline for bladder washouts, they should consider prophylactic IIAL before prostatectomy or abdominoperineal resection of the rectum.

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## Scratching the surface: scabies in the South-West Pacific region

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### SUMMARY

Papua New Guinea and other Pacific Island countries suffer from a substantial burden of scabies, with prevalence estimates from different areas of different countries ranging from 4% to 87%. Scabies causes intense itching and severe itch-related sleep disturbance. Scabies lesions are often secondarily infected by bacteria, mostly *Streptococcus pyogenes* and *Staphylococcus aureus*. Streptococcal infections can progress to acute glomerulonephritis, and possibly acute rheumatic fever. There is not yet a consensus on the best approach to scabies treatment, although treatment of entire communities is required and the use of ivermectin in mass drug administration strategies is gaining favour.

### Overview of scabies infection, morbidity and treatment

Scabies is a parasitic infection with the mite *Sarcoptes scabiei* that affects more than 130 million people globally (1) and is most common in children in tropical areas with overcrowded living conditions. The prevalence of scabies was identified as being highest in Papua New Guinea (PNG), Panama and Fiji in a recent systematic review, while the greatest burden of disability-adjusted life years (DALYs) from scabies in the Global Burden of Disease Study 2015 was in east and south-east Asia and Oceania (2,3). The five countries with the greatest DALY burden were Indonesia, China, Timor-Leste, Vanuatu and Fiji (3).

The female mite burrows under the skin and lays eggs for up to 6 weeks before dying, and it takes around 2 weeks from egg to adult (reviewed in 4,5). The mite is mostly transferred between people with prolonged direct skin contact. The infection is intensely itchy and papules appear commonly in the webs of the fingers, wrists, elbows and arms. The reaction can take 4 to 8 weeks to develop (4,5). Diagnosis can be difficult as the clinical presentation can mimic other skin conditions and in ordinary scabies the mite burden is low; thus scabies is often diagnosed on a clinical

and epidemiological basis (6). Humans can be transiently infected with scabies from animals, but endemic scabies in human populations is caused by the human mite (7).

Scabies causes intense itching and severe itch-related sleep disturbance (8). In an endemic community 80% of people with scabies stated that their quality of life was affected by the infection (for 14% a large or very large effect), with a large proportion of people feeling shame; a higher proportion of adults than children felt shame and social exclusion and dressed differently, while a higher proportion of children were restricted in leisure activities, stigmatized or teased (9). Expenditure of a large proportion of household income on management of scabies and absence from school due to scabies have also been reported (10).

Scabies also underlies a considerable burden of downstream disease. Scabies lesions are often secondarily infected by bacteria, mostly *Streptococcus pyogenes* and *Staphylococcus aureus*. These infections can be associated with considerable morbidity. Beyond the development of impetigo, cellulitis or skin ulcers bacterial invasion can lead to bacteraemia and sepsis, and streptococcal infections can

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progress to acute glomerulonephritis, and possibly acute rheumatic fever (ARF) (11). Research in remote Aboriginal communities in Australia has shown that post-streptococcal glomerulonephritis is a strong risk factor for chronic kidney disease (12). The connection between group A streptococcal (GAS) pharyngitis and ARF has been developed over the last century and is commonly accepted (reviewed in 1). However, the large body of work describing GAS in Australian Aboriginal communities has provided substantial epidemiological evidence that GAS impetigo may also be the precursor to ARF in regions with high levels of impetigo (11,13,14). The substantial disease burden of scabies led to the formation of an International Alliance for the Control of Scabies (15) and the 2014 listing of scabies as a neglected tropical disease by the World Health Organization (16).

Scabies treatment is not straightforward. A number of treatments exist, although topical application of 5% permethrin cream (washed off after 8-14 hours) and oral ivermectin are the most effective, with permethrin described by a Cochrane review as more effective than ivermectin (17). However, topical treatment of a large number of people is often impracticable and there are problems with adherence and sustainability (18). Oral ivermectin is an easier treatment and could be coupled with mass drug administration (MDA) for other diseases (19,20). Studies examining mass treatment of communities with ivermectin to eradicate scabies were not included in the Cochrane review (17). Recent studies in the Pacific on mass treatment with ivermectin in relatively isolated communities, described herein, are promising (21,22). Ivermectin is not currently licensed for treatment of scabies in many countries and is not recommended for children under 5 years or 15 kg, and scabies is more prevalent in younger children. In vitro resistance to both treatments has been described, with some reports of ivermectin treatment failure, although molecular work on the scabies mite may provide new, specific treatments for scabies in the future (4).

An assumption that scabies is a non-life-threatening disease of annoyance, and the substantial gaps in our understanding of scabies and related infections and complications in Papua New Guinea and the Pacific, may contribute to the lack of prioritization of these conditions. This review collates the literature for PNG and the region.

## **Scabies in Papua New Guinea and the South-West Pacific region**

### **Scabies prevalence**

The limited data from PNG and other Pacific Island countries indicate that scabies is a substantial problem, with the literature reported here spanning more than two decades. A very high prevalence (87% and 52-60%) was described in two villages in East Sepik, PNG in 1996 (23), although the study only examined a small number of residents. A study of Tokelau children, and Tokelau children living in New Zealand, found higher scabies rates among the children living in New Zealand: 8% of children aged under 15 years in Tokelau compared with 31% in New Zealand in 1972-1973, 58% in 1975-1976 (24), and 34% by 1979-1980 (25). The rates in New Zealand in the mid-1970s were said to reflect a scabies pandemic, or life style differences such as increased bed sharing in a different climate. Scabies was the most common skin infection in Tanna Island, Vanuatu in 1989, where 24% of children aged under 10 years (16% of all screened) had scabies with no other skin infection (26). This figure underestimates the true burden of scabies as skin lesions were classified as scabies only or sores (12% of children aged under 10 years), and a proportion of those in the sores category would also have had scabies. Scabies was most prevalent in those aged under 5 years. The mean prevalence of scabies on five small islands of the Solomon Islands was 25% (95% confidence interval [CI] 20%-30%) among children aged 12 years and under at the end of the 1990s (20). Similar figures were obtained from 10 rural villages in the Western Province in 2014, where the overall prevalence was estimated at 19% (95%CI 17%-22%), and was 34% in infants (27). In Timor-Leste the prevalence was 39.1% in children aged under 10 years (17.3% of all screened) (28). The authors believed their survey design would underestimate scabies (only one person per household was screened). A study on Taveuni Island, Fiji in 2004 revealed that 32% of children aged 5 to 15 years had scabies, although this varied markedly across the five villages in the study, from 4% to 70% (29). In two central Fijian villages overall scabies prevalence was estimated as 37.9% and 23.7% (median age 16 years) in 2004, with scabies detected in 69% and in 43% of children under the age of five years (30). In Fiji in 2006 and 2007

scabies prevalence in school children aged 5 to 15 years was reported as 18.5% (24.6% in children aged 5-8 years) and 14% in infants, with an incidence density of 51 cases per 100 child years (31). The authors of this study believed that the study design may have led to an underestimation of the burden of disease. A national prevalence estimate for scabies in Fiji from data on 10,887 participants collected in 2007 was 18% (95%CI 15%-23%) (32). In American Samoa during 2011-2012 an average of 2.9% of children aged less than 14 years had received medical care for scabies, including 1 in 10 infants (33). In remote Aboriginal communities in the Northern Territory of Australia scabies prevalence has been reported as being as high as 50%, and was recently reported as 19% among urban Indigenous people in Far North Queensland (Cairns) (34,35).

### Scabies, bacterial infections and sequelae

The peer-reviewed literature on scabies, skin sores and downstream sequelae in PNG is limited, and all studies were published before the year 2000. Two studies of skin lesions in children attending the paediatric clinic or family health clinic of Goroka Base Hospital in the mid-1980s indicated that around a quarter to a third (26-34%) were infected with scabies (36,37). Streptococci were isolated from all, or nearly all, of untreated lesions, and 46-61% of these were GAS. GAS and *S. aureus* were more common in infected scabies than other skin lesion types. One study indicated that infected scabies was more prevalent in under-two-year-olds, and was seen in babies as young as two months old (37). Links between invasive disease and skin infections have also been described in PNG. In children less than 3 months old recruited from Goroka Base Hospital in the early 1990s *S. pyogenes* septicaemia was identified four times more often in infants with skin infections than in those without skin infections (38). Also, a larger proportion of children with skin infections had *S. aureus* bacteraemia than of those without skin infections, though this difference on statistical analysis was not considered significant. Skin and soft tissues were described as the primary foci of infection leading to staphylococcal bacteraemia in a review of adult patients with *S. aureus* bacteraemia in the late 1970s and 1980s in a teaching hospital in PNG (39). Of particular significance is that more than three decades ago rheumatic heart disease (RHD) was

described as one of the predominant cardiac disorders in the major hospitals of PNG (40).

In Fiji in 2006 and 2007 the prevalence of active impetigo was 25.6% in primary school children and impetigo was associated with scabies infection (odds ratio [OR] 2.4, 95%CI 1.6-3.7) (31). Active impetigo was found in 12% of infants, and the impetigo was strongly associated with scabies (OR 36.9, 95%CI 16.9-80.7). The majority of impetigo was caused by GAS although *S. aureus* was also isolated frequently. A national cross-sectional survey of scabies and impetigo from 2007 estimated that the population attributable risk was 93% (32), while a recent study of six island communities determined that the population attributable risk of scabies as a cause of impetigo was 36.3%, and 71.0% in children aged less than five years (41). In the Western Province of the Solomon Islands in 2015 the attributable risk of scabies as the cause of impetigo was 41% (95%CI 33%-48%) (27). Conversely, in Samoa in 1999 the high prevalence of pyoderma (43.6% in school children aged 5 to 17 years) was not attributed to infection subsequent to scabies (prevalence of 4.9%), a consequence of the use of ivermectin in Samoa to eradicate filariasis (42). A clinic review in two remote Aboriginal communities in Northern Australia found that children aged under 1 year with scabies were 6.9 (95%CI 5.8-8.2) times more likely to have skin sores at the presentation than those without scabies (43). Among urban Indigenous people in Cairns, Far North Queensland impetigo was documented in 65% of people aged under 20 years visiting an Indigenous-controlled health service, with 14% with both scabies and pyoderma (35). GAS and dual infections were statistically more likely to be recovered from cases with impetigo than from those with other diagnoses. Successful management of scabies will reduce but will not eliminate GAS infections.

Studies from the region highlight the burden of staphylococcal and GAS disease. The presence of skin sores/scabies was the most important risk factor for invasive staphylococcal infection in a review of cases in the Northern Territory of Australia (44). The all-age incidence of GAS invasive bacteraemia over five years was estimated as 11.6/100,000 in Fiji, with a 28% case fatality rate (45). The available evidence suggests that ARF and RHD are a substantial problem in Pacific Island countries. A retrospective



chart review of paediatric outpatients in the Northern Mariana Islands over the period 1984 to 2006 identified a high incidence of ARF among those aged 5 to 14 years (85.8 per 100,000 person years), with a high rate (40%) of recurrence and a much higher incidence among Pacific Islanders than non-Pacific Island ethnic groups (46). The incidence of ARF in Samoans in Hawaii calculated from a record review covering 1980 to 1984 was 206 per 100,000, compared with 18 for Hawaiians/part-Hawaiians (47). While few data are available it appears that the Pacific region has a higher prevalence of RHD than other areas of the world (48) except perhaps sub-Saharan Africa (49), with prevalence among children aged 5 to 17 years in Samoa reported as 77.8 per 1000 by clinical diagnosis (42) and among Tongan children as 33.2 per 1000 by echocardiography (50), and with definite or probable RHD among Fijian children aged 5 to 15 years reported as 8.4 cases per 1000 (51). GAS *emm* types are highly variable in the region, which will impact on the effectiveness of an *emm*-type-specific GAS vaccine (35,52,53).

Scabies, impetigo and related sequelae place a substantial burden on primary health care services as described above. There is limited information on costs of related hospitalizations in the region. A retrospective review of medical records from Mt Isa Base Hospital in remote Far North Queensland in Australia found that serious scabies/infected scabies cases requiring admission comprised 6.6% of all admissions (10% of bed days for children aged under 5 years) and cost approximately \$10,000 per admission (some children required transport by the Royal Flying Doctor Service, included in the costings) (54). The average cost of admission with invasive staphylococcal infection in the Northern Territory of Australia was almost double for people with skin sores/scabies compared with those without skin sores/scabies (44).

### Treatment experience in the region

Mass community treatment for scabies with 5% permethrin cream was first trialled in Panama in 1986 (55). Permethrin cream was applied to the entire community by trained community members under observation. Scabies prevalence fell from 33% to 1%, and remained below 1.5% for over 3 years, during a period of surveillance and treatment of newly arrived cases. Streptococcal pyoderma

declined from 32% to below 2% while scabies was under control (55). However, this initial study highlighted the vulnerability to disruption of this approach to scabies control. When the USA (United States of America) invaded Panama in 1989 supplies of permethrin cream were exhausted, and scabies prevalence rose to 12% within 3 months (55). A number of community-based treatment programs using 5% permethrin cream have been run in remote Aboriginal communities in Australia, with mixed results. These do not include observation of treatment as this is not considered culturally appropriate. The first program offered initial treatment to all members of the community and incorporated seven follow-up visits for rescreening/retreatment until 25 months after the initial visit (56). Scabies dropped from over 30% to just over 5%. Community involvement and free/low-cost permethrin were deemed essential to success. Another intensive program in a large remote community that screened 94% of children aged under 5 years in the community, incorporated education programs and rescreened children every three months reduced scabies prevalence from 35% to below 5% for 10 months, and to 12% at 15 months (57,58). The prevalence of infected scabies fell from 11.5% to 0.5% 15 months post-intervention.

Based on these findings the East Arnhem Healthy Skin Project was rolled out in five remote communities (59). Active surveillance for skin infections in children aged under 15 years was conducted for three years (2004-2007) with annual healthy skin days that included promotion of mass treatment for all in the community with 5% permethrin cream. The initial prevalence of scabies was lower than expected (average monthly prevalence 13.4%), although still high in young children (23% for children aged under 3 years) (59). The program did not reduce the prevalence of scabies, although it did reduce infected scabies and pyoderma (attributed to an increase in clinic referrals for antibiotics) (59). The lack of impact on scabies was likely due to low levels of treatment uptake – a nested study documented poor adherence, with only 44% of household contacts of scabies cases using the 5% permethrin cream (18) and in almost 20% of households no one used the cream. In contrast, individuals from households where all contacts used the cream were six times more likely to remain scabies free (18). Barriers cited to using the cream included that it was not a priority, that



individuals without scabies felt they did not need to use it, and that they did not want to use the cream as it was uncomfortable, hot and sticky. The authors suggested that the regimen is onerous and given likely rapid reinfection there is low motivation to repeat the treatment process as it is seen to have limited effectiveness. Following this experience a mass drug administration project was run in one community in 2010 using ivermectin to treat *Strongyloides* and scabies. Six months after treatment scabies prevalence was reported to have reduced from 4% to 1%, although a sustained reduction over 18 months was not achieved, which was attributed to exposure to an individual with crusted scabies and high population mobility (60). The authors argue that a mass drug administration program in a mobile environment needs to be incorporated into a regional program including ongoing surveillance in the community (60).

In PNG, an early study examining the mass treatment effect of ivermectin on scabies was conducted in two villages in East Sepik in 1996 and 1997 (23). A dramatic reduction in scabies prevalence was achieved (87% to 26% five months after treatment). In French Polynesia in 1992 treatment of scabies with ivermectin and benzyl benzoate was compared in a small study of 44 people, with some suggestion that treatment outcomes were better in the ivermectin group (61). On five small islands of the Solomon Islands in the late 1990s scabies prevalence fell, following mass treatment with ivermectin and active case finding three times a year, from 25% to a steady level of 1% (20). The proportion of children with skin sores halved, as did the proportion of children with sores with GAS on their fingertips. The authors argued that hand contamination would play a role in transfer of GAS between children, and that scabies, because it leads to scratching or rubbing the skin, would play an important role in spreading GAS as well as damaging the skin. In this study there was also a significant decrease in haematuria, a marker of kidney damage, and haematuria was related to the number of skin sores one month earlier. Importantly, a follow-up study conducted in 2015 indicated that scabies prevalence remained extremely low (0.3%) despite the lack of further active control measures (21). The prevalence of impetigo had fallen further to 12%, suggesting an ongoing impact of reduction in scabies on skin infections. These islands are considered relatively isolated from the mainland

population and house sizes were not large (median size 4 residents). A comparison of ivermectin and benzyl benzoate in Vanuatu in 2001 included children as young as 6 months in the ivermectin treatment group, with no serious side effects attributed to the treatment (62). Both treatments reduced scabies but the authors argued that ivermectin made compliance easier to directly observe and was cheaper and easier to transport than benzyl benzoate.

Most recent work in the region comes from Fiji. In 2004 mass treatment using ivermectin (and 5% permethrin cream for those aged under 2 years) was compared with benzyl benzoate in two Fijian villages (30). Scabies prevalence decreased by 60% for ivermectin and 48% for benzyl benzoate (the difference between treatments was not considered significant). This was despite low participation rates and the potential for reinfection of participants, and high loss to follow-up. Ivermectin was better tolerated than benzyl benzoate (stinging and burning). In 2012-2013 mass treatment was undertaken in three relatively isolated island communities comparing standard care (topical permethrin for people with scabies), mass treatment with permethrin and mass treatment with ivermectin (permethrin where ivermectin was contraindicated) (22). There was no active case finding, although 3 months post-treatment 20% of participants were followed up. At 12 months the prevalence of scabies declined in all study groups, with a significantly greater decline in the ivermectin group (relative reduction 94%, 95%CI 83%-100%). Impetigo also declined in all study groups, with the greatest decline in the ivermectin group (relative reduction 67%, 95%CI 52%-83%), although this was not significantly different from the permethrin mass treatment group (relative reduction 54%, 95%CI 35%-73%).

### Where to from here?

Scabies and associated downstream diseases are a substantial burden in the Pacific. Mass community treatment has been shown to be an effective method of reducing the prevalence of scabies. However, the regular screening and treatment required for successful permethrin programs may not be an effective use of resources in resource-poor settings. While annual treatment with oral ivermectin has been used in the region on children as young as 6 months (62) more safety

data are required. Until better data exist it will be important to include a research component in scabies intervention programs, looking at effectiveness against scabies, impact on skin infections, particularly in larger and/or more mobile populations, cost-effectiveness, safety of ivermectin use in children below 5 years/15 kg and in pregnant women, and safety of drug treatment combinations if a mass drug administration approach is used (15,17,20). Ideally a research component would be built into any ongoing public health interventions that could examine associations with invasive bacterial infections, acute post-streptococcal glomerulonephritis (APSGN) and ARF/RHD (11,15), and resistance to treatments. Operational research should also be conducted during implementation of control strategies (15).

Countries with a high scabies burden often have a limited health budget and diseases with greater morbidity and mortality, so scabies control needs to be integrated into existing clinical and public health programs and systems. A WHO paper on the management of skin conditions called for improved quality of primary health care for skin disorders (63). However, scabies is not always identified as a health problem by the parents of children with scabies (64) and there is limited evidence this will affect population prevalence. An Integrated Management of Childhood Illness (IMCI) algorithm for managing common skin conditions was trialled in Fiji; however, while the tool was found to be robust for many skin conditions it demonstrated low sensitivity for classifying non-infected scabies (64). Diagnostics need to be improved and the value of the algorithm to other settings should be assessed. Management of crusted scabies also requires attention (65). Improved detection, data collection and national (and international) reporting systems are required for accurate estimates of the burden of scabies (15).

Many experts argue that mass treatment with ivermectin could be integrated for a number of diseases. The use of mass drug administration strategies for population-based control of scabies could maximize health benefits with a minimal increase in resources (15,19,20,28,66). Kline et al. argued that PNG could benefit enormously from a national integrated MDA targeting a number of neglected tropical diseases, including ivermectin for *Strongyloides* and scabies (19).

In their study of ivermectin use in the Solomon Islands Lawrence et al. argued that programs for the control of filariasis could provide scabies control if ivermectin were used rather than diethylcarbamazine (20). Stamm and Stroud (67) argue that the omission of scabies from an informal list of seven neglected tropical skin diseases, created to support plans for integrated strategies at the WHO, is a missed opportunity (68).

Scabies is often described as a disease of poverty and overcrowding, with recent work from Fiji highlighting that households with four or more people sharing the same room were more likely to have scabies and impetigo (OR 1.6, 95% CI 1.2-2.2 and OR 2.3, 95% CI 1.6-3.2 respectively) than households with rooms occupied by a single individual (41). For long-term sustainable change improved education and housing and health system strengthening are needed.

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## OBITUARY

### Vale: Dr Wendy Pameh

TREVOR DUKE<sup>1,2</sup>

**Centre for International Child Health, University of Melbourne, Australia and School of Medicine and Health Sciences, University of Papua New Guinea, Port Moresby**

Dr Wendy Pameh died on 8 May 2018 at the age of 47, three years after she was diagnosed with breast cancer (Figure 1). After qualifying as a paediatrician with a Master of Medicine in Child Health in 2005, Wendy provided child health services at two provincial hospitals in Papua New Guinea, before joining the School of Medicine and Health Sciences at the University of Papua New Guinea (UPNG) as a lecturer in 2009. In 2014 she completed a Master of Epidemiology at the University of Melbourne, and was appointed as Senior Lecturer at UPNG in 2016. Dr Pameh was an outstanding academic general paediatrician with a special interest in adolescent health

and community child health. She was a much loved and respected mentor to medical and nursing students and to paediatric trainees, and a wonderful role model for women paediatricians of her generation, and to all of us. Her presence, commitment, spirit, patience, wisdom and humour lifted people and raised standards. These qualities shone through during the last three difficult years when she continued her commitment to her students and colleagues. The paediatric family in Papua New Guinea is saddened by Dr Pameh's passing but deeply grateful to have had such an inspirational friend and colleague.



Figure 1. Dr Wendy Pameh.

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- 1 Centre for International Child Health, University of Melbourne, Royal Children's Hospital, Parkville, Victoria 3052, Australia  
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  - 2 Adjunct Professor of Child Health, School of Medicine and Health Sciences, University of Papua New Guinea, PO Box 5623, Boroko, National Capital District, Papua New Guinea



## List of Medical Research Projects in Papua New Guinea

### Approved or Noted

#### By the Medical Research Advisory Committee in 2017

Asymptomatic skin colonization of yaws and *Haemophilus ducreyi* as a potential infectious reservoir

Ms Wendy Houinei (National Department of Health, PO Box 807, Waigani, National Capital District, Papua New Guinea)

Case study of tuberculosis with drug resistance characteristics in Balimo District, Western Province, PNG

A/Prof. Jeffrey Warner (James Cook University, Townsville, Queensland 4814, Australia)

The last taboo: formative research to inform informal menstrual hygiene management interventions in the Pacific

Ms Lisa Natoli (Abt, JTA, PO Box 1206, Waigani, National Capital District, Papua New Guinea)

Understanding global biomedical technologies in local realities

Dr Angela Kelly-Hanku (Papua New Guinea Institute of Medical Research, PO Box 60, Goroka, Eastern Highlands Province, Papua New Guinea)

A cross-sectional study to better understand factors that contribute to anaemia and malnutrition in Hela Province, Papua New Guinea

Dr Andrew Greenhill, Dr William Pomat, Dr Kevin Miles, Mr Mark Menz, A/Prof. David Piedrafita, Dr Paul Horwood, A/Prof. Andrew Vallely and Dr Lisa Vallely (Papua New Guinea Institute of Medical Research, PO Box 60, Goroka, Eastern Highlands Province, Papua New Guinea)

Economic impact of diabetes mellitus on hospitals in Papua New Guinea: a study assessing the cost of diabetes management at Port Moresby General Hospital

Dr Miriam Boga (James Cook University, Townsville, Queensland 4814, Australia)

Population screening for TB in Daru, South

Fly District, Western Province, 2017

Dr Paison Dakulala (Deputy Secretary NHSS, National Department of Health, PO Box 807, Waigani, National Capital District, Papua New Guinea)

Investigating the impact of community contraceptive implant provision on maternal morbidity and mortality on Karkar Island, Papua New Guinea

Prof. Glen Mola, Dr Hilda Tanimia, Dr Sarika Gupta, Dr John Bolnga, Dr Angela Kelly-Hanku, Prof. Lynday Trevena and A/Prof. Kirsten Black (81/56-62 Anzac Parade, Kensington, New South Wales 2033, Australia)

Comparison of systems of perinatal care in Papua New Guinea and Poland based on analysis of perinatal outcomes in available medical records

Dr Sandra Rehlis (Bergstrasse 17, 36 100 Petersberg, Germany)

A qualitative study on TB: perceptions, health seeking behaviour and delaying factors for diagnosis and treatment initiation (Gulf Province and NCD, Papua New Guinea)

Dr Giulietta Luul Balestra (MSF France, GB House, Office # 3, Spring Garden Road, Kunai Street, Hohola, Port Moresby, Papua New Guinea)

Trilateral malaria project operational research component

Dr Leanne Robinson (Papua New Guinea Institute of Medical Research, PO Box 378, Madang, Madang Province, Papua New Guinea)

Using pharmacokinetics to improve TB treatment outcomes and prevent multi-drug resistance in Papua New Guinea

A/Prof. Harin Karunajeewa, A/Prof. Laurens Manning, Prof. Sir Isi Kevau, Dr William Pomat, Prof. Nakapi Tefuarani, Dr Rendi Moke, Dr Leslie Kawa, Prof. Tawanda Gumbo and Prof. Emma McBryde (PNG Institute of Medical Research, PO Box 60,

Goroka, Eastern Highlands Province, Papua New Guinea)

NCD HPV demonstration program

Dr Edward Waramin (Acting Manager, Family Health Services, Public Health Division, National Department of Health, PO Box 807, Waigani, National Capital District, Papua New Guinea)

Does a machine that sends SMS reminders as part of standard of care improve TB program management at PMGH?

Dr Koni Sobi (Port Moresby General Hospital, Private Mail Bag 1, Boroko, National Capital District, Papua New Guinea)

Feasibility and acceptability of 3D printed spectacles in the Pacific

Dr Anthea Burnett (Brien Holden Vision Institute, Level 4, Rupert Myers Building, North Wing, University of New South Wales, Kensington, New South Wales 2052, Australia)

Reducing visual impairment among children through health system assessment and strengthening at Port Moresby General Hospital and Eastern Highlands Provincial Hospital, Goroka

Dr Geoffrey Wabulembo (CBM Ophthalmologist, Senior Lecturer, Ophthalmology, SHMS UPNG and Director, Edmund Rice Clinic, School of Medicine and Health Sciences, University of Papua New Guinea, PO Box 5623, Boroko, National Capital District, Papua New Guinea)

The development of the gut microbial community of infants in Papua New Guinea and correlations with resistance or susceptibility to gastrointestinal infections

Dr Andrew Greenhill (PNG Institute of Medical Research, PO Box 60, Goroka, Eastern Highlands Province, Papua New Guinea)

Use of hypothermia alert device for reduction of hypothermia and related complications among low birth weight new-borns

Dr Edward Waramin, (Acting Manager, Family Health Services, Public Health Division, National Department of Health, PO Box 807, Waigani, National Capital District, Papua New Guinea)

Defining the best distribution strategy of azithromycin for yaws eradication (The Yaws 3 Trial)

Dr Lucy John (Manager, Disease Control & Surveillance Branch, Public Health Division, National Department of Health, PO Box 807, Waigani, National Capital District, Papua New Guinea)

Client exit interview 2017

Ms Francisca Base (Marie Stopes Papua New Guinea, PO Box 972, Waigani, National Capital District, Papua New Guinea)

An evaluation of treatment outcomes in children treated for tuberculosis at Port Moresby General Hospital, PNG

Ms Verlyn Apis (Port Moresby General Hospital, PO Box 111, National Capital District, Papua New Guinea)

The first experience of bedaquiline-containing regimen to improve DR TB patient outcomes in Daru, Western Province, Papua New Guinea

Dr Magdalene Taune (Daru General Hospital, PO Box 6, Daru, Western Province, Papua New Guinea)

The emergency response to drug resistant tuberculosis in South Fly District, Western Province, 2014-2017

Mrs Lucy Morris (Western Provincial Administration, Division of Health, PO Box 1, Daru, Western Province, Papua New Guinea)

Evaluation of pilot MDR-TB household contact screening in Daru Island, Western Province, over a one year period

Mrs Alice Honjepari (Western Provincial Administration, Division of Health, PO Box 1, Daru, Western Province, Papua New Guinea)

Health system strengthening and the shift in client utilization of TB services away from the provincial hospital

Dr Alexander Maha (Department of Health, Office of the Deputy Chief Physician (Islands), C/- Nonga General Hospital, Private Mail Bag 3, Kokopo, East New Britain Province, Papua New Guinea)

A clinico-epidemiological mortality review of adult tuberculosis inpatients in a provincial hospital in Papua New Guinea, 2015-2017

Dr Kabe Vakadem (Southern Highlands Provincial Health Authority, Private Mail Bag, Mendi, Southern Highlands Province, Papua New Guinea)

Clinical characteristics, treatment outcomes

and risk factors for poor outcome among tuberculosis patients treated with first line therapy in West Sepik Province, Papua New Guinea, 2014-2016

Dr Trevor Kelebi (West Sepik Provincial Health Authority, Office of the Director of Public Health, PO Box 331, Vanimo, Sandaun Province, Papua New Guinea)

An evaluation of linkages to tuberculosis care and quality of treatment for tuberculosis in Kavieng Provincial Hospital, New Ireland Province, PNG

Dr Kenneth Sodeng (Department of Health, Kavieng General Hospital, Hospital Management Services, PO Box 68, Kavieng, New Ireland Province, Papua New Guinea)

Impact of GxAlert on time to treatment initiation and patient outcomes for drug-resistant tuberculosis patients in Port Moresby, Papua New Guinea, 2014-2016

Ms Jennifer Banamu (Department of Health, Central Public Health Laboratory, C/- Port Moresby General Hospital, Private Mailbag 1, Boroko, National Capital District, Papua New Guinea)

Timelines of diagnosis and treatment initiation for TB patients diagnosed at Daru General Hospital in Western Province, PNG

Mr Emmanuel Hapolo (Department of Health, Daru General Hospital, PO Box 6, Daru, Western Province, Papua New Guinea)

Clinical characteristics, treatment outcomes of tuberculosis patients treated with first line therapy in Kerema Hospital in Gulf Province, 2016

Mr Iraingo Moses (Gulf Provincial Health Office, PO Box 60, Kerema, Gulf Province, Papua New Guinea)

Demonstrating the impact of next generation cepheid tools. GeneXpert Ultra and GeneXpert Omni for the diagnosis of tuberculosis at the microscopy centre level: Papua New Guinea. A stepped-wedge cluster-randomized controlled trial

Dr Evelyn Lavu, Dr William Pomat and Dr David Anderson (Director, Central Public Health Laboratory, Private Mail Bag 1, Boroko, National Capital District, Papua New Guinea)

Demonstrating the impact of next generation cepheid tools. Observational study: diagnostic and therapeutic impact of Xpert Ultra on Omni within an active case-finding study in Daru,

Western Province: Papua New Guinea. AIM-TB study, 'Assessing the impact of molecular TB diagnostics in PNG'

Dr Evelyn Lavu, Dr William Pomat and Dr David Anderson (Director, Central Public Health Laboratory, Private Mail Bag 1, Boroko, National Capital District, Papua New Guinea)

People with TB and their contacts: local beliefs, access to services and treatment experiences in Daru, Western Province, Papua New Guinea. The social and cultural determinants of TB in Daru [SCD-TB Daru – Study 1]

Ms Lucy Morris, Dr Suman Majumdar, Dr Paul Mason, Dr Angela Kelly-Hanku, Ms Alice Honjepari, Dr Lucia Gonzalez, Dr Sonia Madjus, Mr Jeoff Chan, Dr Benny Kombuk, Dr William Pomat, Dr Paison Dakulala and Prof. Steven Graham (Western Provincial Administration, Division of Health, PO Box 1, Daru, Western Province, Papua New Guinea)

Effect of ivermectin on malaria and filariasis vector survival in Papua New Guinea

Dr Stephan Karl, Dr Moses Laman, Mr Lincoln Timinao, Dr Leanne Robinson, Prof. Christopher King and Prof. Edward Walker (Papua New Guinea Institute of Medical Research, PO Box 378, Madang, Madang Province, Papua New Guinea)

Prospective cohort study to evaluate point-of-care HPV-DNA testing for the early detection and treatment of cervical pre-cancer in high-burden low-resource settings

A/Prof. Andrew Vallely, A/Prof. Marion Saville, A/Prof. Julia Brotherton, Prof. Glen Mola, Dr Evelyn Lavu, Dr Angela Kelly-Hanku, Dr Alyssa Cornall, Dr Chris Morgan, Dr Kate Simmins, Dr Grace Kariwiga, Prof. John Kaldor, Prof. Karen Canfell, Ms Pamela Toliman, Dr John Bolnga, Dr Steve Badman, Dr Zure Kombati, Dr Joseph Kuk, Dr Praveena Gunaratnam, A/Prof. Rebecca Guy, Prof. Philip Castle, Prof. Sepehr Tabrizi and Prof. Suzanne Garland (Papua New Guinea Institute of Medical Research, PO Box 378, Madang, Madang Province, Papua New Guinea)

Formative research analysis and baseline assessment on the drivers of an approach to family sexual violence for communities within the PNG extractive industries

Dr Sari Jusi (Director, Finnish Overseas Consultants (FinnOC) Ltd, Metsariine 7B, 04220 Kerava, Finland)

Economic evaluation of patient costs associated with tuberculosis diagnosis and care in Papua New Guinea

Dr Paul Aia (Manager, Disease Control & Surveillance Branch, Public Health Division, National Department of Health, PO Box 807, Waigani, National Capital District, Papua New Guinea)

Sustaining children's school attendance during periods of domestic violence in urban PNG families

Ms Michelle Rooney (Development Policy Centre, Crawford School of Public Policy, The Australian National University, ACT 2601, Australia)

Risk factors for unfavourable treatment outcomes among drug susceptible TB patients treated at Kikori Hospital, Gulf Province, Papua New Guinea

Mr Matthew David (Kikori ERT Coordinator, C/HHSIP, PO Box 1206, Waigani, National Capital District, Papua New Guinea)

Drug susceptibility patterns in drug resistant tuberculosis in Papua New Guinea: 2012-2017 laboratory data

Dr Evelyn Lavu (Director, Central Public Laboratory, Private Mail Bag 1, Boroko, National Capital District, Papua New Guinea)

Risk factors in drug resistant tuberculosis in Papua New Guinea

Dr Evelyn Lavu (Director, Central Public Laboratory, Private Mail Bag 1, Boroko, National Capital District, Papua New Guinea)

A study of artemisinin combination therapy given at delivery to prevent postpartum malaria and to young infants to treat uncomplicated malaria

Prof. Timothy Davis, Dr Brioni Moore, Dr Moses Laman, Dr William Pomat, Dr Leanne Robinson, Prof. Kevin Batty, Dr Sam Salman and Dr Laurens Manning (Papua New Guinea Institute of Medical Research, PO Box 378, Madang, Madang Province, Papua New Guinea)

Enhancing clinical management of paediatric malaria in endemic areas with transmission of multiple *Plasmodium* species (NHMRC APP1130301). Study 1: optimized primaquine treatment for children with uncomplicated malaria due to infection with either *Plasmodium vivax* or *Plasmodium*

*falciparum*

Dr Laurens Manning, Dr Timothy Davis, Dr Kevin Batty, Dr Sam Salman, Dr Moses Laman, Dr Brioni Moore, Dr Leanne Robinson and Dr William Pomat (Papua New Guinea Institute of Medical Research, PO Box 378, Madang, Madang Province, Papua New Guinea)

An insight into the experience of users of a long acting contraceptive implant (Sino Implant) and reasons for early removal in Madang, Papua New Guinea

Dr John W. Bolnga, Dr Marilyn Morris and Dr Moses Laman (Papua New Guinea Institute of Medical Research, PO Box 378, Madang, Madang Province, Papua New Guinea)

Surfaces: an interdisciplinary project to understand and enhance health in the vulnerable rainforests of Papua New Guinea (2017 fieldwork)

Dr Alan Steward, Dr Jackie Cassell, Dr William Pomat, Dr Vojtech Novotny, Dr Steve Walker, Dr Gavin Colthart, Dr Michael Head, Dr Hayley MacGregor, Dr Jo Middleton, Dr Joao Inacio Silva, Dr James Fairhead and Dr Mika Peck (Papua New Guinea Institute of Medical Research, PO Box 60, Goroka, Eastern Highlands Province, Papua New Guinea)

Prevalence of *Plasmodium* spp. carriage among people living in Lihir Islands, Papua New Guinea

Dr Quique Bassat, Dr Moses Laman, Dr Ivo Mueller and Dr William Pomat (Papua New Guinea Institute of Medical Research, PO Box 378, Madang, Madang Province, Papua New Guinea)

Effectiveness of 3-drug therapy for lymphatic filariasis elimination in Papua New Guinea: community prevalence and vector surveys to monitor LF indicators following mass drug administration

Dr Moses Laman, Dr Leanne Robinson, Dr Livingstone Tavul, Dr Stephan Karl and Dr Christopher King (Papua New Guinea Institute of Medical Research, PO Box 378, Madang, Madang Province, Papua New Guinea)

Evaluation of public-private partnerships in the health sector in Papua New Guinea, using a case study of Western Province

Ms Georgina Dove and Dr Angela Kelly-Hanku (Papua New Guinea Institute of Medical Research, PO Box 60, Goroka,

Eastern Highlands Province, Papua New Guinea)

Note:

These projects have been examined and cleared by the MRAC but they have not all started, nor is there any guarantee that they all will, since in many cases this still depends on funding. It should be noted that the project

funds for the MRAC were deleted from the Health Budget from 1997 to 2017.

Information about these projects may be obtained from the investigators or from the Chairperson of the Medical Research Advisory Committee (Director of Research and Monitoring, Department of Health, PO Box 807, Waigani, National Capital District, Papua New Guinea).



# MEDLARS BIBLIOGRAPHY

PUBLICATIONS OF RELEVANCE TO PAPUA NEW GUINEA AND MELANESIA

## Bibliographic Citation List generated from MEDLARS

- 1 **Aia P, Wangchuk L, Morishita F, Kisomb J, Yasi R, Kal M, Islam T.** Epidemiology of tuberculosis in Papua New Guinea: analysis of case notification and treatment-outcome data, 2008-2016. *Western Pac Surveill Response J* 2018 Jun 15;9(2):9-19. doi: 10.5365/wpsar.2018.9.1.006. eCollection 2018 Apr-Jun.  
Papua New Guinea has strengthened its surveillance system for tuberculosis (TB) under the National TB Program. This paper provides an overview of TB surveillance data at the national and subnational levels from 2008 to 2016. TB case notification has consistently increased since 2008 with 6184 cases (93 per 100,000 population) in 2008 to 28,598 (359 per 100,000 population) in 2014 and has stabilized since 2014 with 28,244 cases (333 per 100,000 population) in 2016. The population-screening rate for TB rose from 0.1% in 2008 to 0.4% in 2016. Notified cases were dominated by extra-pulmonary TB (EP-TB, 42.4% of all cases in 2016). The proportion of pulmonary TB cases with no sputum test results was high with a national average of 26.6%. The regional variation of case notifications was significant: the Southern Region had the highest number and rate of notified TB cases. Of the nationally reported cases, 26.7% occurred in children. Treatment success rates remained low at 73% for bacteriologically confirmed TB and 64% for all forms of TB in 2016, far below the global target of 90%. For all forms of TB, 19% of patients were lost to follow-up from treatment. An analysis of TB data from the national surveillance system has highlighted critical areas for improvement. A low population-screening rate, a high proportion of pulmonary TB cases without sputum test results and a low treatment success rate suggest areas for improvement in the National TB Program. Our additional subnational analysis helps identify geographical and programmatic areas that need strengthening and should be further promoted to guide the programme's direction in Papua New Guinea.
- 2 **Aime H, Broesch T, Akinin LB, Warneken F.** Evidence for proactive and reactive helping in two- to five-year-olds from a small-scale society. *PLoS One* 2017 Nov 15;12(11):e0187787. doi: 10.1371/journal.pone.0187787. eCollection 2017.  
Humans are unique in their propensity for helping. Not only do we help others in need by reacting to their requests, we also help proactively by assisting in the absence of a request. Proactive helping requires the actor to detect the need for help, recognize the intention of the other, and remedy the situation. Very little is known about the development of this social phenomenon beyond an urban, industrialized setting. We examined helping in nineteen two- to five-year old children in small-scale rural villages of Vanuatu. In the experimental condition, the intentions of the experimenter were made salient, whereas in the control condition they were ambiguous. Children helped more often in the experimental compared to the control condition, suggesting that the propensity to monitor others' goals and act accordingly can be detected in different cultural contexts.
- 3 **Albert S, Kvennefors C, Jacob K, Kera J, Grinham A.** Environmental change in a modified catchment downstream of a gold mine, Solomon Islands. *Environ Pollut* 2017 Dec;231(Pt 1):942-953. doi: 10.1016/j.envpol.2017.08.113. Epub 2017 Sep 25.  
Solomon Islands is rapidly developing its natural resource exploitation sector, but data needed to assess consequent environmental impacts are scarce. We assessed catchments surrounding the Gold Ridge gold mine (Guadalcanal, Solomon Islands) and found that extensive changes in river course, and water and sediment quality have occurred downstream of the gold mine since its development. Sediment run-off from exposed areas associated with the mine pit has increased, elevating turbidity (up to 2450 NTU) and metal and arsenic levels, with levels of the latter being up to 0.141 mg/L in surface waters and 265 mg/kg in sediments. An overfull, inoperative tailings storage facility associated with the currently inactive gold mine with fluctuating arsenic levels (up to 0.087 mg/L in the water; 377 mg/kg in the sediment) presents an ongoing threat to the environment. Arsenic, due to its toxicity, appears to be the greatest threat, with sediment and water guideline levels in rivers exceeded 10-fold and exceeded nearly 20-fold in the tailings dam sediments. Despite elevated metal and arsenic content in the area, no toxic inorganic arsenic was found to have bioaccumulated in locally harvested food. In summary, the natural environment surrounding the Gold Ridge mine has been modified substantially and requires an ongoing monitoring program to ensure the ecosystem services of food and water for the local communities continue to be safe. This study informs not only the local area but also provides a microcosm of the broader global challenges facing the regulation of extractive industries in proximity to subsistence communities.
- 4 **Andersen B.** Careful words: nursing, language, and emotion in Papua New Guinea. *Med Anthropol* 2017 Nov-Dec;36(8):758-771. doi: 10.1080/01459740.2017.1317771. Epub 2017 Apr 12.  
Papua New Guinean nurses work in a sociomedical system in which cultural and linguistic diversity are matters of pressing concern. Using data drawn from ethnographic research with PNG nursing students, I show how nursing education socializes nurses to take stances toward language and communication that impact their care practices. I argue that nurses' use of language is shaped by

their ethical commitments as educated Christians and indigenous concerns about the links between language, emotion, and health. In a resource-poor setting where health workers risk blame for structural inequalities, this 'ethical metapragmatics' is an important but neglected facet of care work.

**5 Andersen BJ, Kumar J, Curtis K, Sanuku N, Satofan S, King CL, Fischer PU, Weil GJ.**

Changes in cytokine, filarial antigen, and DNA levels associated with adverse events following treatment of lymphatic filariasis.

*J Infect Dis* 2018 Jan 4;217(2):280-287. doi: 10.1093/infdis/jix578.

**Background:** Mild to moderate adverse events (AEs) are common after treatment of lymphatic filariasis (LF) and pose a major challenge for the global LF elimination program. We studied changes in cytokine levels and filarial worm components in plasma of subjects with and without AEs following treatment of LF. **Methods:** Participants (n = 24) were hospitalized and monitored for AEs following treatment. Cytokines (27), filarial DNA, circulating filarial antigen (CFA), and immune complexes were measured in plasma samples collected before and after treatment. **Results:** Levels for 16 cytokines increased after treatment in individuals with moderate AEs compared to individuals with no and/or mild AEs. These included 3 major proinflammatory cytokines (interleukin 6, tumor necrosis factor  $\alpha$ , and interleukin  $1\beta$ ). Eotaxin-1 levels were elevated at baseline in individuals who developed moderate AEs after treatment; thus, eotaxin-1 is a potential biomarker for AE risk. CFA and filarial DNA levels increased more in individuals with moderate AEs after treatment than in people with no/mild AEs. **Conclusions:** Increases in cytokine, filarial DNA, and CFA levels were associated with development of AEs following treatment of LF. Improved understanding of the pathogenesis of AEs may lead to improved methods for their prevention or management that could increase compliance in elimination programs.

**6 Asher DM, Gregori L.**

Human transmissible spongiform encephalopathies: historic view.

*Handb Clin Neurol* 2018;153:1-17. doi: 10.1016/B978-0-444-63945-5.00001-5.

The first of several pivotal moments leading to current understanding of human transmissible spongiform encephalopathies (TSEs) occurred in 1959 when veterinary pathologist W.J. Hadlow first recognized several similarities between scrapie – a slow infection of sheep caused by an unusual infectious agent – and kuru, a fatal exotic neurodegenerative disease affecting only people of a single language group in the remote mountainous interior of New Guinea, described two years earlier by D.C. Gajdusek and V. Zigas. Based on the knowledge of scrapie, Gajdusek, C.J. Gibbs, Jr., and M.P. Alpers soon initiated efforts to transmit kuru by inoculating kuru brain tissue into non-human primates, that – although requiring several years – ultimately proved successful. In the same year that Hadlow first proposed that kuru and scrapie might have similar etiology, I. Klatzo noted that kuru's histopathology resembled that of Creutzfeldt-Jakob disease (CJD), another progressive fatal neurodegenerative disease of unknown etiology that A.M. Jakob had first described in 1921. Gajdusek and colleagues went on to demonstrate that not only the

more common sporadic form of CJD but also familial CJD and a generally similar familial brain disease (Gerstmann-Sträussler-Scheinker syndrome) were also transmissible, first to non-human primates and later to other animals. (Other investigators later transmitted an even rarer brain disease, fatal familial insomnia, to animals.) Iatrogenic CJD (spread by human pituitary-derived hormones and tissue grafts) was also transmitted to animals. Much later, in 1996, a new variant of CJD was attributed to human infection with the agent of bovine spongiform encephalopathy; vCJD itself caused an iatrogenic TSE spread by blood transfusion (and probably by a human-plasma-derived clotting factor). Starting in the 1930s, the scrapie agent was found to have a unique constellation of physical properties (marked resistance to inactivation by chemicals, heat and radiation), eventually interpreted as suggesting that it might be an unconventional self-replicating pathogen based on protein and containing no nucleic acid. The work of S.B. Prusiner led to the recognition in the early 1980s that a misfolded form of a ubiquitous normal host protein was usually if not always detectable in tissues containing TSE agents, greatly facilitating the diagnosis of TSEs and understanding their pathogenesis. Prusiner proposed that the TSE agent was likely to be composed partly if not entirely of the abnormal protein, for which he coined the term 'prion' protein and 'prion' for the agent. Expression of the prion protein by animals – while not essential for life – was later found to be obligatory to infect them with TSEs, and a variety of mutations in the protein clearly tracked with TSEs in families, explaining the autosomal dominant pattern of disease and confirming a central role for the protein in pathogenesis. Prusiner's terminology and the prion hypothesis came to be widely though not universally accepted. A popular corollary proposal, that prions arise by spontaneous misfolding of normal prion protein leading to sporadic cases of CJD, BSE, and scrapie, is more problematic and may serve to discourage continued search for environmental sources of exposure to TSE agents.

**7 Bailey PE, van Roosmalen J, Mola G, Evans C, de Bernis L, Dao B.**

Assisted vaginal delivery in low- and middle-income countries: an overview.

*BJOG* 2017 Aug;124(9):1335-1344. doi: 10.1111/1471-0528.14477. Epub 2017 Jan 31.

**OBJECTIVE:** To assess the use of assisted vaginal delivery (AVD) in low- and middle-income countries (LMICs), highlighting what level of care procedures were performed and identifying systemic barriers to its use. **DESIGN:** Cross-sectional health facility assessments. **SETTING:** Up to 40 countries in Latin America, sub-Saharan Africa and Asia. **POPULATION:** Assessments tended to be national in scope and included all hospitals and samples of midlevel facilities in public and private sectors. **METHODS:** Descriptive secondary data analysis. **MAIN OUTCOME MEASURES:** Percentage of facilities where health workers performed AVD in the 3 months prior to the assessment, instrument preference, which health workers performed the procedure, and reasons AVD was not practiced. **RESULTS:** Fewer than 20% of facilities in Latin America reported performing AVD in the last 3 months. In sub-Saharan Africa, 53% of 1728 hospitals had performed AVD but only 6% of nearly 10,000 health centres had done so. It was

not uncommon to find <1% of institutional births delivered by AVD. Vacuum extraction appears preferred over forceps. Lack of equipment and trained health workers were the most frequent reasons for non-performance. CONCLUSIONS: The low use of AVD in LMICs is in contrast with many high-income countries, where high caesarean rates are also associated with significant rates of AVD. In many LMICs, rising caesarean rates have not been associated with maintenance of skills and practice of AVD. AVD is underused precisely in countries where pregnant women continue to face hardships accessing emergency obstetric care and where caesarean delivery can be relatively unsafe.

- 8 **Bainomugisa A, Lavu E, Hiashiri S, Majumdar S, Honjepari A, Moke R, Dakulala P, Hill-Cawthorne GA, Pandey S, Marais BJ, Coulter C, Coin L.**

Multi-clonal evolution of multi-drug-resistant/ extensively drug-resistant *Mycobacterium tuberculosis* in a high-prevalence setting of Papua New Guinea for over three decades. *Microb Genom* 2018 Feb;4(2). doi: 10.1099/mgen.0.000147. Epub 2018 Jan 4.

An outbreak of multi-drug resistant (MDR) tuberculosis (TB) has been reported on Daru Island, Papua New Guinea. *Mycobacterium tuberculosis* strains driving this outbreak and the temporal accrual of drug resistance mutations have not been described. Whole genome sequencing of 100 of 165 clinical isolates referred from Daru General Hospital to the Supranational reference laboratory, Brisbane, during 2012-2015 revealed that 95 belonged to a single modern Beijing sub-lineage strain. Molecular dating suggested acquisition of streptomycin and isoniazid resistance in the 1960s, with potentially enhanced virulence mediated by an *mycP1* mutation. The Beijing sub-lineage strain demonstrated a high degree of co-resistance between isoniazid and ethionamide (80/95; 84.2%) attributed to an *inhA* promoter mutation combined with *inhA* and *ndh* coding mutations. Multi-drug resistance, observed in 78/95 samples, emerged with the acquisition of a typical *rpoB* mutation together with a compensatory *rpoC* mutation in the 1980s. There was independent acquisition of fluoroquinolone and aminoglycoside resistance, and evidence of local transmission of extensively drug resistant (XDR) strains from 2009. These findings underline the importance of whole genome sequencing in informing an effective public health response to MDR/XDR TB.

- 9 **Baird T, Donnan E, Coulter C, Simpson G, Konstantinos A, Eather G.**

Multidrug-resistant tuberculosis in Queensland, Australia: an ongoing cross-border challenge. *Int J Tuberc Lung Dis* 2018 Feb 1;22(2):206-211. doi: 10.5588/ijtld.17.0180.

SETTING: Multidrug-resistant tuberculosis (MDR-TB) is a growing concern worldwide. In Australia, although the incidence of MDR-TB remains low, Queensland is at an increased risk due to its proximity to Papua New Guinea (PNG). OBJECTIVE: To examine the epidemiology, clinical features and outcomes of MDR-TB in Queensland, with a comparison between cross-border PNG and non-cross-border patients. DESIGN: Retrospective case series of all MDR-TB patients in Queensland between 1 January 2000 and 31 December 2014. RESULTS: Ninety-six patients were diagnosed with MDR-TB in Queensland between 2000 and 2014.

The majority were cross-border PNG nationals diagnosed within the Torres Strait Protected Zone (n = 73, 76%). Cross-border patients were younger (27.4 vs. 36.3 years, p = 0.02), had spent less time in Australia before diagnosis (<1 vs. 19 months, p < 0.01), had higher rates of smear positivity (67.1% vs. 40%, p = 0.04) and were less likely to have received a second-line injectable agent (45.8% vs. 71.4%, p = 0.05). Cross-border patients had significantly lower rates of treatment success than non-cross-border patients (47.9% vs. 85.7%; p < 0.01). CONCLUSION: MDR-TB cases in Queensland are largely a result of cross-border PNG nationals, with poorer outcomes seen in this cohort. Continued strengthening of the region's TB programmes, with a focus on cross-border patients, is required.

- 10 **Bell S, Wapling J, Ase S, Boli-Neo R, Vallely AJ, Kaldor JM, Nightingale CE, Kelly-Hanku A.**

Acceptability of testing for anorectal sexually transmitted infections and self-collected anal swabs in female sex workers, men who have sex with men and transgender women in Papua New Guinea. *BMC Public Health* 2018 Jun 20;18(1):776. doi: 10.1186/s12889-018-5684-2.

BACKGROUND: Papua New Guinea (PNG) has some of the highest prevalence of urogenital sexually transmitted infections (STIs) in Pacific Asia, but to date, anorectal STI prevalence data do not exist, and diagnosis of anorectal STIs does not occur. The purpose of this study was to document the acceptability of anorectal STI testing and self-collection of anorectal swabs for testing among populations at risk of anorectal STIs, in advance of a large bio-behavioural survey during which this approach to specimen collection was planned among key populations in PNG. METHODS: Four focus groups were conducted, collecting data from a purposive sample of 35 members of two civil society groups representing female sex workers, men who have sex with men and transgender women in Port Moresby and Goroka. RESULTS: All participants were in favour of anorectal STI testing in PNG. Reasons given for willingness to undertake anorectal STI testing included that anal sex is practised; that anorectal STIs are not perceived to exist; there are self-reported experiences of anorectal symptoms indicative of anorectal STIs; that anorectal STI testing will enhance personal health; and that anorectal STI testing is not currently available in PNG. All participants were confident they could obtain self-collected specimens, although several stated that support from trained health workers should be available for community members who may not feel comfortable with self-collection. CONCLUSIONS: This qualitative research is the first study of acceptability of anorectal STI testing and specimen self-collection procedures in PNG, and Pacific Asia more broadly. Our qualitative findings show support for anorectal STI testing including the use of self-collected swabs among key populations in PNG. Study findings informed the inclusion of anorectal STI testing in a large bio-behavioural survey to be used to estimate anorectal STI prevalence among key populations in PNG for the first time.

- 11 **Bergström A, Tyler-Smith C.**

Human genetics: busy subway networks in Remote Oceania? *Curr Biol* 2018 May 7;28(9):R549-R551. doi: 10.1016/j.cub.2018.03.033.

Ancient human DNA from the Oceanian islands of Vanuatu reveals a surprisingly complex history of human settlement, featuring almost complete replacement shortly after initial colonisation, followed by mixing and a puzzling disconnect between genetic ancestry and language.

- 12 **Bergström A, Oppenheimer SJ, Mentzer AJ, Auckland K, Robson K, Attenborough R, Alpers MP, Koki G, Pomat W, Siba P, Xue Y, Sandhu MS, Tyler-Smith C.**

A Neolithic expansion, but strong genetic structure, in the independent history of New Guinea.

*Science* 2017 Sep 15;357(6356):1160-1163. doi: 10.1126/science.aan3842.

New Guinea shows human occupation since ~50 thousand years ago (ka), independent adoption of plant cultivation ~10 ka, and great cultural and linguistic diversity today. We performed genome-wide single-nucleotide polymorphism genotyping on 381 individuals from 85 language groups in Papua New Guinea and find a sharp divide originating 10 to 20 ka between lowland and highland groups and a lack of non-New Guinean admixture in the latter. All highlanders share ancestry within the last 10 thousand years, with major population growth in the same period, suggesting population structure was reshaped following the Neolithic lifestyle transition. However, genetic differentiation between groups in Papua New Guinea is much stronger than in comparable regions in Eurasia, demonstrating that such a transition does not necessarily limit the genetic and linguistic diversity of human societies.

- 13 **Bolnga JW, Morris M, Totona C, Laman M.** Maternal near-misses at a provincial hospital in Papua New Guinea: a prospective observational study.

*Aust NZ J Obstet Gynaecol* 2017 Dec;57(6):624-629. doi: 10.1111/ajo.12650. Epub 2017 Jun 5.

**BACKGROUND:** Maternal near-miss indices are World Health Organization (WHO)-recognised indicators that may improve our understanding of factors associated with maternal morbidity and mortality. In Papua New Guinea (PNG), where maternal mortality is among the highest in the world, only one study has documented near-miss indices in a tertiary-level hospital, but none from provincial hospitals where the majority of under-privileged women access healthcare services. **AIMS:** To determine the near-miss ratio, maternal mortality index (MMI), and associated maternal indices for Modilon Hospital in Madang Province of PNG. **METHODS:** All women attending Modilon Hospital who met the WHO maternal near-miss definition and/or a WHO-modified (PNG-specific) near-miss definition, were prospectively enrolled. **RESULTS:** There were 6019 live births during the audit period; 163 women presented with life-threatening conditions (153 near-misses and 10 maternal deaths). The maternal near-miss ratio was 25.4/1000 live births and the maternal mortality ratio (MMR) was 166/100,000 live births, with a maternal death to near-miss ratio of 1:15.3. The severe maternal outcome ratio was 27.1/1000 live births and the total mortality index was 6.8%. Higher proportions of near-miss women were aged ≥30 years, nulliparous, illiterate, from rural communities, lacked formal employment, referred from peripheral health facilities, unbooked, had history of still births and were anaemic. **CONCLUSION:** Sociodemographic factors such as

women's rights, education level and status in society, in addition to appropriate health reforms with greater financial and political support are urgently needed to ensure underprivileged women in rural PNG have access to family planning, supervised deliveries and skilled emergency obstetric care.

- 14 **Bradbury RS, Harrington H, Kekeubata E, Esau D, Esau T, Kilivisi F, Harrington N, Gwala J, Speare R, MacLaren D.**

High prevalence of ascariasis on two coral atolls in the Solomon Islands.

*Trans R Soc Trop Med Hyg* 2018 Apr 1;112(4):193-199. doi: 10.1093/trstmh/try041.

**Background:** There is a deficiency in up-to-date soil-transmitted helminth (STH) prevalence data for many regions, including Oceania. This study investigated the prevalence of STH in two closely associated coral atoll communities in East Kwaio, Solomon Islands, reflective of many similar island communities throughout the Oceania region. **Methods:** An STH survey, using the Kato-Katz technique, was conducted on human subjects living on two coral atolls in the Eastern Solomon Islands. The capacity of *Ascaris lumbricoides* eggs to float in seawater was also evaluated by passive flotation. **Results:** Of 583 people tested on both islands, 311 (53.3%) harboured *A. lumbricoides*, with 51.7% (n = 161) of those having moderate to high-intensity infections. Hookworm was detected in 139 (23.7%) participants and *Trichuris trichiura* infection in 18 (3.1%). *A. lumbricoides* eggs were not found to float in seawater. **Discussion:** The high prevalence and intensity of ascariasis on these two atolls was contrasted with previously described STH studies in mainland East Kwaio villages, where hookworm predominates and ascariasis is almost absent. This led to a preliminary consideration that transmission of *A. lumbricoides* on densely populated coral atolls might be associated with defecation into the sea and transmission in seawater, although further work is required to investigate this hypothesis.

- 15 **Broesch T, Bryant GA.** Fathers' infant-directed speech in a small-scale society.

*Child Dev* 2018 Mar;89(2):e29-e41. doi: 10.1111/cdev.12768. Epub 2017 Feb 27.

When speaking to infants, mothers often alter their speech compared to how they speak to adults, but findings for fathers are mixed. This study examined interactions (N = 30) between fathers and infants (M age ± SD = 7.8 ± 4.3 months) in a small-scale society in Vanuatu and two urban societies in North America. Fundamental frequency (F0) and speech rate were measured in infant-directed and adult-directed speech. When speaking to infants, fathers in both groups increased their F0 range, yet only Vanuatu fathers increased their average F0. Conversely, North American fathers slowed down their speech rate to infants, whereas Vanuatu fathers did not. Behavioral traits can vary across distant cultures while still potentially solving similar communicative problems.

- 16 **Brookes VJ, Degeling C, Ward MP.**

Going viral in PNG – exploring routes and circumstances of entry of a rabies-infected dog into Papua New Guinea.

*Soc Sci Med* 2018 Jan;196:10-18. doi: 10.1016/j.socscimed.2017.11.006. Epub 2017 Nov 6.



In this qualitative study implemented in November 2016, we elicited narratives about fictional rabies incursions from key employees ( $n = 16$ ) of the National Agriculture and Quarantine Inspection Authority in Papua New Guinea (PNG) to explore the potential circumstances and routes of entry of a rabies-infected dog, and direct rabies preparedness. Although PNG is rabies free, proximity to rabies-endemic Indonesia poses a risk of introduction and it is expected that an outbreak in PNG would have devastating human health impacts consistent with other countries with similarly low human development indices and abundant free-roaming dogs. Participants used their local and professional knowledge to create plausible narratives in response to contextual, but fictitious, newspaper stories. An ethnographic content analysis was used to extract themes and interpret the narratives. Themes were assessed in the context of their potential influence on rabies preparedness in PNG against the social and political background of PNG and relevant, published literature. Consistent themes included the ubiquity of trade and the complexity of routes between Indonesia and PNG. Dog ownership seemed pragmatic – actors in the narratives readily and rationally involved dogs in transactions in response to trade, exchange or gifting opportunities. Consequently, dogs changed ownership frequently. The findings of this study have important implications for rabies preparedness in PNG; there is potential for wide geographic dissemination of rabies in dogs before outbreak detection. However, common patterns of travel – trade of dogs via Papuan towns and use of traditional trade routes – do provide opportunity for targeted surveillance and response in the event of an incursion.

**17 Brookes VJ, Keponge-Yombo A, Thomson D, Ward MP.**

Risk assessment of the entry of canine-rabies into Papua New Guinea via sea and land routes. *Prev Vet Med* 2017 Sep 15;145:49-66. doi: 10.1016/j.pvetmed.2017.06.011. Epub 2017 Jun 27.

Canine-rabies is endemic in parts of Indonesia and continues to spread eastwards through the Indonesian archipelago. Papua New Guinea (PNG) has a land border with Papua Province, Indonesia, as well as logging and fishing industry connections throughout Asia. PNG has a Human Development Index of 0.505; therefore, an incursion of canine-rabies could have devastating impacts on human (7.5 million) and animal populations. Given the known difficulties of rabies elimination in resource-scarce environments, an incursion of rabies into PNG would also likely compromise the campaign for global elimination of rabies. A previous qualitative study to determine routes for detailed risk assessment identified logging, fishing and three land-routes (unregulated crossers ['shopper-crosser'], traditional border crossers and illegal hunters) as potential high risk routes for entry of rabies-infected dogs into PNG. The objective of the current study was to quantify and compare the probability of entry of a rabies-infected dog via these routes into PNG and to identify the highest risk provinces and border districts to target rabies prevention and control activities. Online questionnaires were used to elicit expert-opinion about quantitative model parameter values. A quantitative, stochastic model was then used to assess risk, and parameters with the greatest influence on the estimated mean number of

rabies-infected dogs introduced/year were identified via global sensitivity analysis (Sobol method). Eight questionnaires – including 7 online – were implemented and >220 empirical distributions were parameterised using >2900 expert-opinions. The highest risk provinces for combined sea routes were West Sepik, Madang and Western Province, driven by the number of vessels and the probability of bringing dogs. The highest risk border districts for combined land routes were Vanimo-Green River and South Fly, driven by the number of people crossing the border and the number of dogs (with hunters). Overall, the risk posed by land routes was much higher than the risk of rabies introduction by sea routes. This study provides a foundation to develop targeted border control measures, surveillance and response strategies for canine-rabies for the highest risk routes and regions in PNG. Sensitivity analysis using the Sobol method played a key role in this study and directed further data collection to refine risk estimates. The ease of expert-elicitation using online methods demonstrates the feasibility of using such methods for animal and human disease surveillance in PNG.

**18 Brown AM.**

Accommodating indigenous nurse-initiated and managed antiretroviral therapy (NIMART) reporting in a developing country context.

*J Assoc Nurses AIDS Care* 2018 Mar-Apr;29(2):220-230. doi: 10.1016/j.jana.2017.09.004. Epub 2017 Sep 21.

Financial reporting represents a critical tool in eliminating HIV across Papua New Guinea (PNG). Using the tenets of the theory of indigenous alternative reporting, this paper considers how the PNG Nursing Council may accommodate nurse-initiated and managed antiretroviral therapy (NIMART) reporting. Textual analysis of indigenous reporting expectations placed on the PNG Nursing Council are examined in a NIMART context to examine levels of reporting compliance exercised by council administrators from year-end reports (1980 to 2016) to accommodate NIMART reporting. The study revealed that the 2014 annual report of the PNG Nursing Council generated a 40% NIMART compliance rate, offering encouraging signs of financial reporting that could make room for NIMART reporting. The study suggested that local mechanisms could be used to meet local indigenous reporting expectations in order to adopt NIMART reporting. The study also has far-reaching implications for other developing country nursing councils wanting to develop NIMART reporting.

**19 Brulé J, Tousignant B, Nicholls G, Pearce MG.**

An in-country model of workforce support for trained mid-level eye care workers in Papua New Guinea and Pacific Islands.

*NZ Med J* 2017 Aug 11;130(1460):83-86.

To alleviate the significant burden of vision impairment and blindness in low-resource settings, addressing the shortage in human resources in eye care is one of the fundamental strategies. With its postgraduate training programmes, The Fred Hollows Foundation New Zealand (FHFNZ) aims to increase workforce capacity in the Pacific Island countries and territories and Papua New Guinea. This paper presents an in-country model to offer support to graduates, an essential element to retain them in the workforce and ensure they are able to



perform the tasks they were trained to do. FHFNZ has designed a workforce support programme employing a standardised process, allowing comparable reporting and providing data for FHFNZ to evaluate its training programmes, outputs as well as professional recognition and integration in the workplace.

20 **Burkot C, Naidi L, Seehofer L, Miles K.**

Perceptions of incentives offered in a community-based malaria diagnosis and treatment program in the Highlands of Papua New Guinea.

*Soc Sci Med* 2017 Oct;190:149-156. doi: 10.1016/j.socscimed.2017.08.026. Epub 2017 Aug 23.

What motivates community-based health workers to provide care in rural and remote areas, often on a voluntary or casual basis, is a key question for program managers and public health officials. This paper examines how a range of incentives offered as part of the Marasin Stoa Kipa program, a community-based malaria diagnosis and treatment program that has been implemented since 2007 within a major oil and gas development area in Papua New Guinea, are perceived and critiqued by community-based health workers. Nineteen interviews and seven focus group discussions with the workers who deliver services and members of the communities served by the program, conducted between November 4 and 25, 2015, reveal a pattern of mixed motivations and changes in motivation over time. This can be attributed partly to the unique social and economic circumstances in which the program is operating. Changes in the burden of disease as well as in global and national health services policy with implications for local level program operations also had an impact, as did the nature of relationships between program managers, community-based health workers, and program beneficiaries. Overall, the findings suggest that while financial and in-kind incentives can be a useful tool to motivate voluntary or minimally-compensated community-based health workers, they must be carefully structured to align with local social, economic, and epidemiological realities over the long-term.

21 **Butcher R, Sokana O, Jack K, Sui L, Russell C, Last A, Martin DL, Burton MJ, Solomon AW, Mabey DCW, Roberts CH.**

Clinical signs of trachoma are prevalent among Solomon Islanders who have no persistent markers of prior infection with *Chlamydia trachomatis*.

*Wellcome Open Res* 2018 Feb 22;3:14. doi: 10.12688/wellcomeopenres.13423.2. eCollection 2018.

**Background:** The low population-prevalence of trachomatous trichiasis and high prevalence of trachomatous inflammation-follicular (TF) provide contradictory estimates of the magnitude of the public health threat from trachoma in the Solomon Islands. Improved characterisation of the biology of trachoma in the region may support policy makers as they decide what interventions are required. Here, age-specific profiles of anti-Pgp3 antibodies and conjunctival scarring were examined to determine whether there is evidence of ongoing transmission and pathology from ocular *Chlamydia trachomatis* (Ct) infection. **Methods:** A total of 1511 individuals aged  $\geq 1$  year were enrolled from randomly selected households in 13 villages in which >10% of children aged 1-9 years had TF prior to a single round of azithromycin mass drug administration undertaken

six months previously. Blood was collected to be screened for antibodies to the Ct antigen Pgp3. Tarsal conjunctival photographs were collected for analysis of scarring severity. **Results:** Anti-Pgp3 seropositivity was 18% in 1-9 year olds, sharply increasing around the age of sexual debut to reach 69% in those over 25 years. Anti-Pgp3 seropositivity did not increase significantly between the ages of 1 and 9 years and was not associated with TF ( $p = 0.581$ ) or scarring in children ( $p = 0.472$ ). Conjunctival scars were visible in 13.1% of photographs. Mild ( $p < 0.0001$ ) but not severe ( $p = 0.149$ ) scars increased in prevalence with age. **Conclusions:** Neither conjunctival scars nor lymphoid follicles were associated with antibodies to Ct, suggesting that they are unlikely to be a direct result of ocular Ct infection. Clinical signs of trachoma were prevalent in this population but were not indicative of the underlying rates of Ct infection. The current World Health Organization guidelines for trachoma elimination indicated that this population should receive intervention with mass distribution of antibiotics, but the data presented here suggest that this may not have been appropriate.

22 **Butcher RMR, Sokana O, Jack K, Kalae E, Sui L, Russell C, Houghton J, Palmer C, Holland MJ, Le Mesurier RT, Solomon AW, Mabey DCW, Roberts CH.**

Active trachoma cases in the Solomon Islands have varied polymicrobial community structures but do not associate with individual non-chlamydial pathogens of the eye.

*Front Med (Lausanne)* 2018 Jan 23;4:251. doi: 10.3389/fmed.2017.00251. eCollection 2017.

**Background:** Several non-chlamydial microbial pathogens are associated with clinical signs of active trachoma in trachoma-endemic communities with a low prevalence of ocular *Chlamydia trachomatis* (Ct) infection. In the Solomon Islands, the prevalence of Ct among children is low despite the prevalence of active trachoma being moderate. Therefore, we set out to investigate whether active trachoma was associated with a common non-chlamydial infection or with a dominant polymicrobial community dysbiosis in the Solomon Islands. **Methods:** We studied DNA from conjunctival swabs collected from 257 Solomon Islanders with active trachoma and matched controls. Droplet digital PCR was used to test for pathogens suspected to be able to induce follicular conjunctivitis. Polymicrobial community diversity and composition were studied by sequencing of hypervariable regions of the 16S ribosomal ribonucleic acid gene in a subset of 54 cases and 53 controls. **Results:** Although Ct was associated with active trachoma, the number of infections was low (cases, 3.9%; controls, 0.4%). Estimated prevalence (cases and controls, respectively) of each non-chlamydial infection was as follows: *Staphylococcus aureus*: 1.9 and 1.9%, *Adenoviridae*: 1.2 and 1.2%, coagulase-negative *Staphylococcus*: 5.8 and 4.3%, *Haemophilus influenzae*: 7.4 and 11.7%, *Moraxella catarrhalis*: 2.3 and 4.7%, and *Streptococcus pneumoniae*: 7.0 and 6.2%. There was no statistically significant association between the clinical signs of trachoma and the presence or load of any of the non-Ct infections that were assayed. Interindividual variations in the conjunctival microbiome were characterized by differences in the levels of *Corynebacterium*, *Propionibacterium*, *Helicobacter*, and *Paracoccus*,

but diversity and relative abundance of these specific genera did not differ significantly between cases and controls. **Discussion:** It is unlikely that the prevalent trachoma-like follicular conjunctivitis in this region of the Solomon Islands has a dominant bacterial etiology. Before implementing community-wide azithromycin distribution for trachoma, policy makers should consider that clinical signs of trachoma can be observed in the absence of any detectable azithromycin-susceptible organism.

**23 Calderón-Celis F, Cid-Barrio L, Encinar JR, Sanz-Medel A, Calvete JJ.**

**Absolute venomomics: absolute quantification of intact venom proteins through elemental mass spectrometry.**  
*J Proteomics* 2017 Jul 5;164:33-42. doi: 10.1016/j.jprot.2017.06.001. Epub 2017 Jun 2.

We report the application of a hybrid element and molecular MS configuration for the parallel absolute quantification of  $\mu$ HPLC-separated intact sulfur-containing venom proteins, via ICP triple quadrupole MS and  $^{32}\text{S}/^{34}\text{S}$  isotope dilution analysis, and identification by ESI-QToF-MS of the toxins of the medically important African black-necked spitting cobra, *Naja nigricollis* (Tanzania); New Guinea small-eyed snake, *Micropechis ikaheka*; and Papuan black snake, *Pseudechis papuanus*. The main advantage of this approach is that only one generic sulfur-containing standard is required to quantify each and all intact Cys- and/or Met-containing toxins of the venom proteome. The results of absolute quantification are in reasonably good agreement with previously reported relative quantification of the most abundant protein families. However, both datasets depart in the quantification of the minor ones, showing a tendency for this set of proteins to be underestimated in standard peptide-centric venomomics approaches. The molecular identity, specific toxic activity, and concentration in the venom, are the pillars on which the toxicovenomics-aimed discovery of the most medically-relevant venom toxins, eg, those that need to be neutralized by an effective therapeutic antivenom, should be based. The pioneering venom proteome-wide absolute quantification shown in this paper represents thus a significant advance towards this goal. The potential of ICP triple quadrupole MS in proteomics in general, and venomomics in particular, is critically discussed. **BIOLOGICAL SIGNIFICANCE:** Animal venoms provide excellent model systems for investigating interactions between predators and prey, and the molecular mechanisms that contribute to adaptive protein evolution. On the other hand, numerous cases of snake bites occur yearly by encounters of humans and snakes in their shared natural environment. Snakebite envenoming is a serious global public health issue that affects the most impoverished and geopolitically disadvantaged rural communities in many tropical and subtropical countries. Unveiling the temporal and spatial patterns of venom variability is of fundamental importance to understand the molecular basis of envenoming, a prerequisite for developing therapeutic strategies against snakebite envenoming. Research on venoms has been continuously enhanced by advances in technology. The combined application of next-generation transcriptomic and venom workflows has demonstrated unparalleled capabilities for venom characterization in unprecedented detail. However, mass spectrometry is not inherently quantitative, and

this analytical limitation has sparked the development of methods to determine absolute abundance of proteins in biological samples. Here we show the potential of a hybrid element and molecular MS configuration for the parallel ESI-QToF-MS and ICP-QQQ detection and absolute quantification of intact sulfur-containing venom proteins via  $^{32}\text{S}/^{34}\text{S}$  isotope dilution analysis. This configuration has been applied to quantify the toxins of the medically important African snake *Naja nigricollis* (Tanzania), and the Papuan species *Micropechis ikaheka* and *Pseudechis papuanus*.

**24 Carmone A, Rodriguez CA, Frank TD, Kiromat M, Bongsi PW, Kuno RG, Palou T, Franke MF.**

**Increasing isoniazid preventive therapy uptake in an HIV program in rural Papua New Guinea.**  
*Public Health Action* 2017 Sep 21;7(3):193-198. doi: 10.5588/pha.17.0011.

**Setting:** Tuberculosis (TB) is the leading cause of death among people living with the human immunodeficiency virus (PLHIV) in Papua New Guinea. Despite a policy for isoniazid preventive therapy (IPT) among PLHIV, implementation has been slow. **Objective:** We prospectively evaluated a standardized guided screening process, including TB diagnostic support, to increase IPT initiation in adult PLHIV on antiretroviral treatment. **Design:** The guided process included a paper-based IPT screening tool that prompted review of patient history and TB symptoms and sputum analysis by smear microscopy and Xpert® MTB/RIF. Chest X-ray was performed at the provider's discretion. We quantified the yield of this guided process on IPT initiation and detection of TB and rifampicin resistance, and examined the contributions of each diagnostic modality. **Results:** Among 532 patients, TB was ruled out and IPT initiated in 450 (84%). TB was diagnosed and treatment was started in 82 (15%) patients. Xpert detected rifampicin resistance in one of 21 patients (5%, 95%CI 0.24-21.3) with a positive Xpert result. All TB cases were diagnosed by chest X-ray and/or Xpert. No cases were diagnosed by sputum smear alone. **Conclusion:** A standardized guided process, including TB diagnostic support, successfully enabled IPT initiation and identified a large burden of undetected TB.

**25 Chan J, Nguyen CD, Lai JYR, Dunne EM, Andrews R, Blyth CC, Datta S, Fox K, Ford R, Hinds J, La Vincente S, Lehmann D, Lim R, Mungun T, Newton PN, Phetsouvanh R, Pomat WS, Xeuatvongsa A, von Mollendorf C, Dance DAB, Satzke C, Muholland K, Russell FM; PneuCAPTIVE Protocol Group.**

**Determining the pneumococcal conjugate vaccine coverage required for indirect protection against vaccine-type pneumococcal carriage in low- and middle-income countries: a protocol for a prospective observational study.**  
*BMJ Open* 2018 May 18;8(5):e021512. doi: 10.1136/bmjopen-2018-021512.

**INTRODUCTION:** Pneumococcal conjugate vaccines (PCVs) prevent disease through both direct protection of vaccinated individuals and indirect protection of unvaccinated individuals by reducing nasopharyngeal (NP) carriage and transmission of vaccine-type (VT) pneumococci. While the indirect effects of PCV vaccination are well described, the PCV coverage required to achieve the indirect effects is unknown. We will investigate the relationship

between PCV coverage and VT carriage among undervaccinated children using hospital-based NP pneumococcal carriage surveillance at three sites in Asia and the Pacific. **METHODS AND ANALYSIS:** We are recruiting cases, defined as children aged 2-59 months admitted to participating hospitals with acute respiratory infection in Lao People's Democratic Republic, Mongolia and Papua New Guinea. Thirteen-valent PCV status is obtained from written records. NP swabs are collected according to standard methods, screened using *lytA* qPCR and serotyped by microarray. Village-level vaccination coverage, for the resident communities of the recruited cases, is determined using administrative data or community survey. Our analysis will investigate the relationship between VT carriage among undervaccinated cases (indirect effects) and vaccine coverage using generalised estimating equations. **ETHICS AND DISSEMINATION:** Ethical approval has been obtained from the relevant ethics committees at participating sites. The results are intended for publication in open-access peer-reviewed journals and will demonstrate methods suitable for low- and middle-income countries to monitor vaccine impact and inform vaccine policy makers about the PCV coverage required to achieve indirect protection.

- 26 **Chan JA, Stanicic DI, Duffy MF, Robinson LJ, Lin E, Kazura JW, King CL, Siba PM, Fowkes FJ, Mueller I, Beeson JG.**

Patterns of protective associations differ for antibodies to *P. falciparum*-infected erythrocytes and merozoites in immunity against malaria in children. *Eur J Immunol* 2017 Dec;47(12):2124-2136. doi: 10.1002/eji.201747032. Epub 2017 Sep 13.

Acquired antibodies play an important role in immunity to *P. falciparum* malaria and are typically directed towards surface antigens expressed by merozoites and infected erythrocytes (IEs). The importance of specific IE surface antigens as immune targets remains unclear. We evaluated antibodies and protective associations in two cohorts of children in Papua New Guinea. We used genetically-modified *P. falciparum* to evaluate the importance of PfEMP1 and a *P. falciparum* isolate with a virulent phenotype. Our findings suggested that PfEMP1 was the dominant target of antibodies to the IE surface, including functional antibodies that promoted opsonic phagocytosis by monocytes. Antibodies were associated with increasing age and concurrent parasitemia, and were higher among children exposed to a higher force-of-infection as determined using molecular detection. Antibodies to IE surface antigens were consistently associated with reduced risk of malaria in both younger and older children. However, protective associations for antibodies to merozoite surface antigens were only observed in older children. This suggests that antibodies to IE surface antigens, particularly PfEMP1, play an earlier role in acquired immunity to malaria, whereas greater exposure is required for protective antibodies to merozoite antigens. These findings have implications for vaccine design and serosurveillance of malaria transmission and immunity.

- 27 **Chen G, Hsieh MY, Chen AW, Kao NH, Chen MK.**  
The effectiveness of school educating program for betel quid chewing: a pilot study in Papua New Guinea.

*J Chin Med Assoc* 2018 Apr;81(4):352-357. doi: 10.1016/j.jcma.2017.10.001. Epub 2017 Nov 7.

**BACKGROUND:** To investigate the effectiveness of an educating program among primary and secondary school students in Papua New Guinea, which has the highest incidence of oral cancer in the world. **METHODS:** A cross-sectional school-based survey was arranged in primary and secondary schools in Papua New Guinea in June, 2015. A self-administrated questionnaire was administered before and after education done by health experts from Taiwan. The subjects were chosen by random. The schools provided the students we educated and supervised the questionnaires. **RESULTS:** Ninety-five primary school students and 55 secondary school students in Papua New Guinea participated in the study. Before education, both groups lacked the knowledge that betel quid is harmful to health and had no motivation to quit betel quid consumption, with the average score 4.580 out of the total score of 8 for primary school students, and the average score of 4.600 out of the total score of 8 for secondary school students. After education, improvements were noted in knowledge of betel quid among both groups, and reached statistical significance for secondary school students (mean difference  $0.700 \pm 0.277$ , 95% CI 0.164-1.248,  $p$  value = 0.018). **CONCLUSION:** A great achievement was gained by a short time of education. To prevent the incidence and mortality of oral cancer in Papua New Guinea, education programs should be arranged aggressively and effectively.

- 28 **Coenders A, Verregghen M, Baerends EP.**

A Papua New Guinean with three foot ulcers. [Du] *Ned Tijdschr Geneesk* 2018;162:D2295.

A 25-year-old Papuan presented with three painless foot ulcers with undermined edges, induration and oedema. The appearance was typical for Buruli ulcer, which is caused by *Mycobacterium ulcerans*. A smear was positive for acid fast bacilli. Buruli ulcers are found in patients from humid and tropical regions and are treated with rifampicin and streptomycin for eight weeks.

- 29 **Colborn KL, Mueller I, Speed TP.**

Joint modeling of mixed *Plasmodium* species infections using a bivariate poisson lognormal model. *Am J Trop Med Hyg* 2018 Jan;98(1):71-76. doi: 10.4269/ajtmh.17-0523.

Infectious diseases often present as coinfections that may affect each other in positive or negative ways. Understanding the relationship between two coinfecting pathogens is thus important to understand the risk of infection and burden of disease caused by each pathogen. Although coinfections with *Plasmodium falciparum* and *Plasmodium vivax* are very common outside Africa, it is yet unclear whether infections by the two parasite species are positively associated or if infection by one parasite suppresses the other. In this study, we use bivariate Poisson lognormal models (BPLM) to estimate covariate-adjusted associations between the incidence of infections (as measured by the force of blood-stage infections, molFOI) and clinical episodes caused by both *P. falciparum* and *P. vivax* in a cohort of Papua New Guinean children. ABPLM permits estimation of either positive or negative correlation, unlike most other multivariate Poisson models. Our results demonstrated a moderately positive association between *P. falciparum* and *P.*

*vivax* infection rates, arguing against the hypothesis that *P. vivax* infections protect against *P. falciparum* infections. Our findings also suggest that the BPLM is only useful for counts with suitably large means and overdispersion.

30 **Cooperrider K, Slotta J, Núñez R.**

The preference for pointing with the hand is not universal.

*Cogn Sci* 2018 May;42(4):1375-1390. doi: 10.1111/cogs.12585. Epub 2018 Jan 19.

Pointing is a cornerstone of human communication, but does it take the same form in all cultures? Manual pointing with the index finger appears to be used universally, and it is often assumed to be universally preferred over other forms. Non-manual pointing with the head and face has also been widely attested, but it is usually considered of marginal significance, both empirically and theoretically. Here, we challenge this assumed marginality. Using a novel communication task, we investigated pointing preferences in the Yupno of Papua New Guinea and in U.S. undergraduates. Speakers in both groups pointed at similar rates, but form preferences differed starkly: the Yupno participants used non-manual pointing (nose- and head-pointing) numerically more often than manual pointing, whereas the U.S. participants stuck unwaveringly to index-finger pointing. The findings raise questions about why groups differ in their pointing preferences and, more broadly, about why humans communicate in the ways they do.

31 **Craig AT, Joshua CA, Sio AR, Teobasi B, Dofai A, Dalipanda T, Hardie K, Kaldor J, Kolbe A.**

Enhanced surveillance during a public health emergency in a resource-limited setting: experience from a large dengue outbreak in Solomon Islands, 2016-2017.

*PLoS One* 2018 Jun 7;13(6):e0198487. doi: 10.1371/journal.pone.0198487. eCollection 2018.

Between August-2016 and April-2017, Solomon Islands experienced the largest and longest-running dengue outbreak on record in the country, with 12,329 suspected cases, 877 hospitalisations and 16 deaths. We conducted a retrospective review of related data and documents, and conducted key informant interviews to characterise the event and investigate the adaptability of syndromic surveillance for enhanced and expanded data collection during a public health emergency in a low resource country setting. While the outbreak quickly consumed available public and clinical resources, we found that authorities were able to scale up the conventional national syndrome-based early warning surveillance system to support the increased information demands during the event, demonstrating the flexibility of the system and syndromic surveillance more broadly. Challenges in scaling up included upskilling and assisting staff with no previous experience of the tasks required; managing large volumes of data; maintaining data quality for the duration of the outbreak; harmonising routine and enhanced surveillance data and maintaining surveillance for other diseases; producing information optimally useful for response planning; and managing staff fatigue. Solomon Islands, along with other countries of the region, remains vulnerable to outbreaks of dengue and other communicable diseases. Ensuring surveillance systems are robust and able to adapt to changing demands during emergencies

should be a health protection priority.

32 **Davis J, Vaughan C, Nankinga J, Davidson L, Kigodi H, Alalo E, Comrie-Thomson L, Luchters S.**

Expectant fathers' participation in antenatal care services in Papua New Guinea: a qualitative inquiry. *BMC Pregnancy Childbirth* 2018 May 8;18(1):138. doi: 10.1186/s12884-018-1759-4.

**BACKGROUND:** The importance of engaging men in maternal and child health programs is well recognised internationally. In Papua New Guinea (PNG), men's involvement in maternal and child health services remains limited and barriers and enablers to involving fathers in antenatal care have not been well studied. The purpose of this paper is to explore attitudes to expectant fathers participating in antenatal care, and to identify barriers and enablers to men's participation in antenatal care with their pregnant partner in PNG. **METHODS:** Twenty-eight focus group discussions were conducted with purposively selected pregnant women, expectant fathers, older men and older women across four provinces of PNG. Fourteen key informant interviews were also conducted with health workers. Qualitative data generated were analysed thematically. **RESULTS:** While some men accompany their pregnant partners to the antenatal clinic and wait outside, very few men participate in antenatal consultations. Factors supporting fathers' participation in antenatal consultations included feelings of shared responsibility for the unborn child, concern for the mother's or baby's health, the child being a first child, friendly health workers, and male health workers. Sociocultural norms and taboos were the most significant barrier to fathers' participation in antenatal care, contributing to men feeling ashamed or embarrassed to attend clinic with their partner. Other barriers to men's participation included fear of HIV or sexually transmitted infection testing, lack of separate waiting spaces for men, rude treatment by health workers, and being in a polygamous relationship. Building community awareness of the benefits of fathers participating in maternal and child health services, inviting fathers to attend antenatal care if their pregnant partner would like them to, and ensuring clinic spaces and staff are welcoming to men were strategies suggested for increasing fathers' participation in antenatal care. **CONCLUSION:** This study identified significant sociocultural and health service barriers to expectant fathers' participation in antenatal care in PNG. Our findings highlight the need to address these barriers – through health staff training and support, changes to health facility layout and community awareness raising – so that couples in PNG can access the benefits of men's participation in antenatal care.

33 **Dennis AT.**

Reducing maternal mortality in Papua New Guinea: contextualizing access to safe surgery and anesthesia.

*Anesth Analg* 2018 Jan;126(1):252-259. doi: 10.1213/ANE.0000000000002550.

Papua New Guinea has one of the world's highest maternal mortality rates with approximately 215 women dying per 100,000 live births. The sustainable development goals outline key priority areas for achieving a reduction in maternal mortality including a focus on universal health coverage with safe surgery and anesthesia for all pregnant



women. This narrative review addresses the issue of reducing maternal mortality in Papua New Guinea by contextualizing the need for safe obstetric surgery and anesthesia within a structure of enabling environments at key times in a woman's life. The 3 pillars of enabling environments are as follows: a stable humanitarian government; a safe, secure, and clean environment; and a strong health system. Key times, and their associated specific issues, in a woman's life include prepregnancy, antenatal, birth and the postpartum period, childhood, adolescence and young womanhood, and the postchildbearing years.

- 34 **Desai M, Hill J, Fernandes S, Walker P, Pell C, Gutman J, Kayentao K, Gonzalez R, Webster J, Greenwood B, Cot M, Ter Kuile FO.** Prevention of malaria in pregnancy. *Lancet Infect Dis* 2018 Apr;18(4):e119-e132. doi: 10.1016/S1473-3099(18)30064-1. Epub 2018 Jan 31.

Malaria remains one of the most preventable causes of adverse birth outcomes. Intermittent preventive treatment in pregnancy (IPTp) with sulfadoxine-pyrimethamine is used to prevent malaria, but resistance to this drug combination has decreased its efficacy and new alternatives are needed. In Africa, a meta-analysis showed three-course or monthly IPTp with sulfadoxine-pyrimethamine to be safe and more effective than the original two-course sulfadoxine-pyrimethamine strategy, prompting WHO to update its policy in 2012. Although resistance to sulfadoxine-pyrimethamine reduces the parasitological efficacy of IPTp, this drug combination remains associated with reduced incidence of low birthweight in areas where prevalence of parasites with quintuple *Plasmodium falciparum* dihydrofolate reductase (*Pf dhfr*) and dihydropteroate synthetase (*Pf dhps*) mutations is greater than 90%. Nevertheless, its effectiveness is compromised in women infected with sextuple mutant parasites. Six trials of IPTp showed that neither amodiaquine, mefloquine, nor chloroquine-azithromycin are suitable replacements for sulfadoxine-pyrimethamine because of poor tolerability. Furthermore, four trials showed that intermittent screening and treatment with the current generation of malaria rapid diagnostic tests was not a suitable alternative strategy to IPTp with sulfadoxine-pyrimethamine, even in areas with high prevalence of quintuple mutations. Two trials showed that IPTp with dihydroartemisinin-piperaquine was well tolerated, effective, and acceptable for IPTp, with monthly regimens being the most effective. Coverage of IPTp and insecticide-treated nets continues to lag behind targets. The key barriers to uptake are well documented, and many are open to intervention. Outside of Africa, a single trial suggests a potential role for integrated approaches that combine sulfadoxine-pyrimethamine with azithromycin for IPTp in areas of Papua New Guinea where malaria transmission is high. Modelling analysis suggests the importance of the prevention of malaria early in pregnancy and the need to protect pregnant women declines more slowly than the rate at which transmission declines. Improved funding has led to an increase in the number of prevention trials in the past decade, showing the value of more sustained protection with monthly IPTp regimens. There is a need for confirmatory trials of the safety, efficacy, and feasibility of IPTp with dihydroartemisinin-

piperaquine, for studies of intermittent screening and treatment with more sensitive rapid diagnostic tests, for studies of integrated strategies for malaria and other co-infections, and for studies of prevention strategies for malaria in pregnant women who are HIV-positive and living outside of Africa. Additional research is required on how to improve uptake of WHO's updated policy on IPTp with sulfadoxine-pyrimethamine and insecticide-treated nets.

- 35 **Dorey HF, Dorey JM, Burman NJ, Zweiback DJ, Hameed JM, Kringel JR, Whalen AE, Jairam RA.** Observations of pediatric disease prevalence from Pacific Partnership 2015. *Mil Med* 2018 Mar 1;183(Suppl 1):530-537. doi: 10.1093/milmed/usx179.

Pacific Partnership is an ongoing yearly humanitarian assistance mission to Pacific Rim countries. Although many case reports and surgical successes have been documented, few data have been published specifically about the primary care mission. This article analyzes outpatient pediatric data collected during Pacific Partnership 2015. Eleven different providers documented care delivered to children from birth through age 18 years, inclusive. Personally de-identified data were entered into spreadsheets, sorted according to country visited, and analyzed with IBM SPSS software looking for disease frequency. One thousand eighty-seven pediatric patients were seen across Fiji, Papua New Guinea (PNG), and the Philippines (PI). Asthma was the first, second, and third most prevalent diagnosis in PNG, Fiji, and PI, with a relative proportion of the total patients seen at 5.4%, 7.2%, and 5%, respectively. In PI, 123 cases of upper respiratory infection were seen, more than four times the next most common diagnosis of normal exam. Thirty-six patients with scabies were seen in Fiji (number 1), with abdominal pain at number 3 (26 cases, 6.5%). Surprisingly, helminths were rarely seen, comprising the sixteenth and fourteenth most common diagnoses in Fiji and PI and only two cases in PNG. Future Pacific Partnership missions can plan medication stock, personnel assignment, equipment needs, and educational literature based on these data.

- 36 **Duke T, Kasa TS, Poka H, Welch H.** Holistic care of complicated tuberculosis in health care settings with limited resources. *Arch Dis Child* 2017 Dec;102(12):1161-1168. doi: 10.1136/archdischild-2017-313095. Epub 2017 Sep 14.

In recent years, most of the focus on improving the quality of paediatric care in low-income countries has been on improving primary care using the Integrated Management of Childhood Illness, and improving triage and emergency treatment in hospitals aimed at reducing deaths in the first 24 hours. There has been little attention paid to improving the quality of care for children with chronic or complex diseases. Children with complicated forms of tuberculosis (TB), including central nervous system and chronic pulmonary TB, provide examples of acute and chronic multisystem paediatric illnesses that commonly present to district-level and second-level referral hospitals in low-income countries. The care of these children requires a holistic clinical and continuous quality improvement approach. This includes timely decisions on the commencement of treatment often when diagnoses are not certain, identification and



management of acute respiratory, neurological and nutritional complications, identification and treatment of comorbidities, supportive care, systematic monitoring of treatment and progress, rehabilitation, psychological support, ensuring adherence, and safe transition to community care. New diagnostics and imaging can assist this, but meticulous attention to clinical detail at the bedside and having a clear plan for all aspects of care that is communicated well to staff and families are essential for good outcomes. The care is multidimensional: biomedical, rehabilitative, social and economic, and multidisciplinary: medical, nursing and allied health. In the era of the Sustainable Development Goals, approaches to these dimensions of health care are needed within the reach of the poorest people who access district hospitals in low-income countries.

- 37 **Dyson L, Marks M, Crook OM, Sokana O, Solomon AW, Bishop A, Mabey DCW, Hollingsworth TD.** Targeted treatment of yaws with household contact tracing: how much do we miss? *Am J Epidemiol* 2018 Apr 1;187(4):837-844. doi: 10.1093/aje/kwx305.

Yaws is a disabling bacterial infection found primarily in warm and humid tropical areas. The World Health Organization strategy mandates an initial round of total community treatment (TCT) with single-dose azithromycin followed either by further TCT or active case-finding and treatment of cases and their contacts (the Morges strategy). We sought to investigate the effectiveness of the Morges strategy. We employed a stochastic household model to study the transmission of infection using data collected from a pre-TCT survey conducted in the Solomon Islands. We used this model to assess the proportion of asymptomatic infections that occurred in households without active cases. This analysis indicated that targeted treatment of cases and their household contacts would miss a large fraction of asymptomatic infections (65%-100%). This fraction was actually higher at lower prevalences. Even assuming that all active cases and their households were successfully treated, our analysis demonstrated that at all prevalences present in the data set, up to 90% of (active and asymptomatic) infections would not be treated under household-based contact tracing. Mapping was undertaken as part of the study "Epidemiology of Yaws in the Solomon Islands and the Impact of a Trachoma Control Programme," in September-October 2013.

- 38 **Engle-Stone R, Aaron GJ, Huang J, Wirth JP, Namaste SM, Williams AM, Pearson JM, Rohner F, Varadhan R, Addo OY, Temple V, Rayco-Solon P, Macdonald B, Suchdev PS.** Predictors of anemia in preschool children: Biomarkers Reflecting Inflammation and Nutritional Determinants of Anemia (BRINDA) project. *Am J Clin Nutr* 2017 Jul;106(Suppl 1):402S-415S. doi: 10.3945/ajcn.116.142323. Epub 2017 Jun 14.

**Background:** A lack of information on the etiology of anemia has hampered the design and monitoring of anemia-control efforts. **Objective:** We aimed to evaluate predictors of anemia in preschool children (PSC) (age range: 6-59 mo) by country and infection-burden category. **Design:** Cross-sectional data from 16 surveys (n = 29,293) from the Biomarkers Reflecting Inflammation and Nutritional Determinants of Anemia (BRINDA)

project were analyzed separately and pooled by category of infection burden. We assessed relations between anemia (hemoglobin concentration <110 g/L) and severe anemia (hemoglobin concentration <70 g/L) and individual-level (age, anthropometric measures, micronutrient deficiencies, malaria, and inflammation) and household-level predictors; we also examined the proportion of anemia with concomitant iron deficiency (defined as an inflammation-adjusted ferritin concentration <12 µg/L). Countries were grouped into 4 categories on the basis of risk and burden of infectious disease, and a pooled multivariable logistic regression analysis was conducted for each group. **Results:** Iron deficiency, malaria, breastfeeding, stunting, underweight, inflammation, low socioeconomic status, and poor sanitation were each associated with anemia in >50% of surveys. Associations between breastfeeding and anemia were attenuated by controlling for child age, which was negatively associated with anemia. The most consistent predictors of severe anemia were malaria, poor sanitation, and underweight. In multivariable pooled models, child age, iron deficiency, and stunting independently predicted anemia and severe anemia. Inflammation was generally associated with anemia in the high- and very high-infection groups but not in the low- and medium-infection groups. In PSC with anemia, 50%, 30%, 55%, and 58% of children had concomitant iron deficiency in low-, medium-, high- and very high-infection categories, respectively. **Conclusions:** Although causal inference is limited by cross-sectional survey data, results suggest anemia-control programs should address both iron deficiency and infections. The relative importance of factors that are associated with anemia varies by setting, and thus, country-specific data are needed to guide programs.

- 39 **Field E, Abo D, Samiak L, Vila M, Dove G, Rosewell A, Nathan S.**

A partnership model for improving service delivery in remote Papua New Guinea: a mixed methods evaluation.

*Int J Health Policy Manag* 2018 Jun 11;7(10):923-933. doi: 10.15171/ijhpm.2018.50.

**BACKGROUND:** The Community Mine Continuation Agreement Middle (CMCA) and South Fly Health Program (the Health Program) is a partnership for improving health service delivery in remote Papua New Guinea (PNG). The Health Program is delivered by a private contractor working in partnership with existing health service providers to improve service delivery using existing government systems, where possible, and aligns with national policies, plans and strategies. A midline evaluation was conducted to determine changes in health service delivery since commencement of the Health Program. **METHODS:** A mixed methods evaluation was undertaken mid-way through implementation of the Health Program, including a pre/post analysis of health service delivery indicators, semi-structured interviews with health workers and assessment of health facility equipment and infrastructure. **RESULTS:** Improvements in many of the long-term expected outcomes of the Health Program were observed when compared to the pre-program period. The number of outpatient visits per person per year and number of outreach clinics per 1000 children under 5 years increased by 15% and 189% respectively (p <0.001). Increases in

vaccination coverage for infants aged <1 year were observed: 58% for pentavalent 1st dose ( $p < 0.001$ ) and 75% for 1st dose Sabin ( $p < 0.001$ ), 30% for 3<sup>rd</sup> dose pentavalent ( $p < 0.001$ ) and 26% for measles vaccination ( $p < 0.001$ ). Family planning coverage remained at similar levels (increasing 5%,  $p = 0.095$ ) and antenatal care coverage increased by 26% ( $p < 0.001$ ). Supervised deliveries coverage declined by 32% ( $p < 0.001$ ), a continuation of the pre-Program trend. The proportion of facilities with standard equipment items, transport and lighting increased. Health worker training, in particular obstetric training, was most commonly cited by health workers as leading to improved services. **CONCLUSION:** Following implementation, substantial improvements in health service delivery indicators were observed in the Health Program area as compared with the pre-program period and the stagnating or declining national performance. This model could be considered for similar contexts where existing health service providers require external assistance to provide basic health services to the community.

40 **File K, Valente T, McLaws ML.**

Hygiene and health: who do mothers in Vanuatu communicate with about health?  
*Int J Environ Res Public Health* 2018 Mar 3;15(3). pii: E443. doi: 10.3390/ijerph15030443.

Health information-seeking behaviour of mothers with children five years of age and younger in Vanuatu was examined using the structural properties of social networks. Data were collected from a rural village from two islands and an urban settlement in the capital, Port Vila, by face-to-face interviews using a structured questionnaire. Sociometric data on the structure of the network, the characteristics of key informants, and associations with outside sources of health information were analysed as interpersonal predictors of health promotion and behavior change. Rural mothers preferred the health advice of biomedical practitioners for diarrheal disease over traditional custom practitioners. Interpersonal connections were restricted in the urban mother network indicating that mothers were merely acquaintances or do not seek health advice from each other. Our findings suggest that biomedical practitioners are the best option for diffusing health and hygiene information for rural and urban mothers. Traditional healers and paraprofessionals could be strategically used to complete the missing links in network connectedness to optimally spread new information. The novel use of cross-sectional social network data can create a baseline evaluation to purposefully frame a health intervention. Our study provided a unique explanation of how network analysis offers insight into how key players can be identified and the circumstances in which they are likely to be able to influence hygiene practices of their peers.

41 **Fola AA, Nate E, Abby Harrison GL, Barnadas C, Hetzel MW, Iga J, Siba P, Mueller I, Barry AE.**

Nationwide genetic surveillance of *Plasmodium vivax* in Papua New Guinea reveals heterogeneous transmission dynamics and routes of migration amongst subdivided populations.  
*Infect Genet Evol* 2018 Mar;58:83-95. doi: 10.1016/j.meegid.2017.11.028. Epub 2017 Dec 5.

The Asia Pacific Leaders in Malaria Alliance (APLMA) have committed to eliminate malaria from the region by 2030. Papua New Guinea (PNG)

has the highest malaria burden in the Asia-Pacific region but with the intensification of control efforts since 2005, transmission has been dramatically reduced and *Plasmodium vivax* is now the dominant malaria infection in some parts of the country. To gain a better understanding of the transmission dynamics and migration patterns of *P. vivax* in PNG, here we investigate population structure in eight geographically and ecologically distinct regions of the country. A total of 219 *P. vivax* isolates (16-30 per population) were successfully haplotyped using 10 microsatellite markers. A wide range of genetic diversity ( $H_e = 0.37-0.87$ ,  $R_s = 3.60-7.58$ ) and significant multilocus linkage disequilibrium (LD) was observed in six of the eight populations ( $IAS = 0.08-0.15$   $p$  value  $< 0.05$ ) reflecting a spectrum of transmission intensities across the country. Genetic differentiation between regions was evident (Jost's  $D = 0.07-0.72$ ), with increasing divergence of populations with geographic distance. Overall, *P. vivax* isolates clustered into three major genetic populations subdividing the Mainland lowland and coastal regions, the Islands and the Highlands. *P. vivax* gene flow follows major human migration routes, and there was higher gene flow amongst Mainland parasite populations than among Island populations. The Central Province (samples collected in villages close to the capital city, Port Moresby) acts as a sink for imported infections from the three major endemic areas. These insights into *P. vivax* transmission dynamics and population networks will inform targeted strategies to contain malaria infections and to prevent the spread of drug resistance in PNG.

42 **Francis JR, Manchikanti P, Blyth CC, Denholm J, Lowbridge C, Coulter C, Donnan E, Stapledon R, Krause VL, Waring J.**

Multidrug-resistant tuberculosis in Australia, 1998-2012.

*Int J Tuberc Lung Dis* 2018 Mar 1;22(3):294-299. doi: 10.5588/ijtld.17.0412.

**OBJECTIVE:** To describe the epidemiology and outcomes of multidrug-resistant tuberculosis (MDR-TB) diagnosed in Australia between 1998 and 2012. **DESIGN:** A retrospective review was undertaken involving all patients with laboratory-confirmed MDR-TB notified in Australia between 1998 and 2012 inclusive. Demographic, clinical and laboratory features are described. Clinical outcomes were defined according to World Health Organization definitions of treatment success (cure and treatment completion), treatment failure, death, loss to follow-up (including transfer out), or not evaluated at treatment completion. **RESULTS:** A total of 244 cases of MDR-TB were diagnosed in Australia during the study period, representing 1.4% of all TB cases notified. The majority were born outside Australia, including one third in Papua New Guinea. Of those with treatment outcome data available, treatment success was demonstrated in 81%. Treatment success was positively associated with use of a second-line injectable agent. Those born in Papua New Guinea were less likely to achieve treatment success. **CONCLUSION:** MDR-TB is uncommon in Australia. The large number of cases born in Papua New Guinea, and the poorer outcomes in this cohort, represent challenges with cross-border management of MDR-TB in the Torres Strait. Australia has an ongoing role in the prevention and management of MDR-TB locally and in the

region.

- 43 **França CT, White MT, He WQ, Hostetler JB, Brewster J, Frato G, Malhotra I, Gruszczak J, Huon C, Lin E, Kiniboro B, Yadava A, Siba P, Galinski MR, Healer J, Chitnis C, Cowman AF, Takashima E, Tsuboi T, Tham WH, Fairhurst RM, Rayner JC, King CL, Mueller I.**

Identification of highly-protective combinations of *Plasmodium vivax* recombinant proteins for vaccine development.

*Elife* 2017 Sep 26;6. pii: e28673. doi: 10.7554/eLife.28673.

The study of antigenic targets of naturally-acquired immunity is essential to identify and prioritize antigens for further functional characterization. We measured total IgG antibodies to 38 *P. vivax* antigens, investigating their relationship with prospective risk of malaria in a cohort of 1-3 years old Papua New Guinean children. Using simulated annealing algorithms, the potential protective efficacy of antibodies to multiple antigen-combinations, and the antibody thresholds associated with protection were investigated for the first time. High antibody levels to multiple known and newly identified proteins were strongly associated with protection (IRR 0.44-0.74,  $p < 0.001-0.041$ ). Among five-antigen combinations with the strongest protective effect ( $>90\%$ ), EBP, DBPII, RBP1a, CyRPA, and PVX\_081550 were most frequently identified, several of them requiring very low antibody levels to show a protective association. These data identify individual antigens that should be prioritized for further functional testing and establish a clear path to testing a multicomponent *P. vivax* vaccine.

- 44 **França CT, Li Wai Suen CSN, Carmagnac A, Lin E, Kiniboro B, Siba P, Schofield L, Mueller I.**

IgG antibodies to synthetic GPI are biomarkers of immune-status to both *Plasmodium falciparum* and *Plasmodium vivax* malaria in young children.

*Malar J* 2017 Sep 25;16(1):386. doi: 10.1186/s12936-017-2042-2.

**BACKGROUND:** Further reduction in malaria prevalence and its eventual elimination would be greatly facilitated by the development of biomarkers of exposure and/or acquired immunity to malaria, as well as the deployment of effective vaccines against *Plasmodium falciparum* and *Plasmodium vivax*. A better understanding of the acquisition of immunity in naturally-exposed populations is essential for the identification of antigens useful as biomarkers, as well as to inform rational vaccine development. **METHODS:** ELISA was used to measure total IgG to a synthetic form of glycosylphosphatidylinositol from *P. falciparum* (PfGPI) in a cohort of 1-3 years old Papua New Guinea children with well-characterized individual differences in exposure to *P. falciparum* and *P. vivax* blood-stage infections. The relationship between IgG levels to PfGPI and measures of recent and past exposure to *P. falciparum* and *P. vivax* infections was investigated, as well as the association between antibody levels and prospective risk of clinical malaria over 16 months of follow-up. **RESULTS:** Total IgG levels to PfGPI were low in the young children tested. Antibody levels were higher in the presence of *P. falciparum* or *P. vivax* infections, but short-lived. High IgG levels were associated with higher risk of *P. falciparum* malaria (IRR 1.33-1.66,  $p = 0.008-0.027$ ), suggesting that they are biomarkers of increased exposure to *P. falciparum*

infections. Given the cross-reactive nature of antibodies to PfGPI, high IgG levels were also associated with reduced risk of *P. vivax* malaria (IRR 0.65-0.67,  $p = 0.039-0.044$ ), indicating that these antibodies are also markers of acquired immunity to *P. vivax*. **CONCLUSIONS:** This study highlights that in young children, IgG to PfGPI might be a useful marker of immune-status to both *P. falciparum* and *P. vivax* infections, and potentially useful to help malaria control programs to identify populations at-risk. Further functional studies are necessary to confirm the potential of PfGPI as a target for vaccine development.

- 45 **Gartrell A, Jennaway M, Manderson L, Fangalasuu J, Dolaiano S.**

Social determinants of disability-based disadvantage in Solomon Islands.

*Health Promot Int* 2018 Apr 1;33(2):250-260. doi: 10.1093/heapro/daw071.

Development discourse widely recognises that disability is the result of economic and social processes and structures that fail to accommodate persons with disabilities. Empirical work on the relationship between disability and poverty, however, conceptualizes poverty through an economic resource lens in high-income countries. To address this conceptual gap this article uses a social determinants of health perspective to examine how socio-cultural, economic and political contexts shape disability-based disadvantage. This article draws upon ethnographic research and supplementary data collected using rapid assessment techniques in Solomon Islands. Findings suggest that the disability-poverty nexus and inequalities in health, wellbeing and quality of life must be understood within broader patterns of social vulnerability that are institutionalised in landownership and patterns of descent, gendered power relations and disability specific stigmas that preclude social and productive engagement. This article demonstrates how a social determinant of health perspective that closely examines lived experiences of disability provides critical analytical insights into the structural mechanisms that constitute disability-based disadvantage. This article provides foundation knowledge on which policies and further research to promote disability-inclusion and equity can be based.

- 46 **Gibbons A.**

Papua New Guinea's genetic diversity withstood farming.

*Science* 2017 Sep 15;357(6356):1086. doi: 10.1126/science.357.6356.1086.

- 47 **Godornes C, Giacani L, Barry AE, Mitjà O, Lukehart SA.**

Development of a multilocus sequence typing (MLST) scheme for *Treponema pallidum* subsp. *pertenue*: application to yaws in Lihir Island, Papua New Guinea.

*PLoS Negl Trop Dis* 2017 Dec 27;11(12):e0006113. doi: 10.1371/journal.pntd.0006113. eCollection 2017 Dec.

**BACKGROUND:** Yaws is a neglected tropical disease, caused by *Treponema pallidum* subsp. *pertenue*. The disease causes chronic lesions, primarily in young children living in remote villages in tropical climates. As part of a global yaws eradication campaign initiated by the World Health

Organization, we sought to develop and evaluate a molecular typing method to distinguish different strains of *T. pallidum* subsp. *pertenue* for disease control and epidemiological purposes. **METHODS AND PRINCIPAL FINDINGS:** Published genome sequences of strains of *T. pallidum* subsp. *pertenue* and *pallidum* were compared to identify polymorphic genetic loci among the strains. DNA from a number of existing historical *Treponema* isolates, as well as a subset of samples from yaws patients collected in Lihir Island, Papua New Guinea, were analyzed using these targets. From these data, three genes (*tp0548*, *tp0136* and *tp0326*) were ultimately selected to give a high discriminating capability among the *T. pallidum* subsp. *pertenue* samples tested. Intragenic regions of these three target genes were then selected to enhance the discriminating capability of the typing scheme using short readily amplifiable loci. This 3-gene multilocus sequence typing (MLST) method was applied to existing historical human yaws strains, the Fribourg-Blanc simian isolate, and DNA from 194 lesion swabs from yaws patients on Lihir Island, Papua New Guinea. Among all samples tested, fourteen molecular types were identified, seven of which were found in patient samples and seven among historical isolates or DNA. Three types (JG8, TD6, and SE7) were predominant on Lihir Island. **CONCLUSIONS:** This MLST approach allows molecular typing and differentiation of yaws strains. This method could be a useful tool to complement epidemiological studies in regions where *T. pallidum* subsp. *pertenue* is prevalent with the overall goals of improving our understanding of yaws transmission dynamics and helping the yaws eradication campaign to succeed.

48 **Goff J, Golitko M, Cochrane E, Curnoe D, Williams S, Terrell J.**

Reassessing the environmental context of the Aitape Skull - the oldest tsunami victim in the world? *PLoS One* 2017 Oct 25;12(10):e0185248. doi: 10.1371/journal.pone.0185248. eCollection 2017.

There is increasing recognition of the long-lasting effects of tsunamis on human populations. This is particularly notable along tectonically active coastlines with repeated inundations occurring over thousands of years. Given the often high death tolls reported from historical events though it is remarkable that so few human skeletal remains have been found in the numerous palaeotsunami deposits studied to date. The 1929 discovery of the Aitape Skull in northern Papua New Guinea and its inferred late Pleistocene age played an important role in discussions about the origins of humans in Australasia for over 25 years until it was more reliably radiocarbon dated to around 6000 years old. However, no similar attention has been given to reassessing the deposit in which it was found – a coastal mangrove swamp inundated by water from a shallow sea. With the benefit of knowledge gained from studies of the 1998 tsunami in the same area, we conclude that the skull was laid down in a tsunami deposit and as such may represent the oldest known tsunami victim in the world. These findings raise the question of whether other coastal archaeological sites with human skeletal remains would benefit from a re-assessment of their geological context.

49 **Goldenberg J, Cipriani V, Jackson TNW, Arbuckle K, Debono J, Dashevsky D, Panagides N, Ikononopoulou MP, Koludarov I, Li B, Santana**

**RC, Nouwens A, Jones A, Hay C, Dunstan N, Allen L, Bush B, Miles JJ, Ge L, Kwok HF, Fry BG.** Proteomic and functional variation within black snake venoms (Elapidae: *Pseudechis*). *Comp Biochem Physiol C Toxicol Pharmacol* 2018 Feb;205:53-61. doi: 10.1016/j.cbpc.2018.01.001. Epub 2018 Jan 17.

*Pseudechis* (black snakes) is an Australasian elapid snake genus that inhabits much of mainland Australia, with two representatives confined to Papua New Guinea. The present study is the first to analyse the venom of all 9 described *Pseudechis* species (plus one undescribed species) to investigate the evolution of venom composition and functional activity. Proteomic results demonstrated that the typical *Pseudechis* venom profile is dominated by phospholipase A2 toxins. Strong cytotoxicity was the dominant function for most species. *P. porphyriacus*, the most basal member of the genus, also exhibited the most divergent venom composition, being the only species with appreciable amounts of procoagulant toxins. The relatively high presence of factor Xa recovered in *P. porphyriacus* venom may be related to a predominantly amphibian diet. Results of this study provide important insights to guide future ecological and toxinological investigations.

50 **González-Beiras C, Kapa A, Vall-Mayans M, Paru R, Gavilán S, Houinei W, Bieb S, Sanz S, Martins R, Mitjà O.**

Single-dose azithromycin for the treatment of *Haemophilus ducreyi* skin ulcers in Papua New Guinea.

*Clin Infect Dis* 2017 Nov 29;65(12):2085-2090. doi: 10.1093/cid/cix723.

**Background:** *Haemophilus ducreyi* (HD) and *Treponema pallidum* subspecies *pertenue* (TP) are major causative agents of cutaneous ulcer (CU) in the tropics. Azithromycin is recommended to treat sexually transmitted HD infections and has good in vitro activity against HD strains from both genital and skin ulcers. We investigated the efficacy of oral single-dose azithromycin on HD-CU. **Methods:** We conducted a community-based cohort study in Lihir Island, Papua New Guinea, from October 2014 through May 2016. Consenting patients with skin ulcers >1 cm in diameter were eligible for this study and had collected a lesional swab for polymerase chain reaction (PCR). All participants were treated with single-dose azithromycin (30 mg/kg) and were followed up for assessment of clinical resolution. We retrospectively classified patients according to PCR results into HD, TP, and PCR-negative groups. The primary endpoint was healing rates of HD-CU at 14 days after treatment. **Results:** We obtained full outcome data from 246 patients; 131 (53.3%) were HD PCR positive, 37 (15.0%) were TP positive, and 78 (31.7%) were negative for all tests. Healing rates were 88.5% (95% confidence interval [CI], 0.82-0.93) in the HD group, 78.4% (95% CI, 0.63-0.89) in the TP group, and 74.4% (95% CI, 0.64-0.83) in the PCR-negative group. If we included the participants with improved ulcers, the healing rates increased to 94.7%, 97.3%, and 89.7% respectively. HD cases classified as not healed all converted to HD-negative PCR. **Conclusions:** Based upon clinical resolution and PCR conversion to HD negative, a single oral dose of azithromycin is efficacious for the treatment of HD-CU. These results have implications for the treatment of individual patients and for the use of



antibiotics in public health strategies to control CU in the tropics.

- 51 **Groyecka A, Żelaźniewicz A, Misiak M, Karwowski M, Sorokowski P.**

Breast shape (ptosis) as a marker of a woman's breast attractiveness and age: evidence from Poland and Papua.

*Am J Hum Biol* 2017 Jul 8;29(4). doi: 10.1002/ajhb.22981. Epub 2017 Feb 17.

**OBJECTIVES:** A women's breast is a sex-specific and aesthetic bodily attribute. It is suggested that breast morphology signals maturity, health, and fecundity. The perception of a woman's attractiveness and age depends on various cues, such as breast size or areola pigmentation. Conducted in Poland and Papua, the current study investigated how breast attractiveness, and the further estimate of a woman's age based on her breast's appearance, is affected by the occurrence of breast ptosis (ie, saggingness, droopiness). **METHODS:** In the Polish sample, 57 women and 50 men (N=107) were presented with sketches of breasts manipulated to represent different stages of ptosis based on two different breast ptosis classifications. The participants were asked to rate the breast attractiveness and age of the woman whose breasts were depicted in each sketch. In Papua, 45 men aged 20 to 75 years took part in the study, which was conducted using only one of the classifications of breast ptosis. **RESULTS:** Regardless of the classification used, the results showed that the assessed attractiveness of the breasts decreased as the estimated age increased with respect to the more ptotic breasts depicted in the sketches. The results for Papuan raters were the same as for the Polish sample. **CONCLUSIONS:** Breast ptosis may be yet another physical trait that affects the perception and preferences of a potential sexual partner. The consistency in ratings between Polish and Papuan raters suggests that the tendency to assess ptotic breasts with aging and a loss of attractiveness is cross-culturally universal.

- 52 **Guernier V, Diefenbach-Elstob T, Pelowa D, Pollard S, Burgess G, McBryde ES, Warner J.**

Molecular diagnosis of suspected tuberculosis from archived smear slides from the Balimo region, Papua New Guinea.

*Int J Infect Dis* 2018 Feb;67:75-81. doi: 10.1016/j.ijid.2017.12.004. Epub 2017 Dec 8.

**BACKGROUND:** Tuberculosis (TB) is a serious health problem in Papua New Guinea (PNG) with an estimated 30000 new cases and 3800 deaths each year. In the Balimo region of the Western Province, diagnosis relies on clinical manifestations and on the microscopic detection of acid-fast bacilli (AFB) in sputum smears, a technique with limited sensitivity. **METHODS:** A molecular diagnosis assay targeting DNA extracted from archived sputum smear slides collected from the Balimo region (2012-2014) was conducted, without the need for a viable culture. The presence of *Mycobacterium* sp. on 1162 slides prepared from 345 sputum samples was assessed using a real-time PCR (qPCR) approach. **RESULTS:** The qPCR technique identified the presence of mycobacteria in 35.4% of the smear slides and 59.7% of the tested sputum samples. Poor agreement was observed between the two diagnosis methods (smear AFB microscopy versus qPCR), with 100 AFB-positive sputum samples compared to 206

qPCR-positive sputum samples overall. Treatment was initiated in 90.2% of the smear-positive cases. Unnecessary treatment of 'false-positive' TB cases (AFB-positive/qPCR-negative) was very low (8.6%) and was even lower when the nine patients diagnosed with extrapulmonary TB were excluded from the analysis. However, the prevalence of false-negatives (AFB-negative/qPCR-positive) was high (28.5%). **CONCLUSIONS:** Undetected smear-negative TB is occurring in the Balimo region of PNG, as well as some unnecessary empirical treatment. Molecular methods of diagnosis could greatly reduce the frequency of inappropriate clinical assessment, as well as providing point-of-care diagnosis. This may provide substantial patient and programmatic benefits, including lowering the economic burden on patients from rural areas seeking medical diagnosis in Balimo.

- 53 **Guest GD, McLeod E, Perry WRG, Tangi V, Pedro J, Ponifasio P, Hedson J, Tudravu J, Pikacha D, Vreede E, Leodoro B, Tapaua N, Kong J, Oten B, Teapa D, Korin S, Wilson L, Mesol S, Tuneti K, Meara JG, Watters DA.**

Collecting data for global surgical indicators: a collaborative approach in the Pacific Region. *BMJ Glob Health* 2017 Nov 25;2(4):e000376. doi: 10.1136/bmjgh-2017-000376. eCollection 2017.

In 2015, the Lancet Commission on Global Surgery (LCoGS) recommended six surgical metrics to enable countries to measure their surgical and anaesthesia care delivery. These indicators have subsequently been accepted by the World Bank for inclusion in the World Development Indicators. With support from the Royal Australasian College of Surgeons and the Pacific Islands Surgical Association, 14 South Pacific countries collaborated to collect the first four of six LCoGS indicators. Thirteen countries collected all four indicators over a 6-month period from October 2015 to April 2016. Australia and New Zealand exceeded the recommended LCoGS target for all four indicators. Only 5 of 13 countries (38%) achieved 2-hour access for at least 80% of their population, with a range of 20% (Papua New Guinea and Solomon Islands) to over 65% (Fiji and Samoa). Five of 13 (38%) countries met the target surgical volume of 5000 procedures per 100,000 population, with six performing less than 1600. Four of 14 (29%) countries had at least 20 surgical, anaesthesia and obstetric providers in their workforce per 100,000 population, with a range of 0.9 (Timor Leste) to 18.5 (Tuvalu). Perioperative mortality rate was reported by 13 of 14 countries, and ranged from 0.11% to 1.0%. We believe it is feasible to collect global surgery indicators across the South Pacific, a diverse geographical region encompassing high-income to low-income countries. Such metrics will allow direct comparison between similar nations, but more importantly provide baseline data that providers and politicians can use in advocacy national health planning.

- 54 **Gutiérrez JM, Calvete JJ, Habib AG, Harrison RA, Williams DJ, Warrell DA.**

Snakebite envenoming.

*Nat Rev Dis Primers* 2017 Sep 14;3:17063. doi: 10.1038/nrdp.2017.63.

Snakebite envenoming is a neglected tropical disease that kills >100,000 people and maims >400,000 people every year. Impoverished



populations living in the rural tropics are particularly vulnerable; snakebite envenoming perpetuates the cycle of poverty. Snake venoms are complex mixtures of proteins that exert a wide range of toxic actions. The high variability in snake venom composition is responsible for the various clinical manifestations in envenomings, ranging from local tissue damage to potentially life-threatening systemic effects. Intravenous administration of antivenom is the only specific treatment to counteract envenoming. Analgesics, ventilator support, fluid therapy, haemodialysis and antibiotic therapy are also used. Novel therapeutic alternatives based on recombinant antibody technologies and new toxin inhibitors are being explored. Confronting snakebite envenoming at a global level demands the implementation of an integrated intervention strategy involving the WHO, the research community, antivenom manufacturers, regulatory agencies, national and regional health authorities, professional health organizations, international funding agencies, advocacy groups and civil society institutions.

- 55 **Hetzel MW, Pulford J, Ura Y, Jamea-Maiasa S, Tandrapah A, Tarongka N, Lorry L, Robinson LJ, Lilley K, Makita L, Siba PM, Mueller I.** Insecticide-treated nets and malaria prevalence, Papua New Guinea, 2008-2014. *Bull World Health Organ* 2017 Oct 1;95(10):695-705B. doi: 10.2471/BLT.16.189902. Epub 2017 Sep 5.

**Objective:** To investigate changes in malaria prevalence in Papua New Guinea after the distribution of long-lasting insecticide-treated nets, starting in 2004, and the introduction of artemisinin-based combination therapy in 2011. **Methods:** Two malaria surveys were conducted in 2010-2011 and 2013-2014. They included 77 and 92 randomly selected villages, respectively. In each village, all members of 30 randomly selected households gave blood samples and were assessed for malaria infection by light microscopy. In addition, data were obtained from a malaria survey performed in 2008-2009. **Results:** The prevalence of malaria below 1600 m in altitude decreased from 11.1% (95% confidence interval, CI: 8.5-14.3) in 2008-2009 to 5.1% (95% CI 3.6-7.4) in 2010-2011 and 0.9% (95% CI 0.6-1.5) in 2013-2014. Prevalence decreased with altitude. *Plasmodium falciparum* was more common than *P. vivax* overall, but not everywhere, and initially the prevalence of *P. vivax* infection decreased more slowly than *P. falciparum* infection. Malaria infections were clustered in households. In contrast to findings in 2008-2009, no significant association between net use and prevalence was found in the later two surveys. The prevalence of both fever and splenomegaly also decreased but their association with malaria infection became stronger. **Conclusion:** Large-scale insecticide-treated net distribution was associated with an unprecedented decline in malaria prevalence throughout Papua New Guinea, including epidemic-prone highland areas. The decline was accompanied by broader health benefits, such as decreased morbidity. Better clinical management of nonmalarial fever and research into residual malaria transmission are required.

- 56 **Hofmann NE, Karl S, Wampfler R, Kiniboro B, Teliki A, Iga J, Waltmann A, Betuela I, Felger I, Robinson LJ, Mueller I.** The complex relationship of exposure to new

*Plasmodium* infections and incidence of clinical malaria in Papua New Guinea. *Elife* 2017 Sep 1;6. pii: e23708. doi: 10.7554/eLife.23708.

The molecular force of blood-stage infection (molFOB) is a quantitative surrogate metric for malaria transmission at population level and for exposure at individual level. Relationships between molFOB, parasite prevalence and clinical incidence were assessed in a treatment-to-reinfection cohort, where *P. vivax* (Pv) hypnozoites were eliminated in half the children by primaquine (PQ). Discounting relapses, children acquired equal numbers of new *P. falciparum* (Pf) and Pv blood-stage infections/year (Pf-molFOB = 0-18, Pv-molFOB = 0-23) resulting in comparable spatial and temporal patterns in incidence and prevalence of infections. Including relapses, Pv-molFOB increased >3 fold (relative to PQ-treated children) showing greater heterogeneity at individual (Pv-molFOB = 0-36) and village levels. Pf- and Pv-molFOB were strongly associated with clinical episode risk. Yearly Pf clinical incidence rate (IR = 0.28) was higher than for Pv (IR = 0.12) despite lower Pf-molFOB. These relationships between molFOB, clinical incidence and parasite prevalence reveal a comparable decline in Pf and Pv transmission that is normally hidden by the high burden of Pv relapses.

- 57 **Horwood PF, Soli KW, Maure T, Naito YI, Morita A, Natsuhara K, Tadokoro K, Baba J, Odani S, Tomitsuka E, Igai K, Larkins JA, Siba PM, Pomat W, McBryde ES, Umezaki M, Greenhill AR.** A high burden of asymptomatic gastrointestinal infections in traditional communities in Papua New Guinea. *Am J Trop Med Hyg* 2017 Dec;97(6):1872-1875. doi: 10.4269/ajtmh.17-0282. Epub 2017 Sep 21.

Stool samples were collected from 148 healthy adults living a traditional subsistence lifestyle in Papua New Guinea and screened for enteric pathogens using real-time RT-PCR/PCR assays. Enteric pathogens were detected in a high proportion (41%) of individuals. Clear differences were observed in the detection of pathogens between highland and lowland communities. In particular, there was a marked difference in detection rates of norovirus GII (20% and 0%, respectively) and *Shigella* sp. (15% and 0%, respectively). Analysis of the relationship between enteric pathogen carriage and microbial community composition of participants, using box plots to compare specific normal flora population numbers, did not suggest that gut microbial composition was directly associated with pathogen carriage. This study suggests that enteric pathogens are common in healthy individuals in Papua New Guinean highland communities, presumably acting as a reservoir of infection and thus contributing to a high burden of gastrointestinal illnesses.

- 58 **Hoy D, Durand AM, Hancock T, Cash HL, Hardie K, Paterson B, Paulino Y, White P, Merritt T, Fitzgibbons D, Gopalani SV, Flint J, Edwin A, Merilles O Jr, Kashiwabara M, Biaukula V, Lepers C, Souares Y, Nilles E, Batikawai A, Huseynova S, Patel M, Saketa ST, Durrheim D, Henderson A, Roth A.** Lessons learnt from a three-year pilot field epidemiology training programme. *Western Pac Surveill Response J* 2017 Sep 25;8(3):21-26. doi: 10.5365/wpsar.2016.7.4.005.

eCollection 2017 Jul-Sep.

**PROBLEM:** The Pacific region has widely dispersed populations, limited financial and human resources and a high burden of disease. There is an urgent need to improve the availability, reliability and timeliness of useable health data. **CONTEXT:** The purpose of this paper is to share lessons learnt from a three-year pilot field epidemiology training programme that was designed to respond to these Pacific health challenges. The pilot programme built on and further developed an existing field epidemiology training programme for Pacific health staff. **ACTION:** The programme was delivered in country by epidemiologists working for Pacific Public Health Surveillance Network partners. The programme consisted of five courses: four one-week classroom-based courses and one field epidemiology project. Sessions were structured so that theoretical understanding was achieved through interaction and reinforced through practical hands-on group activities, case studies and other interactive practical learning methods. **OUTCOME:** As of September 2016, 258 students had commenced the programme. Twenty-six course workshops were delivered and one cohort of students had completed the full five-course programme. The programme proved popular and gained a high level of student engagement. **DISCUSSION:** Face-to-face delivery, a low student-to-facilitator ratio, substantial group work and practical exercises were identified as key factors that contributed to the students developing skills and confidence. Close engagement of leaders and the need to quickly evaluate and adapt the curriculum were important lessons, and the collaboration between external partners was considered important for promoting a harmonized approach to health needs in the Pacific.

- 59 **Hudjashov G, Karafet TM, Lawson DJ, Downey S, Savina O, Sudoyo H, Lansing JS, Hammer MF, Cox MP.**

Complex patterns of admixture across the Indonesian Archipelago.

*Mol Biol Evol* 2017 Oct 1;34(10):2439-2452. doi: 10.1093/molbev/msx196.

Indonesia, an island nation as large as continental Europe, hosts a sizeable proportion of global human diversity, yet remains surprisingly undercharacterized genetically. Here, we substantially expand on existing studies by reporting genome-scale data for nearly 500 individuals from 25 populations in Island Southeast Asia, New Guinea, and Oceania, notably including previously unsampled islands across the Indonesian archipelago. We use high-resolution analyses of haplotype diversity to reveal fine detail of regional admixture patterns, with a particular focus on the Holocene. We find that recent population history within Indonesia is complex, and that populations from the Philippines made important genetic contributions in the early phases of the Austronesian expansion. Different, but interrelated processes, acted in the east and west. The Austronesian migration took several centuries to spread across the eastern part of the archipelago, where genetic admixture postdates the archeological signal. As with the Neolithic expansion further east in Oceania and in Europe, genetic mixing with local inhabitants in eastern Indonesia lagged behind the arrival of farming populations. In contrast, western Indonesia has a more complicated admixture history shaped by interactions with mainland Asian and Austronesian

newcomers, which for some populations occurred more than once. Another layer of complexity in the west was introduced by genetic contact with South Asia and strong demographic events in isolated local groups.

- 60 **Inoue Y, Takahashi D, Kondo N, Yoshii A, Sekihara M, Hombhanje FW, Tsukahara T.**

Village health volunteers' individual social capital and caretakers' health service utilization for febrile children in malaria-endemic villages in Papua New Guinea.

*Trans R Soc Trop Med Hyg* 2017 Nov 1;111(11):490-496. doi: 10.1093/trstmh/try003.

**Background:** Little is known about the association between the social capital of village health volunteers (VHVs) and their performance in relation to malarial care. **Methods:** Data came from 337 children and 13 VHVs working in Dagua, Papua New Guinea. The outcome variable was whether caretakers brought their children to health care services on the incidence of a febrile episode. The social capital of VHVs was assessed by inquiring about relationships with people in 25 social positions/roles. **Results:** Caretakers were more likely to bring their febrile children to health care services when they lived in a village whose VHVs frequently discussed their activities with people in positions/roles outside their village (prevalence ratio [PR] = 1.47 [95% confidence interval {CI} 1.22 to 1.78]). On the other hand, caretakers were less likely to do so when their VHVs had known people in informal positions/roles inside their village (PR = 0.85 [95% CI 0.77 to 0.93]) and when they discussed their activities with people in formal positions/roles inside their village (PR = 0.76 [95% CI 0.61 to 0.95]). **Conclusions:** Our results suggest that the social interactions of VHVs with people in positions/roles outside the village may benefit residents while those with people in positions/roles inside the village might not necessarily benefit them.

- 61 **Irvine MA, Kazura JW, Hollingsworth TD, Reimer LJ.**

Understanding heterogeneities in mosquito-bite exposure and infection distributions for the elimination of lymphatic filariasis.

*Proc Biol Sci* 2018 Jan 31;285(1871). pii: 20172253. doi: 10.1098/rspb.2017.2253.

It is well known that individuals in the same community can be exposed to a highly variable number of mosquito bites. This heterogeneity in bite exposure has consequences for the control of vector-borne diseases because a few people may be contributing significantly to transmission. However, very few studies measure sources of heterogeneity in a way which is relevant to decision-making. We investigate the relationship between two classic measures of heterogeneity, spatial and individual, within the context of lymphatic filariasis, a parasitic mosquito-borne disease. Using infection and mosquito-bite data for five villages in Papua New Guinea, we measure biting characteristics to model what impact bed-nets have had on control of the disease. We combine this analysis with geospatial modelling to understand the spatial relationship between disease indicators and nightly mosquito bites. We found a weak association between biting and infection heterogeneity within villages. The introduction of bed-nets increased biting heterogeneity, but the reduction in mean

biting more than compensated for this, by reducing prevalence closer to elimination thresholds. Nightly biting was explained by a spatial heterogeneity model, while parasite load was better explained by an individual heterogeneity model. Spatial and individual heterogeneity are qualitatively different with profoundly different policy implications.

- 62 **Issiki M, Naka I, Kimura R, Furusawa T, Natsuhara K, Yamauchi T, Nakazawa M, Ishida T, Ohtsuka R, Ohashi J.**

Mitochondrial DNA variations in Austronesian-speaking populations living in the New Georgia Islands, the Western Province of the Solomon Islands.

*J Hum Genet* 2018 Jan;63(1):101-104. doi: 10.1038/s10038-017-0372-0. Epub 2017 Nov 13.

Modern Austronesian (AN)-speaking Melanesians are considered to be derived from the admixture of indigenous non-Austronesian (NAN)-speaking people and AN-speaking people from Southeast Asia. In this study, we analyzed mitochondrial DNA (mtDNA) variations in the D-loop region for two AN-speaking Melanesian populations (Munda and Kusaghe) and an AN-speaking Micronesian population (Rawaki) in the New Georgia Islands, the Western Province of the Solomon Islands to examine their genetic similarities to AN-speaking Polynesians in Tonga and NAN-speaking Melanesians, Gidra, in Papua New Guinea. The 'Polynesian motif', which is a well-characterized mtDNA marker for Polynesians, was frequently observed in Munda and Kusaghe. Of particular interest, haplogroup E1a2+16261, which has been rarely observed in the Solomon Islands, accounted for 12.8% in Kusaghe. It has been reported that the haplogroup E1a2 arose in Island Southeast Asia (ISEA) 9400 ± 2850 years ago. Phylogenetic and principal component analyses for 24 Oceanian populations revealed that Munda and Kusaghe populations were genetically close to the Tongan population, but not to Gidra. Rawaki population showed no apparent genetic similarities to populations of Tonga and Gidra. Our results suggest that considerable gene flow from AN-speaking populations originating from Southeast Asia to indigenous Melanesians occurred in the New Georgia Islands.

- 63 **Jewkes R, Fulu E, Tabassam Naved R, Chirwa E, Dunkle K, Haardörfer R, Garcia-Moreno C; UN Multi-country Study on Men and Violence Study Team.**

Women's and men's reports of past-year prevalence of intimate partner violence and rape and women's risk factors for intimate partner violence: a multicountry cross-sectional study in Asia and the Pacific.

*PLoS Med* 2017 Sep 5;14(9):e1002381. doi: 10.1371/journal.pmed.1002381. eCollection 2017 Sep.

**BACKGROUND:** Understanding the past-year prevalence of male-perpetrated intimate partner violence (IPV) and risk factors is essential for building evidence-based prevention and monitoring progress to Sustainable Development Goal (SDG) 5.2, but so far, population-based research on this remains very limited. The objective of this study is to compare the population prevalence rates of past-year male-perpetrated IPV and nonpartner rape from women's and men's reports across 4 countries

in Asia and the Pacific. A further objective is to describe the risk factors associated with women's experience of past-year physical or sexual IPV from women's reports and factors driving women's past-year experience of partner violence. **METHODS AND FINDINGS:** This paper presents findings from the United Nations Multi-country Study on Men and Violence in Asia and the Pacific. In the course of this study, in population-based cross-sectional surveys, 5,206 men and 3,106 women aged 18-49 years were interviewed from 4 countries: Cambodia, China, Papua New Guinea (PNG), and Sri Lanka. To measure risk factors, we use logistic regression and structural equation modelling to show pathways and mediators. The analysis was not based on a written plan, and following a reviewer's comments, some material was moved to supplementary files and the regression was performed without variable elimination. Men reported more lifetime perpetration of IPV (physical or sexual IPV range 32.5%-80%) than women did experience (physical or sexual IPV range 27.5%-67.4%), but women's reports of past-year experience (physical or sexual IPV range 8.2%-32.1%) were not very clearly different from men's (physical or sexual IPV range 10.1%-34.0%). Women reported much more emotional/economic abuse (past-year ranges 1.4%-5.7% for men and 4.1%-27.7% for women). Reports of nonpartner rape were similar for men (range 0.8%-1.9% in the past year) and women (range 0.4%-2.3% in past year), except in Bougainville, where they were higher for men (11.7% versus 5.7%). The risk factor modeling shows 4 groups of variables to be important in experience of past-year sexual and/or physical IPV: (1) poverty, (2) all childhood trauma, (3) quarrelling and women's limited control in relationships, and (4) partner factors (substance abuse, unemployment, and infidelity). The population attributable fraction (PAF) was largest for quarrelling often, but the second greatest PAF was for the group related to exposure to violence in childhood. The relationship control variable group had the third highest PAF, followed by other partner factors. Currently married women were also more at risk. In the structural model, a resilience pathway showed less poverty, higher education, and more gender-equitable ideas were connected and conveyed protection from IPV. These are all amenable risk factors. This research was cross-sectional, so we cannot be sure of the temporal sequence of exposure, but the outcome being a past-year measure to some extent mitigates this problem. **CONCLUSIONS:** Past-year IPV indicators based on women's reported experience that were developed to track SDG 5 are probably reasonably reliable but will not always give the same prevalence as may be reported by men. Report validity requires further research. Interviews with men to track past-year nonpartner rape perpetration are feasible and important. The findings suggest a range of factors are associated with past-year physical and/or sexual IPV exposure; of particular interest is the resilience pathway suggested by the structural model, which is highly amenable to intervention and explains why combining economic empowerment of women and gender empowerment/relationship skills training has been successful. This study provides additional rationale for scaling up violence prevention interventions that combine economic and gender empowerment/relationship skills building of women, as well as the value of investing in girls' education with a view to long-term

violence reduction.

64 **Jewkes R, Jama-Shai N, Sikweyiya Y.**

Enduring impact of conflict on mental health and gender-based violence perpetration in Bougainville, Papua New Guinea: a cross-sectional study. *PLoS One* 2017 Oct 25;12(10):e0186062. doi: 10.1371/journal.pone.0186062. eCollection 2017.

**BACKGROUND:** Violence against women is often exacerbated by war, but most civilian research has investigated short term impact. We describe the conflict experiences of men and women from the general population of Bougainville, Papua New Guinea, perceptions of the enduring impact of conflict, and the associations between these and the major health and development problems on the islands: mental ill-health and violence against women. **METHODS:** Fourteen years after the end of the decade long civil war, we conducted a household survey with a random sample of adult (n = 864) men and (n = 879) women living in Bougainville. The interviews were mostly conducted face-to-face, with very sensitive questions self-completed. **RESULTS:** Mental ill-health was highly prevalent, 37.8% of women and 32% of men had high levels of depressive symptomatology, 34.4% of men abused alcohol and 15.1% of women and 24.6% of men had high levels of PTSD symptoms. Among women, 23.3% had been raped in the year prior to the interview and 33.3% had experience physical or sexual partner violence. The prevalence of exposure to trauma during the civil war was very high and many of the men and women experienced lingering impact of conflict. Multiple logistic regression models showed that war trauma was associated with PTSD symptoms in women and PTSD symptoms, alcohol abuse and depressive symptoms in men. The perceived enduring impact of conflict was associated with depressive symptoms in men and women, problem drinking and suicidal thoughts in women and drug use in men. The perceived enduring conflict impact was associated with perpetration of past-year rape and physical and/or sexual partner violence. **DISCUSSION:** The Bougainville civil war had a devastating impact on the population's lives. Reversing this legacy is essential but requires addressing what is perceived as the enduring social, economic and psychological impact of the conflict and a major focus on prevention of violence against women.

65 **Kamblijambi JK, Holroyd E.**

Papua New Guinea midwives' perspectives of the effect of a targeted village birth attendant education program. *Midwifery* 2017 Sep;52:11-18. doi: 10.1016/j.midw.2017.04.007. Epub 2017 Apr 23.

66 **Karimkhani C, Colombara DV, Drucker AM, Norton SA, Hay R, Engelman D, Steer A, Whitfield M, Naghavi M, Dellavalle RP.**

The global burden of scabies: a cross-sectional analysis from the Global Burden of Disease Study 2015. *Lancet Infect Dis* 2017 Dec;17(12):1247-1254. doi: 10.1016/S1473-3099(17)30483-8. Epub 2017 Sep 21.

**BACKGROUND:** Numerous population-based studies have documented high prevalence of scabies in overcrowded settings, particularly among children and in tropical regions. We provide an estimate of the global burden of scabies using

data from the Global Burden of Disease (GBD) Study 2015. **METHODS:** We identified scabies epidemiological data sources from an extensive literature search and hospital insurance data and analysed data sources with a Bayesian meta-regression modelling tool, DisMod-MR 2.1, to yield prevalence estimates. We combined prevalence estimates with a disability weight, measuring disfigurement, itch, and pain caused by scabies, to produce years lived with disability (YLDs). With an assumed zero mortality from scabies, YLDs were equivalent to disability-adjusted life-years (DALYs). We estimated DALYs for 195 countries divided into 21 world regions, in both sexes and 20 age groups, between 1990 and 2015. **FINDINGS:** Scabies was responsible for 0.21% of DALYs from all conditions studied by GBD 2015 worldwide. The world regions of east Asia (age-standardised DALYs 136.32), southeast Asia (134.57), Oceania (120.34), tropical Latin America (99.94), and south Asia (69.41) had the greatest burden of DALYs from scabies. Mean percent change of DALY rate from 1990 to 2015 was less than 8% in all world regions, except North America, which had a 23.9% increase. The five individual countries with greatest scabies burden were Indonesia (age-standardised DALYs 153.86), China (138.25), Timor-Leste (136.67), Vanuatu (131.59), and Fiji (130.91). The largest standard deviations of age-standardised DALYs between the 20 age groups were observed in southeast Asia (60.1), Oceania (58.3), and east Asia (56.5), with the greatest DALY burdens in children, adolescents, and the elderly. **INTERPRETATION:** The burden of scabies is greater in tropical regions, especially in children, adolescents, and elderly people. As a worldwide epidemiological assessment, GBD 2015 provides broad and frequently updated measures of scabies burden in terms of skin effects. These global data might help guide research protocols and prioritisation efforts and focus scabies treatment and control measures.

67 **Kasa Tom S, Welch H, Kilalang C, Tefuarani N, Vince J, Lavu E, Johnson K, Magaye R, Duke T.**

Evaluation of Xpert MTB/RIF assay in children with presumed pulmonary tuberculosis in Papua New Guinea.

*Paediatr Int Child Health* 2018 May;38(2):97-105. doi: 10.1080/20469047.2017.1319898. Epub 2017 May 11.

**BACKGROUND:** The Gene Xpert MTB/RIF assay (Xpert) is used for rapid, simultaneous detection of *Mycobacterium tuberculosis* (MTB) and rifampicin resistance. This study examined the accuracy of Xpert in children with suspected pulmonary tuberculosis (PTB). **METHODS:** Children admitted to Port Moresby General Hospital with suspected PTB were prospectively enrolled between September 2014 and March 2015. They were classified into probable, possible and TB-unlikely groups. Sputum or gastric aspirates were tested by Xpert and smear microscopy; mycobacterial culture was undertaken on a subset. Children were diagnosed with TB on the basis of standard criteria which were used as the primary reference standard. Xpert, smear for acid-fast bacilli (AFB) and the Edwards TB score were compared with the primary reference standard. **RESULTS:** A total of 93 children  $\leq 14$  years with suspected PTB were enrolled; 67 (72%) were classified as probable, 21 (22%) possible and 5 (5.4%) TB-unlikely. Eighty



were treated for TB based on the primary reference standard. Xpert was positive in 26/93 (28%) MTB cases overall, including 22/67 (33%) with probable TB and 4/21 (19%) with possible TB. Three (13%) samples identified rifampicin resistance. Xpert confirmed more cases of TB than AFB smear (26 vs 13,  $p = 0.019$ ). The sensitivity of Xpert, AFB smear and an Edwards TB score of  $\geq 7$  was 31% (25/80), 16% (13/80) and 90% (72/80), respectively, and the specificity was 92% (12/13), 100% (13/13) and 31% (4/13), respectively, when compared with the primary reference standard. **CONCLUSION:** Xpert sensitivity is sub-optimal and cannot be relied upon for diagnosing TB, although a positive result is confirmatory. A detailed history and examination, standardised clinical criteria, radiographs and available tests remain the most appropriate way of diagnosing TB in children in resource-limited countries. Xpert helps confirm PTB better than AFB smear, and identifies rifampicin resistance. Practical guidelines should be used to identify children who will benefit from an Xpert assay.

- 68 **Kaspar A, Kei J, Driscoll C, Swanepoel W, Goulios H.**

A public health approach to pediatric hearing impairment in the Pacific Islands. *J Glob Health* 2018 Jun;8(1):010302. doi: 10.7189/jogh.08.010302.

- 69 **Kaspar A, Newton O, Kei J, Driscoll C, Swanepoel W, Goulios H.**

Parental knowledge and attitudes to childhood hearing loss and hearing services in the Solomon Islands.

*Int J Pediatr Otorhinolaryngol* 2017 Dec;103:87-92. doi: 10.1016/j.ijporl.2017.10.003. Epub 2017 Oct 5.

**OBJECTIVE:** An understanding of parental knowledge and attitudes towards childhood hearing loss is essential to the successful implementation of audiology services. The present study aimed to investigate parental knowledge and attitudes among parents in the Solomon Islands. **METHODS AND MATERIALS:** A total of 100 mothers and 50 fathers were administered a questionnaire via semi-structured interviews. **RESULTS:** Highest parental awareness of aetiology of childhood hearing loss was noted for otitis media (94%), noise exposure (87.3%), and family history (72.7%). The highest parental awareness concerning public health initiatives to reduce/prevent otitis media was noted for routine childhood immunizations (84%) and breast-feeding (76%). Higher rates of knowledge in fathers than in mothers included otitis media ( $p = 0.038$ ), noise exposure ( $p = 0.007$ ), and breast-feeding ( $p = 0.031$ ). Approximately half of parents (56%) agreed that curses may cause hearing loss. Overall parental responses showed positive support for infant hearing screening programs (96%) and school-based ear and hearing health examinations (99.3%). **CONCLUSIONS:** High levels of parental readiness and support for childhood hearing services in the Solomon Islands was evident. Knowledge of aetiology of childhood hearing loss was highest for otitis media, noise exposure, and family history. Knowledge and attitudes of fathers to childhood hearing loss and hearing services was either the same or better than that of mothers.

- 70 **Kluckow H, Panisi L, Larui J, Jatobatu A, Kim D, Hodges L, Black Kl.**

Socio-demographic predictors of unintended pregnancy and late antenatal booking in Honiara, Solomon Islands.

*Aust NZ J Obstet Gynaecol* 2018 Jun;58(3):349-357. doi: 10.1111/ajo.12782. Epub 2018 Jan 31.

**BACKGROUND:** The Solomon Islands is a Pacific nation with a maternal mortality of 114 per 100,000 births. Around 57% of pregnancies are unintended and only 15% of women attend their first antenatal visit in the first 12 weeks as recommended by the World Health Organization. **AIMS:** We sought to examine the socio-demographic predictors of unintended pregnancy and late antenatal booking (>18 weeks) among women attending antenatal care in Honiara. **MATERIALS AND METHODS:** From January 2014 to May 2015 we undertook a cross-sectional survey using a structured questionnaire on women presenting to the National Referral Hospital and community clinics in Honiara for antenatal care. **RESULTS:** Of 1441 women, 41.0% of pregnancies were intended, 55.7% were ambivalent and 3.3% were fully unintended. Unintended pregnancy was significantly associated with being unemployed (adjusted odds ratio (aOR) 1.45,  $p = 0.024$ ), being a teenager at first intercourse (aOR 1.53,  $p = 0.004$ ), shared family planning decision making (aOR 0.54,  $p = 0.006$ ), living with a husband (aOR 0.31,  $p < 0.001$ ) and a short interpregnancy interval (OR 4.48,  $p \leq 0.001$ ). Late booking occurred in 1168 (84.7%) women and independent predictors of this included ambivalent or unintended pregnancy (aOR 1.74,  $p = 0.005$ ) and multiparity (aOR 2.05,  $p = 0.001$ ). **CONCLUSIONS:** Unintended pregnancy and late antenatal booking remain a challenge to improving maternal health in the Solomon Islands. Investments in family planning could target reproductive health education and post-partum family planning. Improving the quality of antenatal care as well as addressing social determinants of health, including gender equity, education and employment of women, is required if maternal mortality is to be reduced.

- 71 **Koepfli C, Ome-Kaius M, Jally S, Malau E, Maripal S, Ginny J, Timinao L, Kattenberg JH, Obadia T, White M, Rarau P, Senn N, Barry AE, Kazura JW, Mueller I, Robinson LJ.**

Sustained malaria control over an 8-year period in Papua New Guinea: the challenge of low-density asymptomatic *Plasmodium* infections.

*J Infect Dis* 2017 Dec 12;216(11):1434-1443. doi: 10.1093/infdis/jix507.

**Background:** The scale-up of effective malaria control in the last decade has resulted in a substantial decline in the incidence of clinical malaria in many countries. The effects on the proportions of asymptomatic and submicroscopic infections and on transmission potential are yet poorly understood. **Methods:** In Papua New Guinea, vector control has been intensified since 2008, and improved diagnosis and treatment was introduced in 2012. Cross-sectional surveys were conducted in Madang Province in 2006 (with 1280 survey participants), 2010 (with 2117 participants), and 2014 (with 2516 participants). Infections were quantified by highly sensitive quantitative polymerase chain reaction (PCR) analysis, and gametocytes were quantified by reverse-transcription qPCR analysis. **Results:** *Plasmodium falciparum* prevalence determined by qPCR decreased from 42% in 2006 to 9% in 2014. The *P. vivax* prevalence decreased from 42% in



2006 to 13% in 2010 but then increased to 20% in 2014. Parasite densities decreased 5-fold from 2006 to 2010; 72% of *P. falciparum* and 87% of *P. vivax* infections were submicroscopic in 2014. Gametocyte density and positivity correlated closely with parasitemia, and population gametocyte prevalence decreased 3-fold for *P. falciparum* and 29% for *P. vivax* from 2010 to 2014. **Conclusions:** Sustained control has resulted in reduced malaria transmission potential, but an increasing proportion of gametocyte carriers are asymptomatic and submicroscopic and represent a challenge to malaria control.

- 72 **Kohl C, Tachedjian M, Todd S, Monaghan P, Boyd V, Marsh GA, Cramer G, Field H, Kurth A, Smith I, Wang LF.**

Hervey virus: study on co-circulation with Henipaviruses in pteropid bats within their distribution range from Australia to Africa.

*PLoS One* 2018 Feb 1;13(2):e0191933. doi: 10.1371/journal.pone.0191933. eCollection 2018.

In 2011, an unusually large number of independent Hendra virus outbreaks were recorded on horse properties in Queensland and New South Wales, Australia. Urine from bat colonies adjacent to the outbreak sites were sampled and screened for Hendra and other viruses. Several novel paramyxoviruses were also isolated at different locations. Here one of the novel viruses, named Hervey virus (HerPV), is fully characterized by genome sequencing, annotation, phylogeny and in vitro host range, and its serological cross-reactivity and neutralization patterns are examined. HerPV may have ecological and spatial and temporal patterns similar to Hendra virus and could serve as a sentinel virus for the surveillance of this highly pathogenic virus. The suitability of HerPV as potential sentinel virus is further assessed by determining the serological prevalence of HerPV antibodies in fruit-eating bats from Australia, Indonesia, Papua New Guinea, Tanzania and the Gulf of Guinea, indicating the presence of similar viruses in regions beyond the Australian border.

- 73 **Koimbu G, Czeher C, Katusele M, Sakur M, Kilepak L, Tandrapah A, Hetzel MW, Pulford J, Robinson L, Karl S.**

Status of insecticide resistance in Papua New Guinea: an update from nation-wide monitoring of *Anopheles* mosquitoes.

*Am J Trop Med Hyg* 2018 Jan;98(1):162-165. doi: 10.4269/ajtmh.17-0454. Epub 2018 Jan 1.

Insecticide resistance (IR) monitoring is an important component of vector-borne disease control. The last assessment of IR in Papua New Guinea (PNG) was conducted in 2010. Since then, vector populations have been exposed to higher levels of pyrethroids with the continued nation-wide distribution of insecticide-treated nets. Here, we provide an update on phenotypic IR in four highly malaria-endemic areas of PNG. IR against deltamethrin, lambda-cyhalothrin, and dichlorodiphenyltrichloroethane was assessed using World Health Organization bioassays. A total of 108 bioassays for each insecticide were conducted screening 2,290 adult female anopheline mosquitoes. No phenotypic resistance was observed. Bioassay parameters agreed well with those observed in other studies that used the same assays and insecticides. These results indicate that the three tested insecticides are still universally

effective in PNG. Continued IR monitoring (every 1-2 years) in PNG is recommended to detect reduced susceptibility early and adjust guidelines to prevent widespread resistance.

- 74 **Kuzma J, Hombhanje F.**

Chronic osteomyelitis – bacterial flora, antibiotic sensitivity and treatment challenges.

*Open Orthop J* 2018 Mar 30;12:153-163. doi: 10.2174/1874325001812010153. eCollection 2018.

**Background:** Chronic osteomyelitis is a catastrophic sequel of delayed diagnosis of acute osteomyelitis. **Objectives:** The objectives of the study were to determine bacterial flora and antibiotic sensitivity, and to evaluate the outcome of an aggressive surgical approach to chronic osteomyelitis. **Methods:** This is a single surgeon, prospective cohort study on 30 consecutive patients with clinically and radiologically diagnosed chronic osteomyelitis presented to a hospital. We prospectively recorded demographic, clinical and radiological features, treatment protocol, and microbiologic results of culture and sensitivity. The main treatment outcome measures were clinical signs of eradication of infection. **Results:** Microbiologic results showed that Gram-negative and mixed flora accounts for more than half of chronic osteomyelitis cases while *Staphylococcus aureus* was a dominating single pathogen (39%). We detected a high resistance rate to common antibiotics, eg, 83% of *S. aureus* isolates were resistant to oxacillin (MRSA). The mean duration of bone infection was 4.2 years (3 months to 30 years) and the mean number of operations was 1.5 (1-5). The mean follow-up was 15 months (12-18 months). Infection was eradicated in 95% (21 out of 22) treated by a single procedure and in all patients (n = 8) by double procedure. **Conclusion:** The high rate of MRSA strains is alarming and calls for updating of the antibiotic therapy guidelines in the country. Good results in treatment of chronic osteomyelitis can be achieved by a single-stage protocol including radical debridement combined with systemic and topical antibiotics.

- 75 **Laman M, Greenhill A, Coombs GW, Robinson O, Pearson J, Davis TME, Manning L.**

Methicillin-resistant *Staphylococcus aureus* in Papua New Guinea: a community nasal colonization prevalence study.

*Trans R Soc Trop Med Hyg* 2017 Aug 1;111(8):360-362. doi: 10.1093/trstmh/trx061.

**Background:** There are few epidemiological data available to inform a national response to community-acquired methicillin-resistant *Staphylococcus aureus* (MRSA) in Papua New Guinea (PNG). **Methods:** We performed a cross-sectional survey to determine the pattern of MRSA nasal colonization and the diversity of circulating MRSA clones among adults and adolescents in Madang Province, PNG. **Results:** *S. aureus* nasal colonization was confirmed in 44 (17.1%) of 257 participants. Four (9.1%) isolates were methicillin resistant. Resistance to other antimicrobial agents was uncommon. Detailed molecular typing of three MRSA isolates demonstrated multiple MRSA clones in this community, of which two carried the Panton-Valentin leukocidin-associated virulence genes. **Conclusions:** MRSA is likely to account for a clinically important proportion of staphylococcal disease in PNG. There are multiple MRSA clones

in PNG. Ongoing surveillance of community and invasive isolates is a critical component of an effective response to the challenge of community-acquired MRSA in this and many other resource-limited contexts.

- 76 **Lang T, Lee JPW, Elgass K, Pinar AA, Tate MD, Aitken EH, Fan H, Creed SJ, Deen NS, Traore DAK, Mueller I, Stanisic D, Baiwog FS, Skene C, Wilce MCJ, Mansell A, Morand EF, Harris J.** Macrophage migration inhibitory factor is required for NLRP3 inflammasome activation. *Nat Commun* 2018 Jun 8;9(1):2223. doi: 10.1038/s41467-018-04581-2.

Macrophage migration inhibitory factor (MIF) exerts multiple effects on immune cells, as well as having functions outside the immune system. MIF can promote inflammation through the induction of other cytokines, including TNF, IL-6, and IL-1 family cytokines. Here, we show that inhibition of MIF regulates the release of IL-1 $\alpha$ , IL-1 $\beta$ , and IL-18, not by affecting transcription or translation of these cytokines, but via activation of the NLRP3 inflammasome. MIF is required for the interaction between NLRP3 and the intermediate filament protein vimentin, which is critical for NLRP3 activation. Further, we demonstrate that MIF interacts with NLRP3, indicating a role for MIF in inflammasome activation independent of its role as a cytokine. These data advance our understanding of how MIF regulates inflammation and identify it as a factor critical for NLRP3 inflammasome activation.

- 77 **Larson LM, Namaste SM, Williams AM, Engle-Stone R, Addo OY, Suchdev PS, Wirth JP, Temple V, Sordula M, Northrop-Clewes CA.**

Adjusting retinol-binding protein concentrations for inflammation: Biomarkers Reflecting Inflammation and Nutritional Determinants of Anemia (BRINDA) project.

*Am J Clin Nutr* 2017 Jul;106(Suppl 1):390S-401S. doi: 10.3945/ajcn.116.142166. Epub 2017 Jun 14.

**Background:** The accurate estimation of the prevalence of vitamin A deficiency (VAD) is important in planning and implementing interventions. Retinol-binding protein (RBP) is often used in population surveys to measure vitamin A status, but its interpretation is challenging in settings where inflammation is common because RBP concentrations decrease during the acute-phase response. **Objectives:** We aimed to assess the relation between RBP concentrations and inflammation and malaria in preschool children (PSC) (age range: 6-59 mo) and women of reproductive age (WRA) (age range: 15-49 y) and to investigate adjustment algorithms to account for these effects. **Design:** Cross-sectional data from 8 surveys for PSC (n = 8803) and 4 surveys for WRA (n = 4191) from the Biomarkers Reflecting Inflammation and Nutritional Determinants of Anemia (BRINDA) project were analyzed individually and combined with the use of a meta-analysis. Several approaches were explored to adjust RBP concentrations in PSC in inflammation and malaria settings as follows: 1) the exclusion of subjects with C-reactive protein (CRP) concentrations >5 mg/L or  $\alpha$ -1-acid glycoprotein (AGP) concentrations >1 g/L, 2) the application of arithmetic correction factors, and 3) the use of a regression correction approach. The impact of adjustment on the estimated prevalence of VAD (defined as <0.7  $\mu$ mol/L) was

examined in PSC. **Results:** The relation between estimated VAD and CRP and AGP deciles followed a linear pattern in PSC. In women, the correlations between RBP and CRP and AGP were too weak to justify adjustments for inflammation. Depending on the approach used to adjust for inflammation (CRP+AGP), the estimated prevalence of VAD decreased by a median of 11-18 percentage points in PSC compared with unadjusted values. There was no added effect of adjusting for malaria on the estimated VAD after adjusting for CRP and AGP. **Conclusions:** The use of a regression correction (derived from internal data) which accounts for the severity of inflammation to estimate the prevalence of VAD in PSC in regions with inflammation and malaria is supported by the analysis of the BRINDA data. These findings contribute to the evidence on adjusting for inflammation when estimating VAD with the use of RBP.

- 78 **Lehmann D, Kirarock W, van den Biggelaar AHJ, Passey M, Jacoby P, Saleu G, Masiria G, Nivio B, Greenhill A, Orami T, Francis J, Ford R, Kirkham LA, Solomon V, Richmond PC, Pomat WS; 10v13v PCV trial team.**

Rationale and methods of a randomized controlled trial of immunogenicity, safety and impact on carriage of pneumococcal conjugate and polysaccharide vaccines in infants in Papua New Guinea.

*Pneumonia (Nathan)* 2017 Dec 25;9:20. doi: 10.1186/s41479-017-0044-z. eCollection 2017.

**Background:** Children in third-world settings including Papua New Guinea (PNG) experience early onset of carriage with a broad range of pneumococcal serotypes, resulting in a high incidence of severe pneumococcal disease and deaths in the first 2 years of life. Vaccination trials in high endemicity settings are needed to provide evidence and guidance on optimal strategies to protect children in these settings against pneumococcal infections.

**Methods:** This report describes the rationale, objectives, methods, study population, follow-up and specimen collection for a vaccination trial conducted in an endemic and logistically challenging setting in PNG. The trial aimed to determine whether currently available pneumococcal conjugate vaccines (PCV) are suitable for use under PNG's accelerated immunization schedule, and that a schedule including pneumococcal polysaccharide vaccine (PPV) in later infancy is safe and immunogenic in this high-risk population. **Results:** This open randomized-controlled trial was conducted between November 2011 and March 2016, enrolling 262 children aged 1 month between November 2011 and April 2014. The participants were randomly allocated (1:1) to receive 10-valent PCV (10vPCV) or 13-valent PCV (13vPCV) in a 1-2-3-month schedule, with further randomization to receive PPV or no PPV at age 9 months, followed by a 1/5th PPV challenge at age 23 months. A total of 1229 blood samples were collected to measure humoral and cellular immune responses and 1238 nasopharyngeal swabs to assess upper respiratory tract colonization and carriage load. Serious adverse events were monitored throughout the study. Of the 262 children enrolled, 87% received 3 doses of PCV, 79% were randomized to receive PPV or no PPV at age 9 months, and 67% completed the study at 24 months of age with appropriate immunization and challenge. **Conclusion:** Laboratory testing of the many samples collected during this trial will determine the impact of

the different vaccine schedules and formulations on nasopharyngeal carriage, antibody production and function, and immune memory. The final data will inform policy on pneumococcal vaccine schedules in countries with children at high risk of pneumococcal disease by providing direct comparison of an accelerated schedule of 10vPCV and 13vPCV and the potential advantages of PPV following PCV immunization. *Trial registration:* ClinicalTrials.gov CTN NCT01619462, retrospectively registered on May 28, 2012.

- 79 **Lerch A, Koepfli C, Hofmann NE, Messerli C, Wilcox S, Kattenberg JH, Betuela I, O'Connor L, Mueller I, Felger I.**

Development of amplicon deep sequencing markers and data analysis pipeline for genotyping multi-clonal malaria infections.

*BMC Genomics* 2017 Nov 13;18(1):864. doi: 10.1186/s12864-017-4260-y.

**BACKGROUND:** Amplicon deep sequencing permits sensitive detection of minority clones and improves discriminatory power for genotyping multi-clone *Plasmodium falciparum* infections. New amplicon sequencing and data analysis protocols are needed for genotyping in epidemiological studies and drug efficacy trials of *P. falciparum*. **METHODS:** Targeted sequencing of molecular marker csp and novel marker cpm was conducted in duplicate on mixtures of parasite culture strains and 37 field samples. A protocol allowing to multiplex up to 384 samples in a single sequencing run was applied. Software "HaplotypR" was developed for data analysis. **RESULTS:** Cpm was highly diverse ( $H_e = 0.96$ ) in contrast to csp ( $H_e = 0.57$ ). Minority clones were robustly detected if their frequency was  $>1\%$ . False haplotype calls owing to sequencing errors were observed below that threshold. **CONCLUSIONS:** To reliably detect haplotypes at very low frequencies, experiments are best performed in duplicate and should aim for coverage of  $>10,000$  reads/amplicon. When compared to length polymorphic marker msp2, highly multiplexed amplicon sequencing displayed greater sensitivity in detecting minority clones.

- 80 **Lipson M, Skoglund P, Spriggs M, Valentin F, Bedford S, Shing R, Buckley H, Phillip I, Ward GK, Mallick S, Rohland N, Broomandkhoshbacht N, Cheronet O, Ferry M, Harper TK, Michel M, Oppenheimer J, Sirak K, Stewardson K, Auckland K, Hill AVS, Maitland K, Oppenheimer SJ, Parks T, Robson K, Williams TN, Kennett DJ, Mentzer AJ, Pinhasi R, Reich D.**

Population turnover in Remote Oceania shortly after initial settlement.

*Curr Biol* 2018 Apr 2;28(7):1157-1165.e7. doi: 10.1016/j.cub.2018.02.051. Epub 2018 Feb 28.

Ancient DNA from Vanuatu and Tonga dating to about 2900-2600 years ago (before present, BP) has revealed that the 'First Remote Oceanian' people associated with the Lapita archaeological culture were directly descended from the population that, beginning around 5000 BP, spread Austronesian languages from Taiwan to the Philippines, western Melanesia, and eventually Remote Oceania. Thus, ancestors of the First Remote Oceanians must have passed by the Papuan-ancestry populations they encountered in New Guinea, the Bismarck Archipelago, and the Solomon Islands with minimal admixture. However, all present-day populations in

Near and Remote Oceania harbor  $>25\%$  Papuan ancestry, implying that additional eastward migration must have occurred. We generated genome-wide data for 14 ancient individuals from Efate and Epi Islands in Vanuatu from 2900-150 BP, as well as 185 present-day individuals from 18 islands. We find that people of almost entirely Papuan ancestry arrived in Vanuatu by around 2300 BP, most likely reflecting migrations a few hundred years earlier at the end of the Lapita period, when there is also evidence of changes in skeletal morphology and cessation of long-distance trade between Near and Remote Oceania. Papuan ancestry was subsequently diluted through admixture but remains at least 80%-90% in most islands. Through a fine-grained analysis of ancestry profiles, we show that the Papuan ancestry in Vanuatu derives from the Bismarck Archipelago rather than the geographically closer Solomon Islands. However, the Papuan ancestry in Polynesia – the most remote Pacific islands – derives from different sources, documenting a third stream of migration from Near to Remote Oceania.

- 81 **Lombardo P, Vaucher P, Rarau P, Mueller I, Favrat B, Senn N.**

Hemoglobin levels and the risk of malaria in Papua New Guinean infants: a nested cohort study.

*Am J Trop Med Hyg* 2017 Dec;97(6):1770-1776. doi: 10.4269/ajtmh.17-0093. Epub 2017 Sep 21.

Studies are available that assess the risk of malaria in accordance to the body's iron store and the systematic iron supplementation of preschool children. However, only a few studies evaluated the temporal association between hemoglobin and malaria and their results are opposing. A total of 1,650 3-month-old Papua New Guinean infants were enrolled in this study and followed-up for 12 months. The risk of malaria was assessed in all children every 3 months and with each episode of fever. The incidence of clinical malaria between 3 and 15 months of age was 249 cases per 1,000 infants per year. After adjustment for potential confounding factors, a decrease of 1 g/dL of hemoglobin was associated with a nonsignificant increase of 11% for risk of malaria infection (hazard ratio, 1.11, 95% confidence interval [CI], 0.99-1.25,  $p = 0.076$ ). Only children with severe anemia (hemoglobin  $<8.0$  g/dL) at baseline were at higher risk of malaria infection (hazard ratio, 1.72, 95% CI, 1.08-2.76,  $p = 0.023$ ) during the follow-up year compared with the control group (hemoglobin  $>10.0$  g/dL). This association was not statistically significant if only clinical malaria episodes were taken into account (hazard ratio, 1.42, 95% CI, 0.77-2.61,  $p = 0.26$ ). Our study suggests that infants with lower hemoglobin levels are not protected against malaria infection. Further research that examines the risk of malaria in relation to both hemoglobin and iron store levels would be important to better understand this complex interaction.

- 82 **Longley RJ, White MT, Takashima E, Morita M, Kanoi BN, Li Wai Suen CSN, Betuela I, Kuehn A, Sriporote P, França CT, Siba P, Robinson LJ, Lacerda M, Sattabongkot J, Tsuboi T, Mueller I.**

Naturally acquired antibody responses to more than 300 *Plasmodium vivax* proteins in three geographic regions.

*PLoS Negl Trop Dis* 2017 Sep 11;11(9):e0005888. doi: 10.1371/journal.pntd.0005888. eCollection 2017 Sep.

*Plasmodium vivax* remains an important cause

of malaria in South America and the Asia-Pacific. Naturally acquired antibody responses against multiple *P. vivax* proteins have been described in numerous countries; however, direct comparison of these responses has been difficult with different methodologies employed. We measured antibody responses against 307 *P. vivax* proteins at the time of *P. vivax* infection, and at 2-3 later time-points in three countries. We observed that seropositivity rates at the time of infection were highest in Thailand, followed by Brazil then PNG, reflecting the level of antigenic input. The majority of sero-reactive antigens in all sites induced short-lived antibody responses with estimated half-lives of less than 6 months, although there was a trend towards longer-lived responses in PNG children. Despite these differences, IgG seropositivity rates, magnitude and longevity were highly and significantly rank-correlated between the different regions, suggesting such features are reflective of the individual protein.

**83 Luang-Suarkia D, Mitjà O, Ernst T, Bennett S, Tay A, Hays R, Smith DW, Imrie A.**

Hyperendemic dengue transmission and identification of a locally evolved DENV-3 lineage, Papua New Guinea 2007-2010. *PLoS Negl Trop Dis* 2018 Mar 1;12(3):e0006254. doi: 10.1371/journal.pntd.0006254. eCollection 2018 Mar.

**BACKGROUND:** Dengue is endemic in the Western Pacific and Oceania and the region reports more than 200,000 cases annually. Outbreaks of dengue and severe dengue occur regularly and movement of virus throughout the region has been reported. Disease surveillance systems, however, in many areas are not fully established and dengue incidence is underreported. Dengue epidemiology is likely least understood in Papua New Guinea (PNG), where the prototype DENV-2 strain New Guinea C was first isolated by Sabin in 1944 but where routine surveillance is not undertaken and little incidence and prevalence data are available. **METHODOLOGY/PRINCIPAL FINDINGS:** Serum samples from individuals with recent acute febrile illness or with non-febrile conditions collected between 2007 and 2010 were tested for anti-DENV neutralizing antibody. Responses were predominantly multitypic and seroprevalence increased with age, a pattern indicative of endemic dengue. DENV-1, DENV-2 and DENV-3 genomes were detected by RT-PCR within a nine-month period and in several instances two serotypes were identified in individuals sampled within a period of 10 days. Phylogenetic analysis of whole genome sequences identified a DENV-3 Genotype 1 lineage which had evolved on the northern coast of PNG which was likely exported to the western Pacific five years later, in addition to a DENV-2 Cosmopolitan Genotype lineage which had previously circulated in the region. **CONCLUSIONS/SIGNIFICANCE:** We show that dengue is hyperendemic in PNG and identify an endemic, locally evolved lineage of DENV-3 that was associated with an outbreak of severe dengue in Pacific countries in subsequent years, although severe disease was not identified in PNG. Additional studies need to be undertaken to understand dengue epidemiology and burden of disease in PNG.

**84 Lufele E, Umbers A, Ordi J, Ome-Kaius M, Wangnapi R, Unger H, Tarongka N, Siba P,**

**Mueller I, Robinson L, Rogerson S.**

Risk factors and pregnancy outcomes associated with placental malaria in a prospective cohort of Papua New Guinean women.

*Malar J* 2017 Oct 24;16(1):427. doi: 10.1186/s12936-017-2077-4.

**BACKGROUND:** *Plasmodium falciparum* in pregnancy results in substantial poor health outcomes for both mother and child, particularly in young, primigravid mothers who are at greatest risk of placental malaria (PM) infection. Complications of PM include maternal anaemia, low birth weight and preterm delivery, which contribute to maternal and infant morbidity and mortality in coastal Papua New Guinea (PNG). **METHODS:** Placental biopsies were examined from 1451 pregnant women who were enrolled in a malaria prevention study at 14-26 weeks gestation. Clinical and demographic information were collected at first antenatal clinic visits and women were followed until delivery. Placental biopsies were collected and examined for PM using histology. The presence of infected erythrocytes and/or the malaria pigment in monocytes or fibrin was used to determine the type of placental infection. **RESULTS:** Of 1451 placentas examined, PM infection was detected in 269 (18.5%), of which 54 (3.7%) were acute, 55 (3.8%) chronic, and 160 (11.0%) were past infections. Risk factors for PM included residing in rural areas (adjusted odds ratio (AOR) 3.65, 95% CI 1.76-7.51;  $p \leq 0.001$ ), being primigravid (AOR 2.45, 95% CI 1.26-4.77;  $p = 0.008$ ) and having symptomatic malaria during pregnancy (AOR 2.05, 95% CI 1.16-3.62;  $p = 0.013$ ). After adjustment for covariates, compared to uninfected women, acute infections (AOR 1.97, 95% CI 0.98-3.95;  $p = 0.056$ ) were associated with low birth weight babies, whereas chronic infections were associated with preterm delivery (AOR 3.92, 95% CI 1.64-9.38;  $p = 0.002$ ) and anaemia (AOR 2.22, 95% CI 1.02-4.84;  $p = 0.045$ ). **CONCLUSIONS:** Among pregnant PNG women receiving at least one dose of intermittent preventive treatment in pregnancy and using insecticide-treated bed nets, active PM infections were associated with adverse outcomes. Improved malaria prevention is required to optimize pregnancy outcomes.

**85 Lui PSC, Dunne MP, Baker P, Isom V.**

Sexual difficulties faced by men in the Solomon Islands: a mixed-methods study.

*Sex Health* 2017 Aug;14(4):338-344. doi: 10.1071/SH16170.

**BACKGROUND:** To date there has been little research into men's sexual and reproductive health in Pacific Island countries. The aim of this study was to describe men's sexual difficulties and barriers to their seeking reproductive health care in the Solomon Islands. **METHODS:** The study included qualitative inquiry (17 individual interviews and three focus group discussions with a total of 21 men) and a quantitative quasi-randomised quota sample household survey ( $n = 400$ ). The prevalence of sexual difficulties and potential risk factors, such as chronic diseases, health risk behaviours, depression and psychological distress were measured using standardised questions translated into pidgin. **RESULTS:** The most commonly self-reported sexual difficulties were premature ejaculation (39.5%), low sexual desire (29.0%), orgasm difficulty (27.3%) and erectile difficulty (4.3%). More than half (56%) of the men experienced at least one sexual



difficulty. Relatively few men (7.3%) had ever sought professional health care for reproductive health problems, and 15.4% of men preferred to use kastom (traditional) medicine for sexual problems. Multivariate analysis revealed that comorbid non-communicable diseases (NCDs), low health-related quality of life and dissatisfaction with sexual relationships were independently correlated with sexual difficulties. Contrary to expectations, self-reported psychological distress was inversely associated with these difficulties. In general, the insights gained from in-depth interviews validated the survey findings. **CONCLUSION:** This study adds the first data on symptoms of sexual dysfunction among men in the Solomon Islands and is one of few studies from the Pacific region. The findings strongly suggest the need for comprehensive health services that are gender-specific and sensitive to the sexual difficulties of Islander men.

- 86 **Manineng CM, MacLaren D, Baigry M, Trowalle E, Muller R, Vallye A, Gesch P, Hombhanje F, McBride WJ.**

Re-establishing safer medical-circumcision-integrated initiation ceremonies for HIV prevention in a rural setting in Papua New Guinea. A multi-method acceptability study.

*PLoS One* 2017 Nov 8;12(11):e0187577. doi: 10.1371/journal.pone.0187577. eCollection 2017.

**BACKGROUND:** Efforts to stem the spread of human immunodeficiency virus (HIV) in Papua New Guinea (PNG) are hampered by multiple interrelated factors including limited health services, extreme diversities in culture and language and highly prevalent gender inequity, domestic violence and poverty. In the rural district of Yangoru-Saussia, a revival of previously ceased male initiation ceremonies (MICs) is being considered for a comprehensive approach to HIV prevention. In this study, we explore the local acceptability of this undertaking including replacing traditional penile cutting practices with medical male circumcision (MMC). **METHODS:** A multi-method study comprising three phases. Phase one, focus group discussions with male elders to explore locally appropriate approaches to HIV prevention; Phase two, interviews and a cross-sectional survey with community men and women to assess views on MICs that include MMC for HIV prevention; Phase three, interviews with cultural leaders and a cross sectional survey to assess the acceptability of replacing traditional penile bleeding with MMC. **RESULTS:** Cultural leaders expressed that re-establishing MICs was locally appropriate for HIV prevention given the focus on character building and cultural preservation. Most surveyed participants (81.5%) supported re-establishing MICs and 92.2% supported adapting MICs with MMC. Changes to penile bleeding emerged as a contentious and contested issue given its cultural significance in symbolizing initiates' transition from childhood to adulthood. Participants were concerned about potential clash with modern education, introduced religious beliefs and limited government support in leadership and funding. **CONCLUSIONS:** Most people in this study in Yangoru-Saussia support re-establishing MICs and replacing traditional penile bleeding with MMC. This culturally-sensitive alignment of MMC (and HIV prevention) with revived MICs responds to a national health priority in PNG and acts as an example of providing culturally-sensitive male circumcision for HIV prevention recommended by WHO/UNAIDS.

However, the implementation of this undertaking will require considerable effort, especially when modern pursuits in education and religion must be factored and when there is expectation for local authorities to lead and provide funding.

- 87 **Marks M, Fookes M, Wagner J, Butcher R, Ghinai R, Sokana O, Sarkodie YA, Lukehart SA, Solomon AW, Mabey DCW, Thomson N.**

Diagnostics for yaws eradication: insights from direct next-generation sequencing of cutaneous strains of *Treponema pallidum*.

*Clin Infect Dis* 2018 Mar 5;66(6):818-824. doi: 10.1093/cid/cix892.

**Background:** Yaws-like chronic ulcers can be caused by *Treponema pallidum* subspecies *pertenue*, *Haemophilus ducreyi*, or other, still-undefined bacteria. To permit accurate evaluation of yaws elimination efforts, programmatic use of molecular diagnostics is required. The accuracy and sensitivity of current tools remain unclear because our understanding of *T. pallidum* diversity is limited by the low number of sequenced genomes. **Methods:** We tested samples from patients with suspected yaws collected in the Solomon Islands and Ghana. All samples were from patients whose lesions had previously tested negative using the Centers for Disease Control and Prevention (CDC) diagnostic assay in widespread use. However, some of these patients had positive serological assays for yaws on blood. We used direct whole-genome sequencing to identify *T. pallidum* subsp. *pertenue* strains missed by the current assay. **Results:** From 45 Solomon Islands and 27 Ghanaian samples, 11 were positive for *T. pallidum* DNA using the species-wide quantitative polymerase chain reaction (PCR) assay, from which we obtained 6 previously undetected *T. pallidum* subsp. *pertenue* whole-genome sequences. These show that Solomon Islands sequences represent distinct *T. pallidum* subsp. *pertenue* clades. These isolates were invisible to the CDC diagnostic PCR assay, due to sequence variation in the primer binding site. **Conclusions:** Our data double the number of published *T. pallidum* subsp. *pertenue* genomes. We show that Solomon Islands strains are undetectable by the PCR used in many studies and by health ministries. This assay is therefore not adequate for the eradication program. Next-generation genome sequence data are essential for these efforts.

- 88 **Marks M, Esau T, Asugeni R, Harrington R, Diau J, Toloka H, Asugeni J, Ansbro E, Solomon AW, Maclaren D, Redman-Maclaren M, Mabey DCW.**

Point-of-care tests for syphilis and yaws in a low-income setting – a qualitative study of healthcare worker and patient experiences.

*PLoS Negl Trop Dis* 2018 Apr 19;12(4):e0006360. doi: 10.1371/journal.pntd.0006360. eCollection 2018 Apr.

**INTRODUCTION:** The human treponematoses comprise venereal syphilis and the three non-venereal or endemic treponematoses yaws, bejel, and pinta. Serological assays remain the most common diagnostic method for all treponemal infections. Point-of-care tests (POCTs) for syphilis and yaws allow testing without further development of infrastructure in populations where routine laboratory facilities are not available. Alongside the test's performance characteristics assessed through diagnostic evaluation, it is important to consider



broader issues when rolling out a POCT. Experience with malaria POCT roll-out in sub-Saharan Africa has demonstrated that both healthcare worker and patient beliefs may play a major role in shaping the real-world use of POCTs. We conducted a qualitative study evaluating healthcare worker and patient perceptions of using a syphilis/yaws POCT in clinics in the East Malaita region of Malaita province in the Solomon Islands. Prior to the study serology was only routinely available at the local district hospital. **METHODS:** The POCT was deployed in the outpatient and ante-natal departments of a district hospital and four rural health clinics served by the hospital. Each site was provided with training and an SOP on the performance, interpretation and recording of results. Treatment for those testing positive was provided, in line with Solomon Islands Ministry of Health and Medical Services' guidelines for syphilis and yaws respectively. Alongside the implementation of the POCT we facilitated semi-structured interviews with both nurses and patients to explore individuals' experiences and beliefs in relation to use of the POCT. **RESULTS AND DISCUSSION:** Four main themes emerged in the interviews: 1) training and ease of performing the test; 2) time taken and ability to fit the test into a clinical workflow; 3) perceived reliability and trustworthiness of the test; and 4) level of the health care system where the test was most usefully deployed. Many healthcare workers related their experience with the POCT to their experience using similar tests for malaria. Although the test was considered to take a relatively long time to perform the benefits of improved access to testing were considered positive by most healthcare workers. Qualitative data is needed to help inform better training packages to support the implementation of POCT in low-resource settings.

- 89 **Marks M, Fookes M, Wagner J, Ghinai R, Sokana O, Sarkodie YA, Solomon AW, Mabey DCW, Thomson NR.**

Direct whole-genome sequencing of cutaneous strains of *Haemophilus ducreyi*. *Emerg Infect Dis* 2018 Apr;24(4):786-789. doi: 10.3201/eid2404.171726.

*Haemophilus ducreyi*, which causes chancroid, has emerged as a cause of pediatric skin disease. Isolation of *H. ducreyi* in low-income settings is challenging, limiting phylogenetic investigation. Next-generation sequencing demonstrates that cutaneous strains arise from class I and II *H. ducreyi* clades and that class II may represent a distinct subspecies.

- 90 **Marks M, Mitjà O, Bottomley C, Kwakye C, Houine W, Bauri M, Adwere P, Abdulai AA, Dua F, Boateng L, Wangi J, Ohene SA, Wangnapi R, Simpson SV, Miag H, Addo KK, Basing LA, Danavall D, Chi KH, Pillay A, Ballard R, Solomon AW, Chen CY, Bieb SV, Adu-Sarkodie Y, Mabey DCW, Asiedu K; Study Team.**

Comparative efficacy of low-dose versus standard-dose azithromycin for patients with yaws: a randomised non-inferiority trial in Ghana and Papua New Guinea. *Lancet Glob Health* 2018 Apr;6(4):e401-e410. doi: 10.1016/S2214-109X(18)30023-8. Epub 2018 Feb 16.

**BACKGROUND:** A dose of 30 mg/kg of azithromycin is recommended for treatment of yaws,

a disease targeted for global eradication. Treatment with 20 mg/kg of azithromycin is recommended for the elimination of trachoma as a public health problem. In some settings, these diseases are co-endemic. We aimed to determine the efficacy of 20 mg/kg of azithromycin compared with 30 mg/kg azithromycin for the treatment of active and latent yaws. **METHODS:** We did a non-inferiority, open-label, randomised controlled trial in children aged 6-15 years who were recruited from schools in Ghana and schools and the community in Papua New Guinea. Participants were enrolled based on the presence of a clinical lesion that was consistent with infectious primary or secondary yaws and a positive rapid diagnostic test for treponemal and non-treponemal antibodies. Participants were randomly assigned (1:1) to receive either standard-dose (30 mg/kg) or low-dose (20 mg/kg) azithromycin by a computer-generated random number sequence. Health-care workers assessing clinical outcomes in the field were not blinded to the patient's treatment, but investigators involved in statistical or laboratory analyses and the participants were blinded to treatment group. We followed up participants at 4 weeks and 6 months. The primary outcome was cure at 6 months, defined as lesion healing at 4 weeks in patients with active yaws and at least a four-fold decrease in rapid plasma reagin titre from baseline to 6 months in patients with active and latent yaws. Active yaws was defined as a skin lesion that was positive for *Treponema pallidum* ssp. *pertenue* in PCR testing. We used a non-inferiority margin of 10%. This trial was registered with ClinicalTrials.gov, number NCT02344628. **FINDINGS:** Between June 12, 2015, and July 2, 2016, 583 (65.1%) of 895 children screened were enrolled; 292 patients were assigned a low dose of azithromycin and 291 patients were assigned a standard dose of azithromycin. 191 participants had active yaws and 392 had presumed latent yaws. Complete follow-up to 6 months was available for 157 (82.2%) of 191 patients with active yaws. In cases of active yaws, cure was achieved in 61 (80.3%) of 76 patients in the low-dose group and in 68 (84.0%) of 81 patients in the standard-dose group (difference 3.7%; 95% CI -8.4 to 15.7%; this result did not meet the non-inferiority criterion). There were no serious adverse events reported in response to treatment in either group. The most commonly reported adverse event at 4 weeks was gastrointestinal upset, with eight (2.7%) participants in each group reporting this symptom. **INTERPRETATION:** In this study, low-dose azithromycin did not meet the prespecified non-inferiority margin compared with standard-dose azithromycin in achieving clinical and serological cure in PCR-confirmed active yaws. Only a single participant (with presumed latent yaws) had definitive serological failure. This work suggests that 20 mg/kg of azithromycin is probably effective against yaws, but further data are needed.

- 91 **Martiniuk A, Jagilli R, Natuzzi E, Ilopitu JW, Oipata M, Christie AM, Korini J, Vujovich-Dunn C, Yu W.**

Cancer in the Solomon Islands.

*Cancer Epidemiol* 2017 Oct;50(Pt B):176-183. doi: 10.1016/j.canep.2017.04.016.

**INTRODUCTION:** The Solomon Islands, with a population of 550,000, has significant challenges in addressing non-communicable diseases, including cancer, in the face of significant economic, cultural,

general awareness and health system challenges. **OBJECTIVES:** To summarise the existing knowledge regarding cancer in the Solomon Islands, to gather new data and make recommendations. **METHODS:** A literature review was undertaken and cancer data from the National Referral Hospital, Honiara were analysed and are presented. Key stakeholders were interviewed for their perspectives including areas to target for ongoing, incremental improvements. Last, a health services audit for cancer using the WHO SARA tool was undertaken. **RESULTS:** Breast and cervical cancer remain the first and second most commonly identified cancers in the Solomon Islands. The Solomons cancer registry is hospital based and suffers from incomplete data collection due to its passive nature, lack of resources for data entry and processing resulting in weak data which is rarely used for decision-making. The health system audit revealed system and individual reasons for delayed diagnosis or lack of cancer treatment or palliation in the Solomon Islands. Reasons included lack of patient knowledge regarding symptoms, late referrals to the National Referral Hospital and inability of health care workers to detect cancers either due to lack of skills to do so, or lack of diagnostic capabilities, and an overall lack of access to any health care, due to geographical barriers and overall national economic fragility. **CONCLUSION:** The Solomon Islands is challenged in preventing, diagnosing, treating and palliating cancer. Stakeholders recommend establishing specialty expertise (in the form of a cancer unit), improved registry processes and increased collaboration between the sole tertiary hospital nationwide and other Solomon Islands health services as important targets for incremental improvement.

- 92 **McGlynn PJ, Renzaho AM, Pham MD, Toole M, Fisher J, Luchters S.**

Critical examination of evidence for the nutritional status of children in Papua New Guinea – a systematic review.

*Asia Pac J Clin Nutr* 2018;27(1):1-18. doi: 10.6133/apjcn.042017.02.

**BACKGROUND AND OBJECTIVES:** Undernutrition remains a significant cause of childhood illness, poor growth, development, and death in Papua New Guinea (PNG). Studies on child nutritional outcomes in PNG vary by design, measurement protocols and quality. We conducted a systematic review to assess the evidence for the prevalence of child undernutrition across different study populations, geographical locations and time periods. **METHODS AND STUDY DESIGN:** Six electronic databases and additional grey literature were searched for articles describing the nutritional status by wasting, stunting and underweight, of PNG children under five years of age, published between 1990 and April 2015. Prevalence data using different scales of measurement and reference populations were standardized according to WHO protocols. **RESULTS:** The search yielded 566 articles, of which 31 studies met the inclusion criteria. The prevalence of child undernutrition varied from 1% to 76% for wasting (median 11%), 5% to 92% for stunting (median 51%), and 14% to 59% for underweight (median 32%). Wide variations exist according to the index used for measurement, the population characteristics and the geographical region in which they live. Prevalence estimates increase significantly when data using different scales of measurement and

population references are standardized to the WHO protocols. **CONCLUSIONS:** Child undernutrition in PNG is regionally variable due to a complex interplay of poverty, disease, food-security, cultural, environmental and sociopolitical issues requiring a complex mix of solutions by governments, health systems and local communities. Area-specific surveys using multiple measures are necessary to inform local solutions for this important problem.

- 93 **McLean ARD, Stanisic D, McGready R, Chotivanich K, Clapham C, Baiwog F, Pimanpanarak M, Siba P, Mueller I, King CL, Nosten F, Beeson JG, Rogerson S, Simpson JA, Fowkes FJL.**

*P. falciparum* infection and maternofetal antibody transfer in malaria-endemic settings of varying transmission.

*PLoS One* 2017 Oct 13;12(10):e0186577. doi: 10.1371/journal.pone.0186577. eCollection 2017.

**INTRODUCTION:** During pregnancy, immunoglobulin G (IgG) is transferred from the mother to the fetus, providing protection from disease in early infancy. *Plasmodium falciparum* infections may reduce maternofetal antibody transfer efficiency, but mechanisms remain unclear. **METHODS:** Mother-cord paired serum samples collected at delivery from Papua New Guinea (PNG) and the Thailand-Myanmar Border Area (TMBA) were tested for IgG1 and IgG3 to four *P. falciparum* antigens and measles antigen, as well as total serum IgG. Multivariable linear regression was conducted to assess the association of peripheral *P. falciparum* infection during pregnancy or placental *P. falciparum* infection assessed at delivery with maternofetal antibody transfer efficiency. Path analysis assessed the extent to which associations between *P. falciparum* infection and antibody transfer were mediated by gestational age at delivery or levels of maternal total serum IgG. **RESULTS:** Maternofetal antibody transfer efficiency of IgG1 and IgG3 was lower in PNG compared to TMBA (mean difference in cord antibody levels (controlling for maternal antibody levels) ranged from -0.88 to 0.09, median of -0.20 log<sub>2</sub> units). Placental *P. falciparum* infections were associated with substantially lower maternofetal antibody transfer efficiency in PNG primigravid women (mean difference in cord antibody levels (controlling for maternal antibody levels) ranged from -0.62 to -0.10, median of -0.36 log<sub>2</sub> units), but not multigravid women. The lower antibody transfer efficiency amongst primigravid women with placental infection was only partially mediated by gestational age at delivery (proportion indirect effect ranged from 0% to 18%), whereas no mediation effects of maternal total serum IgG were observed. **DISCUSSION:** Primigravid women may be at risk of impaired maternofetal antibody transport with placental *P. falciparum* infection. Direct effects of *P. falciparum* on the placenta, rather than earlier gestational age and elevated serum IgG, are likely responsible for the majority of the reduction in maternofetal antibody transfer efficiency with placental infection.

- 94 **Mita T, Hombhanje F, Takahashi N, Sekihara M, Yamauchi M, Tsukahara T, Kaneko A, Endo H, Ohashi J.**

Rapid selection of sulphadoxine-resistant *Plasmodium falciparum* and its effect on within-population genetic diversity in Papua New Guinea.

*Sci Rep* 2018 Apr 3;8(1):5565. doi: 10.1038/s41598-018-23811-7.

The ability of the human malarial parasite *Plasmodium falciparum* to adapt to environmental changes depends considerably on its ability to maintain within-population genetic variation. Strong selection, consequent to widespread antimalarial drug usage, occasionally elicits a rapid expansion of drug-resistant isolates, which can act as founders. To investigate whether this phenomenon induces a loss of within-population genetic variation, we performed a population genetic analysis on 302 *P. falciparum* cases detected during two cross-sectional surveys in 2002-2003, just after the official introduction of sulphadoxine-pyrimethamine as a first-line treatment, and again in 2010-2011, in highly endemic areas in Papua New Guinea. We found that a single-origin sulphadoxine-resistant parasite isolate rapidly increased from 0% in 2002-2003 to 54% in 2010 and 84% in 2011. However, a considerable number of pairs exhibited random associations among 10 neutral microsatellite markers located in various chromosomes, suggesting that outcrossing effectively reduced non-random associations, albeit at a low average multiplicity of infection (1.35-1.52). Within-population genetic diversity was maintained throughout the study period. This indicates that the parasites maintained within-population variation, even after a clonal expansion of drug-resistant parasites. Outcrossing played a role in the preservation of within-population genetic diversity despite low levels of multiplicity of infection.

- 95 **Mitjà O, Godornes C, Houinei W, Kapa A, Paru R, Abel H, González-Beiras C, Bieb SV, Wangi J, Barry AE, Sanz S, Bassat Q, Lukehart SA.** Re-emergence of yaws after single mass azithromycin treatment followed by targeted treatment: a longitudinal study. *Lancet* 2018 Apr 21;391(10130):1599-1607. doi: 10.1016/S0140-6736(18)30204-6. Epub 2018 Feb 7.

**BACKGROUND:** Yaws is a substantial cause of chronic disfiguring ulcers in children in at least 14 countries in the tropics. WHO's newly adopted strategy for yaws eradication uses a single round of mass azithromycin treatment followed by targeted treatment programmes, and data from pilot studies have shown a short-term significant reduction of yaws. We assessed the long-term efficacy of the WHO strategy for yaws eradication. **METHODS:** Between April 15, 2013, and Oct 24, 2016, we did a longitudinal study on a Papua New Guinea island (Lihir; 16,092 population) in which yaws was endemic. In the initial study, the participants were followed for 12 months; in this extended follow-up study, clinical, serological, and PCR surveys were continued every 6 months for 42 months. We used genotyping and travel history to identify importation events. Active yaws confirmed by PCR specific for *Treponema pallidum* was the primary outcome indicator. The study is registered with ClinicalTrials.gov, number NCT01955252. **FINDINGS:** Mass azithromycin treatment (coverage rate of 84%) followed by targeted treatment programmes reduced the prevalence of active yaws from 1.8% to a minimum of 0.1% at 18 months (difference from baseline -1.7%, 95% CI, -1.9 to -1.4;  $p < 0.0001$ ), but the infection began to re-emerge after 24 months with a significant increase to 0.4% at 42 months (difference from 18 months 0.3%, 95% CI 0.1 to

0.4;  $p < 0.0001$ ). At each timepoint after baseline, more than 70% of the total community burden of yaws was found in individuals who had not had the mass treatment or as new infections in non-travelling residents. At months 36 and 42, five cases of active yaws, all from the same village, showed clinical failure following azithromycin treatment, with PCR-detected mutations in the 23S ribosomal RNA genes conferring resistance to azithromycin. A sustained decrease in the prevalence of high-titre latent yaws from 13.7% to <1.5% in asymptomatic children aged 1-5 years old and of genetic diversity of yaws strains from 0.139 to less than 0.046 between months 24 and 42 indicated a reduction in transmission of infection. **INTERPRETATION:** The implementation of the WHO strategy did not, in the long-term, achieve elimination in a high-endemic community mainly due to the individuals who were absent at the time of mass treatment in whom yaws reactivated; repeated mass treatment might be necessary to eliminate yaws. To our knowledge, this is the first report of the emergence of azithromycin-resistant *T. p. pertenue* and spread within one village. Communities' surveillance should be strengthened to detect any possible treatment failure and biological markers of resistance. **FUNDING:** ISDIN laboratories, Newcrest Mining Limited, and US Public Health Service, National Institutes of Health.

- 96 **Mitjà O, González-Beiras C, Godornes C, Kolm R, Houinei W, Abel H, Kapa A, Paru R, Bieb SV, Wangi J, Sanz S, Asiedu K, Lukehart SA, Bassat Q.** Effectiveness of single-dose azithromycin to treat latent yaws: a longitudinal comparative cohort study. *Lancet Glob Health* 2017 Dec;5(12):e1268-e1274. doi: 10.1016/S2214-109X(17)30388-1. Epub 2017 Oct 26.

**BACKGROUND:** Treatment of latent yaws is a crucial component of the WHO yaws eradication strategy to prevent relapse and the resulting transmission to uninfected children. We assessed the effectiveness of single-dose azithromycin to treat patients with latent yaws. **METHODS:** This population-based cohort study included children (age <20 years) living on Lihir Island, Papua New Guinea, with high-titre (rapid plasma reagin titre  $\geq 8$ ) latent or active yaws, between April, 2013, and May, 2015. Latent yaws was defined as lack of suspicious skin lesions or presence of ulcers negative for *Treponema pallidum* subsp. *pertenue* on PCR, and active yaws was defined as ulcers positive for *T. pertenue* on PCR. All children received one oral dose of 30 mg/kg azithromycin. The primary endpoint was serological cure, defined as a two-dilution decrease in rapid plasma reagin titre by 24 months after treatment. Treatment of latent yaws was taken to be non-inferior to that of active yaws if the lower limit of the two-sided 95% CI for the difference in rates was higher than or equal to -10%. This study is registered with ClinicalTrials.gov, number NCT01955252. **FINDINGS:** Of 311 participants enrolled, 273 (88%; 165 with latent yaws and 108 with active yaws) completed follow-up. The primary endpoint was achieved in 151 (92%) participants with latent yaws and 101 (94%) with active yaws (risk difference -2.0%, 95% CI -8.3 to 4.3), meeting the prespecified criteria for non-inferiority. **INTERPRETATION:** On the basis of decline in serological titre, oral single-dose azithromycin was effective in participants with latent

yaws. This finding supports the WHO strategy for the eradication of yaws based on mass administration of the entire endemic community irrespective of clinical status.

97 **Moore BR, Davis WA, Clarke PM, Robinson LJ, Laman M, Davis TME.**

Cost-effectiveness of artemisinin-naphthoquine versus artemether-lumefantrine for the treatment of uncomplicated malaria in Papua New Guinean children.

*Malar J* 2017 Oct 30;16(1):438. doi: 10.1186/s12936-017-2081-8.

**BACKGROUND:** A recent randomized trial showed that artemisinin-naphthoquine (AN) was non-inferior to artemether-lumefantrine (AL) for falciparum malaria and superior for vivax malaria in young Papua New Guinean children. The aim of this study was to compare the cost-effectiveness of these two regimens. **METHODS:** An incremental cost-effectiveness analysis was performed using data from 231 children with *Plasmodium falciparum* and/or *Plasmodium vivax* infections in an open-label, randomized, parallel-group trial. Recruited children were randomized 1:1 to receive once daily AN for 3 days with water or twice daily AL for 3 days given with fat. World Health Organization (WHO) definitions were used to determine clinical/parasitological outcomes. The cost of transport between the home and clinic, plus direct health-care costs, served as a basis for determining each regimen's incremental cost per incremental treatment success relative to AL by Day 42 and its cost per life year saved. **RESULTS:** In the usual care setting, AN was more effective for the treatment of uncomplicated malaria in children aged 0.5-5.9 years. AL and AN were equally efficacious for the treatment of falciparum malaria; however, AN had increased anti-malarial treatment costs per patient of \$10.46 compared with AL. AN was the most effective regimen for treatment of vivax malaria, but had increased treatment costs of \$14.83 per treatment success compared with AL. **CONCLUSIONS:** Whilst AN has superior overall efficacy for the treatment of uncomplicated malaria in PNG children, AL was the less costly regimen. An indicative extrapolation estimated the cost per life year saved by using AN instead of AL to treat uncomplicated malaria to be \$12,165 for girls and \$12,469 for boys (discounted), which means AN may not be cost-effective and affordable for PNG at current cost. However, AN may become acceptable should it become WHO prequalified and/or should a donated/subsidized drug supply become available.

98 **Moore PR, van den Hurk AF, Mackenzie JS, Pyke AT.**

Dengue viruses in Papua New Guinea: evidence of endemicity and phylogenetic variation, including the evolution of new genetic lineages.

*Emerg Microbes Infect* 2017 Dec 20;6(12):e114. doi: 10.1038/em.2017.103.

Dengue is the most common cause of mosquito-borne viral disease in humans, and is endemic in more than 100 tropical and subtropical countries. Periodic outbreaks of dengue have been reported in Papua New Guinea (PNG), but there is only limited knowledge of its endemicity and disease burden. To help elucidate the status of the dengue viruses (DENVs) in PNG, we performed envelope (E) gene sequencing of DENV serotypes 1-4 (DENV 1-4) obtained from infected patients who traveled to

Australia or from patients diagnosed during local DENV transmission events between 2001 and 2016. Phylogenetic analysis and comparison with globally available DENV sequences revealed new endemic PNG lineages for DENV 1-3 which have emerged within the last decade. We also identified another possible PNG lineage for DENV-4 from 2016. The DENV-1 and -3 PNG lineages were most closely related to recent lineages circulating on Pacific island nations while the DENV-2 lineage and putative DENV-4 PNG lineage were most similar to Indonesian sequences. This study has demonstrated for the first time the co-circulation of DENV 1-4 strains in PNG and provided molecular evidence of endemic DENV transmission. Our results provide an important platform for improved surveillance and monitoring of DENVs in PNG and broaden the global understanding of DENV genetic diversity.

99 **Moro C, Covino J.**

Nutrition and growth: assessing the impact of regional nutritional intake on childhood development and metacarpal parameters.

*Anat Cell Biol* 2018 Mar;51(1):31-40. doi: 10.5115/acb.2018.51.1.31. Epub 2018 Mar 28.

Measuring skeletal development throughout juvenile growth can provide a greater understanding into the health, hormonal function and genetics of children. The metacarpals have been of interest for their potential to provide insights into healthy juvenile skeletal development. This study investigated the growth patterns of developing females from isolated communities who had varied diets. Anthropometrical measurements and hand-wrist X-rays were taken of 353 juvenile females from three populations: Pari Coastal Village and Bundi Highlands Village, Papua New Guinea (PNG); and Brisbane, Australia between 1968 and 1983. Radiographs were digitized, and the length and width of the second and third metacarpals compared to each subject's height and weight. As subject heights increased, metacarpal length and width increased. However, stature and second metacarpal length indicated the strongest correlation ( $p < 0.01$ ), compared to third metacarpal length ( $p < 0.01$ ) or width. From 11 to 13 years of age, Brisbane subjects were significantly heavier and taller in comparison to subjects from PNG, and coastal females were heavier and taller than the highland females. A prominent difference between the two PNG populations was the regional intake of protein in their diets. The second metacarpal presents particularly accurate measurements when determining the height or development of a child. Nutritional intake appears to have a major influence on normal childhood growth, with a potential for protein deficiency to strongly inhibit growth. Any delayed growth is particularly evident in the child's stature, as well as in the development of the metacarpal long bones of the hand.

100 **Morris M, Bolnga JW, Verave O, Aipit J, Rero A, Laman M.**

Safety and effectiveness of oral misoprostol for induction of labour in a resource-limited setting: a dose escalation study.

*BMC Pregnancy Childbirth* 2017 Sep 8;17(1):298. doi: 10.1186/s12884-017-1483-5.

**BACKGROUND:** Oral misoprostol as an induction of labour (IOL) agent is rapidly gaining popularity in resource-limited settings because



it is cheap, stable at ambient temperatures, and logistically easier to administer than dinoprostone and oxytocin. We aim to investigate the safety and effectiveness of a regimen of oral misoprostol in Papua New Guinean women undergoing IOL. **METHODS:** As part of a prospective dose escalation study conducted at Modilon Hospital in Papua New Guinea, women with a singleton pregnancy in cephalic presentation and an unfavourable cervix who gave written informed consent were administered oral misoprostol, commencing at 25 mcg once every 2 h for 4 doses and increased to 50 mcg once every 2 h for 8 doses within 24 h. The primary outcomes studied were i) the proportion of women delivering within 24 h of oral misoprostol administration, and ii) rates of maternal and perinatal severe adverse events. **RESULTS:** Of 6167 labour ward screened admissions, 209 women (3%) fulfilled the study inclusion criteria and underwent IOL. Overall, 74% (155/209 [95% confidence interval 67.6-79.9]) delivered within 24 h. Most women (90%; 188/209; 95% CI [84.9-93.5]) delivered vaginally with 86% (180/209) having a good outcome for both the mother and baby. Of the 10% (21/209) who failed IOL and underwent caesarean section, a significant proportion of their babies were admitted to special-care nursery compared to babies delivered vaginally (20/21 [95%] versus 8/188 [4%]; Fisher Exact test  $p < 0.001$ ), but their perinatal mortality rate was not significantly higher (1/21 [5%] versus 2/188 [1%];  $p = 0.30$ ). The only maternal death was not study related and occurred in a patient with post-partum haemorrhage, 15 h post-delivery. **CONCLUSION:** The oral misoprostol regimen for IOL described in the present study is safe, effective and logistically feasible to administer in a resource-limited setting.

**101 Moulin PA, Nivaggioni V, Saut N, Grosdidier C, Bernot D, Baccini V.**

Southeast Asian ovalocytosis: the need for a careful observation of red cell indices and blood smear. *Ann Biol Clin (Paris)* 2017 Dec 1;75(6):699-702. doi: 10.1684/abc.2017.1291.

Southeast Asian ovalocytosis (SAO) is characterized by macro-ovalocytes and oval-stomatocytes on blood smear. SAO is common in Malaysia and Papua New Guinea where up to 40 per cent of the population is affected in some coastal regions. Inherited in an autosomal dominant way, illness results from deletion of codons 400-408 in the *SLC4A1* gene which encodes for band 3 erythrocyte membrane protein. This deletion is responsible for an unusual erythrocyte stiffness and oval shape of the cells on blood smear. Heterozygous carriers are usually asymptomatic whereas homozygous are not viable without intensive antenatal care. Here, we describe 4 patients diagnosed incidentally by the cytogram appearance of the Advia® 2120i (Siemens) representing hemoglobin concentration, according to red blood mean cellular volume (GR/VCH).

**102 Naka I, Furusawa T, Kimura R, Natsuhara K, Yamauchi T, Nakazawa M, Ataka Y, Ishida T, Inaoka T, Matsumura Y, Ohtsuka R, Ohashi J.**

A missense variant, rs373863828-A (p.Arg457Gln), of *CREBRF* and body mass index in Oceanic populations.

*J Hum Genet* 2017 Sep;62(9):847-849. doi: 10.1038/jhg.2017.44. Epub 2017 Apr 13.

It has been suggested that a 'thrifty' genotype hypothesis can account for the high prevalence

of obesity in the island populations of Oceania. A recent genome-wide association study revealed that a missense variant, rs373863828-A (p.Arg457Gln), of the *CREBRF* gene (encoding CREB3 regulatory factor) was associated with an excessive increase in body mass index (BMI) in Samoans. In the present study, the association of rs373863828-A with an increase in BMI was examined in four Austronesian (AN)-speaking populations in Oceania. We found that rs373863828-A was frequently observed (frequency of 0.15) in Tongans (Polynesians), and was strongly associated with higher BMI ( $p = 6.1 \times 10^{-4}$ ). A single copy of the rs373863828-A allele increased BMI by  $3.09 \text{ kg m}^{-2}$  after adjustment for age and sex. No significant association was detected in the other three AN-speaking populations (Melanesians and Micronesians) living in Solomon Islands. This was probably due to the low allele frequency (0.02-0.06) of rs373863828-A as well as small sample size. The rs373863828-A allele was not found in both AN-speaking and non-AN-speaking Melanesians living in Papua New Guinea. Our results suggest that rs373863828-A of *CREBRF*, a promising thrifty variant, arose in recent ancestors of AN-speaking Polynesians.

**103 Nosa V, Duffy S, Singh D, Lavelio S, Amber U, Homasi-Paelate A, Alfred J.**

The use of home brew in Pacific Islands countries and territories.

*J Ethn Subst Abuse* 2018 Jan-Mar;17(1):7-15. doi: 10.1080/15332640.2017.1362732.

This review examines what is known about the production and use of home brew in the Pacific Islands countries and territories. Data collection involved interviews of 78 men and women from the Marshall Islands, Papua New Guinea, Tonga, and Tuvalu. The interviews were conducted in 2013 by local interviewers. The questions fell into four key areas: people's history of home-brew consumption, the reasons for home-brew use, the effects of home brew, and people's perceptions about home brew. An open ethnographic approach revealed that males are the main consumers of home brew, that home brew is consumed in private venues by those with low socioeconomic status, and that there are positive and negative outcomes associated with the use of home brew. Finally, policy implications of the findings are included in this article.

**104 Oberli H, Martin C.**

Trauma surgery in Pacific Small Island Developing States (SIDS). [Ger]

*Unfallchirurg* 2017 Oct;120(10):830-836. doi: 10.1007/s00113-017-0376-4.

**BACKGROUND:** The small developing countries in the Pacific are grouped together as Small Island Development States (SIDS) because they face similar problems which they cannot cope with nationally. They are developing countries, so-called low and lower middle income countries (LMIC), are economically weak and the islands of the different nations are widely scattered. Approximately 80% of the 10 million inhabitants live in rural regions. **EPIDEMIOLOGY AND SURGICAL CAPACITY:** Over 40% of patients in the surgical departments of hospitals are hospitalized for injuries, and this tendency is increasing. Fractures of the upper extremities are relatively more frequent in the Pacific than in the countries of the North. Long distances, lack of possibilities for treatment and lack of transport



often cause complications, such as infected open fractures, pseudarthrosis and posttraumatic malformations. There are too few hospitals with sufficiently competent surgeons, anesthetists and obstetricians (SAO) and appropriate equipment. PACIFIC ISLANDS ORTHOPEDIC ASSOCIATION (PIOA): The PIOA was founded in Honiara, Solomon Islands, and offers surgeons of the Pacific SIDS comprehensive, structured trauma and orthopedic surgery training in their own countries. It lasts 4 years and leads to an M-Med (orthopaedic surgery) diploma and to a Fellowship of the International College of Surgeons (FICS), which are both recognized by the participating hospitals. It is free for participants. THE AO ALLIANCE FOUNDATION (AOAF): The AOAF is an independent organization with the only aim to enhance trauma surgery capacity in LMICs. The AOAF supports the PIOA program together with the Wyss Medical Foundation. Currently, 18 trainees from 8 Pacific SIDS are participating in the PIOA training program.

- 105 **Ohashi J, Naka I, Furusawa T, Kimura R, Natsuhara K, Yamauchi T, Nakazawa M, Ishida T, Inaoka T, Matsumura Y, Ohtsuka R.**

Association study of *CREBRF* missense variant (rs373863828:G>A; p.Arg457Gln) with levels of serum lipid profile in the Pacific populations. *Ann Hum Biol* 2018 May;45(3):215-219. doi: 10.1080/03014460.2018.1461928.

**BACKGROUND:** A missense variant (rs373863828:G>A; p.Arg457Gln) of the *CREBRF* gene is strongly associated with a higher body mass index (BMI; kg/m<sup>2</sup>) in Polynesian populations. This variant has also been reported to be associated with lower total cholesterol in Samoans. **AIM:** The aim of this study is to examine the association of rs373863828:G>A with levels of serum lipids in four Pacific populations. **METHODS:** A total of 613 adult subjects were recruited from Tonga (Polynesians) and the Solomon Islands (Melanesians and Micronesians). Multiple regression analyses adjusted for age and sex were performed to examine the association of rs373863828 with levels of serum lipids in each population. **RESULTS:** A significant association of rs373863828:G>A with lower level of HDL-cholesterol was detected in the Tonga population ( $\beta = -3.32$  and  $p$  value = 0.030). The expected change in HDL-cholesterol with respect to a single copy of the rs373863828-A allele was 3.32 mg/dL. However, the association between rs373863828-A and lower levels of HDL-cholesterol was not significant after further adjustment for BMI in the Tonga population ( $\beta = -2.32$  and  $p$  value = 0.13). **CONCLUSIONS:** The rs373863828-A allele may not directly affect the level of serum HDL-cholesterol independent of BMI. To confirm the present findings, association studies with large sample sizes and functional analyses are required.

- 106 **Olafuyi O, Coleman M, Badhan RKS.**

The application of physiologically based pharmacokinetic modelling to assess the impact of antiretroviral-mediated drug-drug interactions on piperazine antimalarial therapy during pregnancy. *Biopharm Drug Dispos* 2017 Nov;38(8):464-478. doi: 10.1002/bdd.2087. Epub 2017 Sep 29.

Antimalarial therapy during pregnancy poses important safety concerns due to potential teratogenicity and maternal physiological and biochemical changes during gestation. Piperazine

(PQ) has gained interest for use in pregnancy in response to increasing resistance towards sulfadoxine-pyrimethamine in sub-Saharan Africa. Coinfection with HIV is common in many developing countries; however, little is known about the impact of antiretroviral (ARV) mediated drug-drug interaction (DDI) on piperazine pharmacokinetics during pregnancy. This study applied mechanistic pharmacokinetic modelling to predict pharmacokinetics in non-pregnant and pregnant patients, which was validated in distinct customised population groups from Thailand, Sudan and Papua New Guinea. In each population group, no significant differences in day 7 concentrations were observed during different gestational weeks (GW) (weeks 10-40), supporting the notion that piperazine is safe throughout pregnancy with consistent pharmacokinetics, although possible teratogenicity may limit this. Antiretroviral-mediated DDIs (efavirenz and ritonavir) had moderate effects on piperazine during different gestational weeks with a predicted AUC ratio in the range 0.56-0.8 and 1.64-1.79 for efavirenz and ritonavir, respectively, over GW 10-40, with a reduction in circulating human serum albumin significantly reducing the number of subjects attaining the day 7 (post-dose) therapeutic efficacy concentrations under both efavirenz and ritonavir DDIs. This present model successfully mechanistically predicted the pharmacokinetics of piperazine in pregnancy to be unchanged with respect to non-pregnant women, in the light of factors such as malaria/HIV co-infection. However, antiretroviral-mediated DDIs could significantly alter piperazine pharmacokinetics. Further model refinement will include collation of relevant physiological and biochemical alterations common to HIV/malaria patients.

- 107 **Olszowy KM, Sun C, Silverman H, Pomer A, Dancause KN, Chan CW, Lee G, Tarivonda L, Kaneko A, Weitz C, Koji Lum J, Garruto RM.**

Secular change in adult stature associated with modernization in Vanuatu. *Am J Hum Biol* 2017 Sep 10;29(5). doi: 10.1002/ajhb.23008. Epub 2017 Apr 14.

**OBJECTIVE:** To determine whether: (1) there is a secular increase in adult stature in Vanuatu, and (2) whether adult stature is positively associated with modernization in Vanuatu. **METHODS:** This study reports on stature measurements collected on 650 adult (age >17 years) men and women from four islands of varying economic development in Vanuatu. Measurements were collected as part of the Vanuatu Health Transitions Research Project in 2007 and 2011. **RESULTS:** Stature increased significantly in adults born between the 1940s and 1960s in Vanuatu, before leveling off in those born between the 1970s and 1990s. Adults are significantly taller on Efate, the most modernized island in the study sample, than on the less economically developed islands. **CONCLUSIONS:** Modernization is likely associated with improvements in child growth in Vanuatu, as assessed by gains in adult stature.

- 108 **Oseni Z, Than HH, Kolakowska E, Chalmers L, Hanboonkunupakarn B, McGready R.**

Video-based feedback as a method for training rural healthcare workers to manage medical emergencies: a pilot study. *BMC Med Educ* 2017 Aug 31;17(1):149. doi: 10.1186/s12909-017-0975-3.

**BACKGROUND:** Video-based feedback has been shown to aid knowledge retention, skills learning and improve team functionality. We explored the use of video-based feedback and low fidelity simulation for training rural healthcare workers along the Thailand-Myanmar border and Papua New Guinea (PNG) to manage medical emergencies effectively. **METHODS:** Twenty-four study participants were recruited from three Shoklo Malaria Research Unit clinics along the Thailand-Myanmar border and eight participants from Kudjip Nazarene Hospital, PNG. The teams were recorded on video managing a simulated medical emergency scenario and the video was used to aid feedback and assess performance using Observed Structured Clinical Examination (OSCE) scoring and a Team Emergency Assessment Measure (TEAM) questionnaire. The process was repeated post-feedback at both sites and at 6 weeks at the Thailand-Myanmar border site. Thailand-Myanmar border participants' individual confidence levels and baseline knowledge (using OSCE scoring) were assessed before team assessment and feedback at week 1 and repeated post-feedback and at 6 weeks. Focus group discussions (FGD) were held at each Thailand-Myanmar border clinic at week 1 (8 participants at each clinic). **RESULTS:** Individual paired tests of OSCE scores showed significant improvement post-feedback at week 1 ( $p < 0.001$ ) and week 6 ( $p < 0.001$ ) compared to baseline OSCE scores. There was a trend for increased team OSCE scores compared to baseline at week 1 ( $p = 0.068$ ) and week 6 ( $p = 0.109$ ) although not significant. Thailand-Myanmar border TEAM scores demonstrated improvement post-feedback mainly in leadership, teamwork and task management, which was sustained up to week 6. PNG showed an improvement mainly in teamwork and task management. The global rating of the teams' non-technical performance at both sites improved post-feedback and at week 6 on the Thailand-Myanmar border site. Self-rated confidence scores by Thailand-Myanmar border participants increased significantly from baseline following training at week 1 ( $p = 0.020$ ), and while higher at 6 weeks follow up than at baseline, this was not significant ( $p = 0.471$ ). The FGD revealed majority of participants felt that watching the video recording of their performance and the video-based feedback contributed most to their learning. **CONCLUSION:** Video-assisted feedback resulted in an improvement in clinical knowledge, confidence and quality of teamwork for managing medical emergencies in two low resource medical facilities in South East Asia and the South Pacific.

- 109 **Pakoa JG, Soupé-Gilbert ME, Girault D, Takau D, Gaviga J, Gourinat AC, Tarantola A, Goarant C.** High incidence of leptospirosis in an observational study of hospital outpatients in Vanuatu highlights the need for improved awareness and diagnostic capacities. *PLoS Negl Trop Dis* 2018 Jun 4;12(6):e0006564. doi: 10.1371/journal.pntd.0006564. eCollection 2018 Jun.

**BACKGROUND:** Estimates of leptospirosis morbidity identified Oceania as the region with highest burden. Besides Australia and New Zealand, Oceania is the home of Pacific Island Countries and Territories, most of which are developing countries facing a number of challenges. Their archipelago

geography notably affects health infrastructure and access to healthcare. Although human leptospirosis was formerly identified in Vanuatu, there is a lack of knowledge of this disease in the country. We aimed to identify leptospirosis in outpatients visiting the hospital. **METHODOLOGY/PRINCIPAL FINDINGS:** We conducted a clinical study to investigate leptospirosis as a cause of non-malarial acute febrile illness in Vanuatu. A total 161 outpatients visiting the outpatient clinics at Port Vila Central Hospital for internal medicine were recruited over 20 months. We showed that leptospirosis significantly affects humans in Vanuatu: 12 cases were confirmed by real-time PCR on acute blood samples ( $n = 5$ ) or by high serology titers evidencing a recent infection (MAT titer  $\geq 800$  or ELISA  $\geq 18$  Units,  $n = 7$ ). A high rate of positive serology was also evidenced, by MAT ( $100 < \text{titer} < 800$ , 9 patients) or ELISA IgM (ELISA  $\geq 12$  Units, 20 patients, including 6 also positive in MAT), showing frequent exposure to pathogenic leptospires, notably from serogroup Australis. **CONCLUSIONS/SIGNIFICANCE:** The high numbers of both seropositive patients and acute leptospirosis cases observed in outpatients visiting Port Vila Central Hospital suggest a high exposure to pathogenic *Leptospira* in the population studied. The MAT serology pointing to serogroup Australis as well as exposure history suggest that livestock animals largely contribute to the burden of human leptospirosis in Vanuatu. The analysis of residential and travel data suggests that the risk might even be higher in other islands of the Vanuatu archipelago. Altogether, our study emphasizes the need to increase awareness and build laboratory capacity to improve the medical care of leptospirosis in Vanuatu.

#### 110 **Pape R, Spuur K, Umo P.**

Mammographic parenchymal pattern and breast cancer risk profile of Papua New Guinean women – a baseline study of the screening population. *Radiography (Lond)* 2017 Nov;23(4):e93-e98. doi: 10.1016/j.radi.2017.05.006. Epub 2017 May 28.

**INTRODUCTION:** The aim of this research is to evidence for the first time the breast density of Papua New Guinean (PNG) women as described by mammographic parenchymal patterns (MPPs) and profile breast cancer risk; to examine the relationship of age and MPPs. **METHODS:** A retrospective analysis of 1161 screening mammograms of women who had undergone imaging at the Pacific International Hospital (PIH) was undertaken. Mammograms were classified into one of five Tabár MPPs; age was recorded in years. Descriptive analysis of the data for pattern distribution and a chi-square test, to test for relationships between age and pattern type were undertaken. **RESULTS:** The majority (51.42%) of women had Pattern I breasts; others had Pattern II (30.58%), Pattern III (4.31%), Pattern IV (7.24%), and Pattern V (6.46%). The mean age was 38.8 with a range of 30-80 years; there were no obvious differences in mean age across the categories of patterns. A chi-square test reported no evidence of a relationship between age and pattern type ( $p$  value = 0.504). Pattern V differed from other patterns, with proportionally more women aged over 50 and less aged in their 40s. **CONCLUSION:** This study sets a baseline for future studies of the MPPs of PNG women, and demonstrated that in this snapshot of PNG women, there is no unique distribution of MPPs and no increased risk of breast cancer based on breast density profile. This result

does not help to explain the high incidence of breast cancer in PNG. A more comprehensive study of the PNG screening population is required to validate this study.

111 **Pilang CL, Gray MA, Opreescu FI.**

The evolution of the community health worker program in Papua New Guinea.

*Rural Remote Health* 2017 Oct-Dec;17(4):3961. doi: 10.22605/RRH3961. Epub 2017 Nov 1.

Papua New Guinea (PNG) has a special history in regard to the training of community health workers (CHWs) and is currently preparing its frontline health workforce to serve the 85% of the total PNG population of 7.3 million people who live in rural and remote settings. This article identifies and explains the five major developmental stages in the current CHW training program, as well as the changes that have occurred over the past century. The developmental stages are: (1) traditional; (2) early contact; (3) innovation; (4) the 1980s; and (5) new millennium. These developmental stages are discussed in the context of the early literature and investigation by the primary author and examination of the lived experiences of early missionary health workers and local people. This paper documents the development of a CHW program in PNG from the colonisation period, which began in 1883, to the present day. As a developing nation, PNG has gone through many challenges and changes to its healthcare system and has gradually developed an effective program to train its frontline primary health care (PHC) workforce. This article contributes new information with regard to the past and current development of CHW programs in PNG as well as in other developing countries. The training of competent CHWs with the essential skills and knowledge may help deliver quality and cost-effective PHC services to the rural majority and the urban disadvantaged, thereby fulfilling the PNG government's National Health Plan for 2011-2020. Systematic evaluation of the effectiveness of the CHW program will provide guidance for continued development of this frontline health workforce. Improving and introducing a competency-based curriculum is an essential step towards building a healthier nation.

112 **Pomer A, Buffa G, Taleo F, Sizemore JH, Tokon A, Taleo G, Tarivonda L, Chan CW, Kaneko A, Dancause KN.**

Relationships between psychosocial distress and diet during pregnancy and infant birthweight in a lower-middle income country: 'healthy mothers, healthy communities' study in Vanuatu.

*Ann Hum Biol* 2018 May;45(3):220-228. doi: 10.1080/03014460.2018.1459837.

**BACKGROUND:** Maternal stress during pregnancy is associated with birth outcomes, including birthweight. Exposure to natural disasters during pregnancy provides a model to study these relationships. However, few studies assess both stress and diet, which might have interactive effects. Furthermore, most are conducted in high-income countries. Patterns might differ in low- and middle-income countries (LMICs). **AIM:** To study relationships between stress and diet during pregnancy, and infant birthweight, following a natural disaster in a lower-middle income country. **SUBJECTS AND METHODS:** In 2015, the island nation of Vanuatu suffered a Category 5 cyclone. Three months later, the authors assessed hardship

due to the cyclone, distress, and dietary diversity among 900 women, including 187 pregnant women. Of these, 70 had birth records available. Multivariate linear regression was used to analyse relationships between cyclone exposure and infant birthweight among this sub-sample. **RESULTS:** Neither hardship nor dietary diversity predicted birthweight. Distress was a robust predictor, explaining 8.5% of variance ( $p=0.012$ ). There were no interactive relationships between distress and other exposure variables. **CONCLUSIONS:** Maternal distress following a natural disaster has important implications for maternal and child health. In LMICs, low birthweight remains a pressing public health concern. Distress during pregnancy might represent one underlying risk factor.

113 **Posth C, Nägele K, Collieran H, Valentin F, Bedford S, Kami KW, Shing R, Buckley H, Kinaston R, Walworth M, Clark GR, Reepmeyer C, Flexner J, Maric T, Moser J, Gresky J, Kiko L, Robson KJ, Auckland K, Oppenheimer SJ, Hill AVS, Mentzer AJ, Zech J, Petchey F, Roberts P, Jeong C, Gray RD, Krause J, Powell A.**

Language continuity despite population replacement in Remote Oceania.

*Nat Ecol Evol* 2018 Apr;2(4):731-740. doi: 10.1038/s41559-018-0498-2. Epub 2018 Feb 27.

Recent genomic analyses show that the earliest peoples reaching Remote Oceania – associated with Austronesian-speaking Lapita culture – were almost completely East Asian, without detectable Papuan ancestry. However, Papuan-related genetic ancestry is found across present-day Pacific populations, indicating that peoples from Near Oceania have played a significant, but largely unknown, ancestral role. Here, new genome-wide data from 19 ancient South Pacific individuals provide direct evidence of a so-far undescribed Papuan expansion into Remote Oceania starting ~2,500 yrBP, far earlier than previously estimated and supporting a model from historical linguistics. New genome-wide data from 27 contemporary ni-Vanuatu demonstrate a subsequent and almost complete replacement of Lapita-Austronesian by Near Oceanian ancestry. Despite this massive demographic change, incoming Papuan languages did not replace Austronesian languages. Population replacement with language continuity is extremely rare – if not unprecedented – in human history. Our analyses show that rather than one large-scale event, the process was incremental and complex, with repeated migrations and sex-biased admixture with peoples from the Bismarck Archipelago.

114 **Prosser C, Meyer W, Ellis J, Lee R.**

Resistance screening and trend analysis of imported falciparum malaria in NSW, Australia (2010 to 2016). *PLoS One* 2018 May 29;13(5):e0197369. doi: 10.1371/journal.pone.0197369. eCollection 2018.

**BACKGROUND:** The World Health Organization currently recommends artemisinin (along with a partner drug) as the global frontline treatment for *Plasmodium falciparum* malaria. Artemisinin-resistant *P. falciparum* are now found throughout the greater Mekong subregion of South East Asia. Several polymorphisms in the parasite's kelch gene have been demonstrated to confer artemisinin resistance. While genotypes within the greater Mekong subregion are thoroughly examined in the literature, *P. falciparum* populations within several

areas that do not (yet) have endemic resistance are underrepresented. **RESULTS:** This investigation characterised the *Pfkelch13* propeller domains from 153 blood samples of 140 imported cases of *P. falciparum* malaria in New South Wales from 2010 to 2016. A low level of propeller domain diversity was observed, including the C580Y coding mutation most strongly associated with artemisinin resistance in South East Asia. The resistance genotype was found in a sample originating in Papua New Guinea, where this mutation, or artemisinin treatment failure, has not been previously reported. Sequencing a panel of geographically informative polymorphisms within the organellar genomes identified the C580Y parasite as having Oceanic origins. Patient data analysis revealed that New South Wales, Australia, *P. falciparum* malaria cases often originated from regions with limited drug resistance screening. **CONCLUSIONS:** The C580Y finding from outside of the greater Mekong subregion supports the consensus to upscale molecular surveillance of artemisinin resistance outside of South East Asia. The genetic screening results identify a risk of importing resistant *falciparum* malaria to Australia, supporting an ongoing surveillance protocol to pre-empt treatment failure and contribute to global data gathering.

115 **Pugach I, Duggan AT, Merriwether DA, Friedlaender FR, Friedlaender JS, Stoneking M.**

The gateway from Near into Remote Oceania: new insights from genome-wide data. *Mol Biol Evol* 2018 Apr 1;35(4):871-886. doi: 10.1093/molbev/msx333.

A widely accepted two-wave scenario of human settlement of Oceania involves the first out-of-Africa migration circa 50,000 years ago (ya), and the more recent Austronesian expansion, which reached the Bismarck Archipelago by 3,450 ya. Whereas earlier genetic studies provided evidence for extensive sex-biased admixture between the incoming and the indigenous populations, some archaeological, linguistic, and genetic evidence indicates a more complicated picture of settlement. To study regional variation in Oceania in more detail, we have compiled a genome-wide data set of 823 individuals from 72 populations (including 50 populations from Oceania) and over 620,000 autosomal single nucleotide polymorphisms (SNPs). We show that the initial dispersal of people from the Bismarck Archipelago into Remote Oceania occurred in a 'leapfrog' fashion, completely by-passing the main chain of the Solomon Islands, and that the colonization of the Solomon Islands proceeded in a bidirectional manner. Our results also support a divergence between western and eastern Solomons, in agreement with the sharp linguistic divide known as the Tryon-Hackman line. We also report substantial post-Austronesian gene flow across the Solomons. In particular, Santa Cruz (in Remote Oceania) exhibits extraordinarily high levels of Papuan ancestry that cannot be explained by a simple bottleneck/founder event scenario. Finally, we use simulations to show that discrepancies between different methods for dating admixture likely reflect different sensitivities of the methods to multiple admixture events from the same (or similar) sources. Overall, this study points to the importance of fine-scale sampling to understand the complexities of human population history.

116 **Pulford J, Kurumop S, Mueller I, Siba PM, Hetzel**

**MW.**

The impact of the scale-up of malaria rapid diagnostic tests on the routine clinical diagnosis procedures for febrile illness: a series of repeated cross-sectional studies in Papua New Guinea.

*Malar J* 2018 May 16;17(1):202. doi: 10.1186/s12936-018-2351-0.

**BACKGROUND:** This paper examines the impact of the scale-up of malaria rapid diagnostic tests (RDTs) on routine clinical diagnosis procedures for febrile illness in primary healthcare settings in Papua New Guinea. **METHODS:** Repeat, cross-sectional surveys in randomly selected primary healthcare services were conducted. Surveys included passive observation of consecutive febrile case management cases and were completed immediately prior to RDT scale-up (2011) and at 12- (2012) and 60-months (2016) post scale-up. The frequency with which specified diagnostic questions and procedures were observed to occur, with corresponding 95% CIs, was calculated for febrile patients prescribed anti-malarials pre- and post-RDT scale-up and between febrile patients who tested either negative or positive for malaria infection by RDT (post scale-up only). **RESULTS:** A total of 1809 observations from 120 health facilities were completed across the three survey periods of which 915 (51%) were prescribed an anti-malarial. The mean number of diagnostic questions and procedures asked or performed, leading to anti-malarial prescription, remained consistent pre- and post-RDT scale-up (range 7.4-7.7). However, alterations in diagnostic content were evident with the RDT replacing body temperature as the primary diagnostic procedure performed (observed in 5.3 and 84.4% of cases, respectively, in 2011 vs. 77.9 and 58.2% of cases in 2016). Verbal questioning, especially experience of fever, cough and duration of symptoms, remained the most common feature of a diagnostic examination leading to anti-malarial prescription irrespective of RDT use (observed in 96.1, 86.8 and 84.8% of cases, respectively, in 2011 vs. 97.5, 76.6 and 85.7% of cases in 2016). Diagnostic content did not vary substantially by RDT result. **CONCLUSIONS:** Rapid diagnostic tests scale-up has led to a reduction in body temperature measurement. Investigations are very limited when malaria infection is ruled out as a cause of febrile illness by RDT.

117 **Quinn B, Peach E, Wright CJC, Lim MSC, Davidson L, Dietze P.**

Alcohol and other substance use among a sample of young people in the Solomon Islands. *Aust NZ J Public Health* 2017 Aug;41(4):358-364. doi: 10.1111/1753-6405.12669. Epub 2017 Jun 14.

**OBJECTIVE:** Investigate alcohol and other substance use, with a focus on harmful alcohol use patterns, among young people in the Solomon Islands. **METHODS:** A structured, interviewer-administered questionnaire was administered to respondents aged 15-24 years across four of the country's provinces in late 2015. **RESULTS:** Four hundred young people completed the questionnaire across urban, peri-urban and rural communities. The most common substances ever used by participants were betel nut (94%), licit/store-bought and/or illicit alcohol (79%) and tobacco (76%). Lifetime and recent substance use was particularly common among male respondents; e.g. 89% of male participants reported ever using any alcohol



versus 54% of females ( $p < 0.001$ ). Harmful alcohol use patterns were common. **CONCLUSIONS:** Our sample generally reported higher levels of substance use compared to previous research in the Solomon Islands, including in relation to the country's relatively recent (2012/13) Household Income and Expenditure Survey. **IMPLICATIONS FOR PUBLIC HEALTH:** Our study made considerable advances in addressing key knowledge gaps regarding alcohol and other substance use among young people in the Solomon Islands. Evidence-based initiatives to address early initiation of alcohol and other substance use and the progression to more problematic use patterns among young people in the Solomon Islands need to be explored.

# 118 Raducha T, Gubiec T.

Predicting language diversity with complex networks. *PLoS One* 2018 Apr 27;13(4):e0196593. doi: 10.1371/journal.pone.0196593. eCollection 2018.

We analyze the model of social interactions with coevolution of the topology and states of the nodes. This model can be interpreted as a model of language change. We propose different rewiring mechanisms and perform numerical simulations for each. Obtained results are compared with the empirical data gathered from two online databases and anthropological study of Solomon Islands. We study the behavior of the number of languages for different system sizes and we find that only local rewiring, ie, triadic closure, is capable of reproducing results for the empirical data in a qualitative manner. Furthermore, we cancel the contradiction between previous models and the Solomon Islands case. Our results demonstrate the importance of the topology of the network, and the rewiring mechanism in the process of language change.

# 119 Redman-MacLaren M, Mills J, Tommbe R, MacLaren D, Speare R, McBride WJH.

Implications of male circumcision for women in Papua New Guinea: a transformational grounded theory study.

*BMC Womens Health* 2017 Jul 27;17(1):53. doi: 10.1186/s12905-017-0406-y.

**BACKGROUND:** Male circumcision reduces the risk of female-to-male transmission of human immunodeficiency virus (HIV) and is being explored for HIV prevention in Papua New Guinea (PNG). PNG has a concentrated HIV epidemic which is largely heterosexually transmitted. There are a diverse range of male circumcision and penile modification practices across PNG. Exploring the implications of male circumcision for women in PNG is important to inform evidence-based health policy that will result in positive, intended consequences. **METHODS:** The transformational grounded theory study incorporated participatory action research and decolonizing methodologies. In Phase One, an existing data set from a male circumcision study of 861 male and 519 female participants was theoretically sampled and analyzed for women's understanding and experience of male circumcision. In Phase Two of the study, primary data were co-generated with 64 women in seven interpretive focus group discussions and 11 semi-structured interviews to develop a theoretical model of the processes used by women to manage the outcomes of male circumcision. In Phase Three participants assisted to refine the developing transformational grounded theory and identify actions required to

improve health. **RESULTS:** Many women know a lot about male circumcision and penile modification and the consequences for themselves, their families and communities. Their ability to act on this knowledge is determined by numerous social, cultural and economic factors. A transformational grounded theory was developed with connecting categories of: Women Know a Lot; Increasing Knowledge; Increasing Options; and Acting on Choices. Properties and dimensions of each category are represented in the model, along with the intervening condition of Safety. The condition of Safety contextualises the overarching lived reality for women in PNG, enables the inclusion of men in the transformational grounded theory model, and helps to explain relationships between men and women. The theory presents the core category as Power of Choice. **CONCLUSIONS:** This transformational grounded theory provides a means to explore how women experience male circumcision and penile modification in PNG, including for HIV prevention. Women who have had opportunities for education have a greater range of choices and an increased opportunity to act upon these choices. However, women can only exercise their power of choice in the context of safety. The concept of Peace drawn from the Social Determinants of Health is applied in order to extend the explanatory power of the transformational grounded theory. This study shows that women's ambivalence about male circumcision is often related to lack of safety, a consequence of gender inequality in PNG.

# 120 Robbins E, Shepard J, Rochat P.

Variations in judgments of intentional action and moral evaluation across eight cultures.

*Cognition* 2017 Jul;164:22-30. doi: 10.1016/j.cognition.2017.02.012. Epub 2017 Mar 29.

Individuals tend to judge bad side effects as more intentional than good side effects (the Knobe or side-effect effect). Here, we assessed how widespread these findings are by testing eleven adult cohorts of eight highly contrasted cultures on their attributions of intentional action as well as ratings of blame and praise. We found limited generalizability of the original side-effect effect, and even a reversal of the effect in two rural, traditional cultures (Samoa and Vanuatu), where participants were more likely to judge the good side effect as intentional. Three follow-up experiments indicate that this reversal of the side-effect effect is not due to semantics and may be linked to the perception of the status of the protagonist. These results highlight the importance of factoring cultural context in our understanding of moral cognition.

# 121 Rosewell A, Makita L, Muscatello D, John LN, Bieb S, Hutton R, Ramamurthy S, Shearman P.

Health information system strengthening and malaria elimination in Papua New Guinea.

*Malar J* 2017 Jul 5;16(1):278. doi: 10.1186/s12936-017-1910-0.

**BACKGROUND:** The objective of the study was to describe an m-health initiative to strengthen malaria surveillance in a 184-health facility, multi-province, project aimed at strengthening the National Health Information System (NHIS) in a country with fragmented malaria surveillance, striving towards enhanced control, pre-elimination. **METHODS:** A remote-loading mobile application and secure online platform for health professionals was created



to interface with the new system (eNHIS). A case-based malaria testing register was developed and integrated geo-coded households, villages and health facilities. A malaria programme management dashboard was created, with village-level malaria mapping tools, and statistical algorithms to identify malaria outbreaks. **RESULTS:** Since its inception in 2015, 160,750 malaria testing records, including village of residence, have been reported to the eNHIS. These case-based, geo-coded malaria data are 100% complete, with a median data entry delay of 9 days from the date of testing. The system maps malaria to the village level in near real-time as well as the availability of treatment and diagnostics to health facility level. Data aggregation, analysis, outbreak detection, and reporting are automated. **CONCLUSIONS:** The study demonstrates that using mobile technologies and GIS in the capture and reporting of NHIS data in Papua New Guinea provides timely, high quality, geo-coded, case-based malaria data required for malaria elimination. The health systems strengthening approach of integrating malaria information management into the eNHIS optimizes sustainability and provides enormous flexibility to cater for future malaria programme needs.

- 122 **Rybanska V, McKay R, Jong J, Whitehouse H.** Rituals improve children's ability to delay gratification. *Child Dev* 2018 Mar;89(2):349-359. doi: 10.1111/cdev.12762. Epub 2017 Feb 18.

To be accepted into social groups, individuals must internalize and reproduce appropriate group conventions, such as rituals. The copying of such rigid and socially stipulated behavioral sequences places heavy demands on executive function. Given previous research showing that challenging executive functioning improves it, it was hypothesized that engagement in ritualistic behaviors improves children's executive functioning, in turn improving their ability to delay gratification. A 3-month circle time games intervention with 210 schoolchildren (M age = 7.78 years, SD = 1.47) in two contrasting cultural environments (Slovakia and Vanuatu) was conducted. The intervention improved children's executive function and in turn their ability to delay gratification. Moreover, these effects were amplified when the intervention task was imbued with ritual, rather than instrumental, cues.

- 123 **Salman S, Baiwog F, Page-Sharp M, Kose K, Karunajeewa HA, Mueller I, Rogerson SJ, Siba PM, Ilett KF, Davis TME.** Optimal antimalarial dose regimens for chloroquine in pregnancy based on population pharmacokinetic modelling. *Int J Antimicrob Agents* 2017 Oct;50(4):542-551. doi: 10.1016/j.ijantimicag.2017.05.011. Epub 2017 Jun 29.

Despite extensive use and accumulated evidence of safety, there have been few pharmacokinetic studies from which appropriate chloroquine (CQ) dosing regimens could be developed specifically for pregnant women. Such optimised CQ-based regimens, used as treatment for acute malaria or as intermittent preventive treatment in pregnancy (IPTp), may have a valuable role if parasite CQ sensitivity returns following reduced drug pressure. In this study, population pharmacokinetic/pharmacodynamic modelling was used to simultaneously analyse plasma concentration-time data for CQ and its

active metabolite desethylchloroquine (DCQ) in 44 non-pregnant and 45 pregnant Papua New Guinean women treated with CQ and sulfadoxine-pyrimethamine or azithromycin (AZM). Pregnancy was associated with 16% and 49% increases in CQ and DCQ clearance, respectively, as well as a 24% reduction in CQ relative bioavailability. Clearance of DCQ was 22% lower in those who received AZM in both groups. Simulations based on the final multicompartmental model demonstrated that a 33% CQ dose increase may be suitable for acute treatment for malaria in pregnancy as it resulted in equivalent exposure to that in non-pregnant women receiving recommended doses, whilst a double dose would likely be required for an effective duration of post-treatment prophylaxis when used as IPTp especially in areas of CQ resistance. The impact of co-administered AZM was clinically insignificant in simulations. The results of past/ongoing trials employing recommended adult doses of CQ-based regimens in pregnant women should be interpreted in light of these findings, and consideration should be given to using increased doses in future trials.

- 124 **Samia L, Emeto TI.**

Vaccination and nutritional status of children in Karawari, East Sepik Province, Papua New Guinea. *PLoS One* 2017 Nov 9;12(11):e0187796. doi: 10.1371/journal.pone.0187796. eCollection 2017.

Delivery of health care services to rural and remote populations in Papua New Guinea (PNG) is problematic. This is mainly due to difficulties with transportation and communication. Hence, the children in this region of PNG are likely to be at risk of malnutrition compounded by inadequate vaccination that may predispose them to preventable diseases. This study was conducted to determine the vaccination and nutritional status of children less than 5 years old in the remote and rural Karawari area of PNG. 105 children were included in the study, of whom 55% were male and 45% female. The mean age of children included in the study was 32.6 months. Their age, height, and weight by gender was not significantly different. Overall, 85% of children had incomplete vaccination. However, children above the median age of 32 months (34%) were more likely to be fully vaccinated for their age,  $\chi^2(1) = 23.294$ ,  $p < 0.005$ . In addition, 25% of children were below the -1 SD (Z-scores) for weight-for-height, 33% below the -1 SD for weight-for-age, and 25.5% below the -1 SD for height-for-age compared to WHO standards. A large proportion of children had poor nutrition status and lack protection from vaccine preventable diseases. This study recommends that the government should introduce a surveillance system for detecting issues of importance to the rural majority. We also recommend that the PNG government reopen the nearby health centre, and/or establish new facilities within the region, with adequately trained and compensated staff.

- 125 **Shanks GD.**

The multifactorial epidemiology of blackwater fever. *Am J Trop Med Hyg* 2017 Dec;97(6):1804-1807. doi: 10.4269/ajtmh.17-0533. Epub 2017 Sep 28.

Blackwater fever is a massive hemolytic event usually occurring in the context of repeated falciparum malaria infections and intermittent quinine use. Its etiology is poorly understood, and it is rarely seen today. Historical epidemiological observations from the 20th century demonstrated

variable patterns in prisoners in Andaman Islands, refugees in Macedonia, canal workers in Panama, expatriates in Rhodesia, and Second World War soldiers. Rates of blackwater fever per 1,000 malaria cases varied over two orders of magnitude. Islands, such as the Andaman Islands and New Guinea, had lower blackwater fever rates than continental areas. During the Second World War, blackwater fever rates in British soldiers in West Africa and Australian soldiers in New Guinea differed by a factor of 40 despite similar treatment regimens and falciparum malaria transmission risks. Blackwater fever is a complex interaction between host erythrocyte, falciparum malaria, and antimalarial drugs which remains poorly understood.

#### 126 Shanks GD.

Malaria-associated mortality in the Australian Defence Force during the twentieth century. *Am J Trop Med Hyg* 2017 Aug;97(2):544-547. doi: 10.4269/ajtmh.16-0748. Epub 2017 Jul 19.

Malaria has been a military problem throughout history capable of causing epidemics that stop military operations. Individual mortality was examined from records of the three major wars of the 20th century that involved Australia in which 133 (1914-1919), 92 (1943-1945), and two (1965-1967) soldiers are known to have died with malaria. Those dying were predominately enlisted soldiers with a mean age of 29 years often complicated by other infections such as influenza, pneumonia or scrub typhus. Lethal epidemics of falciparum malaria occurred in Palestine/Syria in October 1918 and New Guinea in September 1943 to March 1944. Although no Australian soldier has died in nearly 50 years from malaria, there were three serious falciparum infections in soldiers in East Timor 1999-2000 who might have died if intensive care had not been provided. Recent military deployments into Africa including United Nations contingents still show falciparum malaria's lethality despite the availability of effective malaria chemoprophylaxis.

#### 127 Sharma B, Lee TH, Nam EW.

Loneliness, insomnia and suicidal behavior among school-going adolescents in Western Pacific island countries: role of violence and injury. *Int J Environ Res Public Health* 2017 Jul 15;14(7). pii: E791. doi: 10.3390/ijerph14070791.

This study aimed to examine whether being bullied, fighting, and injury, regarded in terms of frequency and nature, were significantly associated with psychological distress and suicidal behavior, independent of substance abuse and parental support in adolescents. Secondary analysis of data from the Global School-based Student Health Survey from Kiribati, the Solomon Islands, and Vanuatu was conducted. Binomial logistic regression analysis was used to examine the association of being bullied, fighting and injury with psychological health outcomes (loneliness, insomnia, suicidal ideation and suicide attempt) at a 5% level of significance. A total of 4122 students were included; 45.5% were male, and 52.0% were 14 years of age or younger. Of the total, 9.3% felt lonely and 9.5% had insomnia most of the time over the last 12 months; 27.6% had suicidal ideation, and 30.9% reported at least one suicide attempt in the last 12 months. Multivariable logistic regression analysis showed that being bullied, fighting and injury were significantly associated with psychological health outcomes;

adjusted odds ratios (AORs) of loneliness, insomnia, suicidal ideation and suicide attempt increased with increased exposure to bullying, fighting, and injury compared to the non-exposed group. Among the types of bullying victimization, the highest AORs of insomnia and suicide attempt were among students who were left out of activities, compared to the non-bullied. Among the causes of injury, adolescents injured due to a physical attack were the most likely to report the highest AORs of loneliness, insomnia and suicidal ideation compared to those not injured. Preventing violence and injury among adolescents might contribute to better mental health and reduction of suicidal behavior.

#### 128 Shih P, Worth H, Travaglia J, Kelly-Hanku A.

'Good culture, bad culture': polygyny, cultural change and structural drivers of HIV in Papua New Guinea. *Cult Health Sex* 2017 Sep;19(9):1024-1037. doi: 10.1080/13691058.2017.1287957. Epub 2017 Feb 16.

Culture is often problematised as a key structural driver of HIV transmission in Papua New Guinea. Official HIV programmes, as well as church teachings, tend to focus on customary marital practices of polygyny and bride price payments as 'harmful traditions'. This focus can oversimplify the effects of current and historical nuances of cultural, political and economic change on sexual concurrency and gender inequality. Community-based healthcare workers in Southern Highlands Province explain that customary marital practices are now highly reconfigured from their traditional forms. A recent mining boom has financially advantaged local and travelling men, who are driving an increase of sexual concurrency, transactional sex and inflation of bride price payments. Healthcare workers suggest that the erosion of important social relationships and kinship obligations by the expanding cash economy has caused an intensification of individual male power while enhancing the vulnerability of women. Yet without the means to challenge the effects of uneven economic development, healthcare workers are left to target 'culture' as the central influence on individual behaviours. A commitment to address structural inequality by political leadership and in HIV prevention programmes and a careful contextualisation of cultural change is needed.

#### 129 Shih P, Worth H, Travaglia J, Kelly-Hanku A.

Pastoral power in HIV prevention: converging rationalities of care in Christian and medical practices in Papua New Guinea. *Soc Sci Med* 2017 Nov;193:51-58. doi: 10.1016/j.socscimed.2017.09.049. Epub 2017 Sep 29.

In his conceptualisation of pastoral power, Michel Foucault argues that modern healthcare practices derive a specific power technique from pastors of the early Christian church. As experts in a position of authority, pastors practise the care of others through implicitly guiding them towards thoughts and actions that effect self-care, and towards a predefined realm of acceptable conduct, thus having a regulatory effect. This qualitative study of healthcare workers from two Christian faith-based organisations in Papua New Guinea examines the pastoral rationalities of HIV prevention practices which draw together globally circulated modern medical knowledge and Christian teachings in sexual morality for implicit social regulation. Community-based HIV awareness education,

voluntary counseling and testing services, mobile outreach, and economic empowerment programs are standardised by promoting behavioural choice and individual responsibility for health. Through pastoral rationalities of care, healthcare practices become part of the social production of negative differences, and condemn those who become ill due to perceived immorality. This emphasis assumes that all individuals are equal in their ability to make behavioural choices, and downplays social inequality and structural drivers of HIV risk that are outside individual control. Given healthcare workers' recognition of the structural drivers of HIV, yet their lack of language and practical strategies to address these issues, political commitment is needed to enhance structural competency among HIV prevention programs and healthcare workers.

- 130 **Smith J, Tahani L, Bobogare A, Bugoro H, Otto F, Fafale G, Hiriassa D, Kazazic A, Beard G, Amjadali A, Jeanne I.**

Malaria early warning tool: linking inter-annual climate and malaria variability in northern Guadalcanal, Solomon Islands.

*Malar J* 2017 Nov 21;16(1):472. doi: 10.1186/s12936-017-2120-5.

**BACKGROUND:** Malaria control remains a significant challenge in the Solomon Islands. Despite progress made by local malaria control agencies over the past decade, case rates remain high in some areas of the country. Studies from around the world have confirmed important links between climate and malaria transmission. This study focuses on understanding the links between malaria and climate in Guadalcanal, Solomon Islands, with a view towards developing a climate-based monitoring and early warning for periods of enhanced malaria transmission. **METHODS:** Climate records were sourced from the Solomon Islands meteorological service (SIMS) and historical malaria case records were sourced from the National Vector-Borne Disease Control Programme (NVBDP). A declining trend in malaria cases over the last decade associated with improved malaria control was adjusted for. A stepwise regression was performed between climate variables and climate-associated malaria transmission (CMT) at different lag intervals to determine where significant relationships existed. The suitability of these results for use in a three-tiered categorical warning system was then assessed using a Mann-Whitney U test. **RESULTS:** Of the climate variables considered, only rainfall had a consistently significant relationship with malaria in North Guadalcanal. Optimal lag intervals were determined for prediction using  $R^2$  skill scores. A highly significant negative correlation ( $R = -0.86$ ,  $R^2 = 0.74$ ,  $p < 0.05$ ,  $n = 14$ ) was found between October and December rainfall at Honiara and CMT in northern Guadalcanal for the subsequent January-June. This indicates that drier October-December periods are followed by higher malaria transmission periods in January-June. Cross-validation emphasized the suitability of this relationship for forecasting purposes as did Mann-Whitney U test results showing that rainfall below or above specific thresholds was significantly associated with above or below normal malaria transmission, respectively. **CONCLUSION:** This study demonstrated that rainfall provides the best predictor of malaria transmission in North Guadalcanal. This relationship is thought to be underpinned by the unique hydrological conditions in

northern Guadalcanal which allow sandbars to form across the mouths of estuaries which act to develop or increase stagnant brackish marshes in low rainfall periods. These are ideal habitats for the main mosquito vector, *Anopheles farauti*. High rainfall accumulations result in the flushing of these habitats, reducing their viability. The results of this study are now being used as the basis of a malaria early warning system which has been jointly implemented by the SIMS, NVBDP and the Australian Bureau of Meteorology.

- 131 **Smith TE, Pond CD, Pierce E, Harmer ZP, Kwan J, Zachariah MM, Harper MK, Wyche TP, Matainaho TK, Bugni TS, Barrows LR, Ireland CM, Schmidt EW.**

Accessing chemical diversity from the uncultivated symbionts of small marine animals.

*Nat Chem Biol* 2018 Feb;14(2):179-185. doi: 10.1038/nchembio.2537. Epub 2018 Jan 1.

Chemistry drives many biological interactions between the microbiota and host animals, yet it is often challenging to identify the chemicals involved. This poses a problem, as such small molecules are excellent sources of potential pharmaceuticals, pretested by nature for animal compatibility. We discovered anti-HIV compounds from small, marine tunicates from the Eastern Fields of Papua New Guinea. Tunicates are a reservoir for new bioactive chemicals, yet their small size often impedes identification or even detection of the chemicals within. We solved this problem by combining chemistry, metagenomics, and synthetic biology to directly identify and synthesize the natural products. We show that these anti-HIV compounds, the divamides, are a novel family of lanthipeptides produced by symbiotic bacteria living in the tunicate. Neighboring animal colonies contain structurally related divamides that differ starkly in their biological properties, suggesting a role for biosynthetic plasticity in a native context wherein biological interactions take place.

- 132 **Sundram S, Ventevogel P.**

The mental health of refugees and asylum seekers on Manus Island.

*Lancet* 2017 Dec 9;390(10112):2534-2536. doi: 10.1016/S0140-6736(17)33051-9. Epub 2017 Nov 27.

- 133 **Tervonen H, Foliaki S, Bray F, Roder D.**

Cancer epidemiology in the small nations of Pacific Islands.

*Cancer Epidemiol* 2017 Oct;50(Pt B):184-192. doi: 10.1016/j.canep.2017.09.002.

**BACKGROUND:** Pacific island countries and territories (PICTs) comprise 20,000-30,000 islands in the Pacific Ocean. PICTs face challenges in relation to small population sizes, geographic dispersion, increasing adoption of unhealthy lifestyles and the burden of both communicable and non-communicable diseases, including cancer. This study reviews data on cancer incidence and mortality in the PICTs, with special focus on indigenous populations. **METHODS:** PICTs with populations of <1.5 million ('small nations') were included in this study. Information on cancer incidence and mortality was extracted from the GLOBOCAN 2012 database. Scientific and grey literature was narratively reviewed for publications published after 2000. **RESULTS:** Of the 21 PICTs, seven countries were included in the

GLOBOCAN 2012 (Fiji, French Polynesia, Guam, New Caledonia, Samoa, Solomon Islands, Vanuatu). The highest cancer incidence and mortality rates were reported in New Caledonia (age-standardized incidence and mortality rates 297.9 and 127.3 per 100,000) and French Polynesia (age-standardized incidence and mortality rates 255.0 and 134.4 per 100,000), with relatively low rates in other countries. Literature indicated that cancer was among the leading causes of death in most PICTs; thus they now experience a double burden of cancers linked to infections and life-style and reproductive factors. Further, ethnic differences in cancer incidence and mortality have been reported in some PICTs, including Fiji, Guam, New Caledonia and Northern Mariana Islands. **CONCLUSION:** Cancer incidence in the PICTs was recorded to be relatively low, with New Caledonia and French Polynesia being exceptions. Low recorded incidence is likely to be explained by incomplete cancer registration as cancer had an important contribution to mortality. Further endeavors are needed to develop and strengthen cancer registration infrastructure and practices and to improve data quality and registration coverage in the PICTs.

- 134 **Thriemer K, Bobogare A, Ley B, Gudo CS, Alam MS, Anstey NM, Ashley E, Baird JK, Gryseels C, Jambert E, Lacerda M, Laird F, Marfurt J, Pasaribu AP, Poesprodjo JR, Sutanto I, Taylor WR, van den Boogaard C, Battle KE, Dysoley L, Ghimire P, Hawley B, Hwang J, Khan WA, Mudin RNB, Sumiwi ME, Ahmed R, Aktaruzzaman MM, Awasthi KR, Bardaji A, Bell D, Boaz L, Burdam FH, Chandramohan D, Cheng Q, Chindawongsa K, Culpepper J, Das S, Deray R, Desai M, Domingo G, Duoquan W, Duparc S, Floranita R, Gerth-Guyette E, Howes RE, Hugo C, Jagoe G, Sariwati E, Jhora ST, Jinwei W, Karunajeewa H, Kenangalem E, Lal BK, Landuwulang C, Le Perru E, Lee SE, Makita LS, McCarthy J, Mekuria A, Mishra N, Naket E, Nambanya S, Nausien J, Duc TN, Thi TN, Noviyanti R, Pfeffer D, Qi G, Rahmalia A, Rogerson S, Samad I, Sattabongkot J, Satyagraha A, Shanks D, Sharma SN, Sibley CH, Sungkar A, Syafruddin D, Talukdar A, Tarning J, Ter Kuile F, Thapa S, Theodora M, Huy TT, Waramin E, Waramori G, Woyessa A, Wongsrichanalai C, Xa NX, Yeom JS, Hermawan L, Devine A, Nowak S, Jaya I, Supargiyono S, Grietens KP, Price RN.**

Quantifying primaquine effectiveness and improving adherence: a round table discussion of the APMEN Vivax Working Group.

*Malar J* 2018 Jun 20;17(1):241. doi: 10.1186/s12936-018-2380-8.

The goal to eliminate malaria from the Asia-Pacific by 2030 will require the safe and widespread delivery of effective radical cure of malaria. In October 2017, the Asia Pacific Malaria Elimination Network Vivax Working Group met to discuss the impediments to primaquine (PQ) radical cure, how these can be overcome and the methodological difficulties in assessing clinical effectiveness of radical cure. The salient discussions of this meeting which involved 110 representatives from 18 partner countries and 21 institutional partner organizations are reported. Context specific strategies to improve adherence are needed to increase understanding and awareness of PQ within affected communities; these must include education and health promotion

programs. Lessons learned from other disease programs highlight that a package of approaches has the greatest potential to change patient and prescriber habits; however, optimizing the components of this approach and quantifying their effectiveness is challenging. In a trial setting, the reactivity of participants results in patients altering their behaviour and creates inherent bias. Although bias can be reduced by integrating data collection into the routine health care and surveillance systems, this comes at a cost of decreasing the detection of clinical outcomes. Measuring adherence and the factors that relate to it, also requires an in-depth understanding of the context and the underlying sociocultural logic that supports it. Reaching the elimination goal will require innovative approaches to improve radical cure for vivax malaria, as well as the methods to evaluate its effectiveness.

- 135 **Tiller R, Jones J.**

Ethical reflection for medical electives.

*Clin Teach* 2018 Apr;15(2):169-172. doi: 10.1111/tct.12657. Epub 2017 May 10.

**BACKGROUND:** Forty per cent of UK medical students undertake their elective in a developing country. Although these opportunities are often rewarding, students encounter ethical questions, both in preparation and undertaking these projects. The British Medical Association highlights three key ethical considerations for elective students: clinical challenges, cultural challenges and impact on the host institution. This report reflects on these considerations in the context of a 4-week medical elective conducted by UK medical students in the Solomon Islands. **METHODS:** Daily interviews were conducted with a focus group of six medical students in the Solomon Islands over a 4-week elective period. Descriptive analysis identified key themes. **FINDINGS:** Students were aware of guidelines stating that they must act within their competency, but found it difficult to assess their own skills and capacities in unfamiliar non-UK settings. Culturally different societal and medical norms proved particularly challenging. The impact of the student elective on the host hospital was also larger than anticipated. **DISCUSSION:** In UK medical education, formal assessment sets the benchmark for competency. Assessments cannot cover every situation encountered on elective, and so students must therefore develop an alternative benchmark to measure their ability. The lack of research into the impact of electives on host institutions makes assessing the ethical nature of electives challenging. The British Medical Association highlights three key ethical considerations for elective students. **CONCLUSION:** Prospective elective students would benefit from pre-departure training on self-assessment of competency and cultural awareness. UK medical schools have an ethical duty to encourage students to consider the impact of their elective placements on host institutions.

- 136 **Toliman PJ, Kaldor JM, Tabrizi SN, Vallely AJ.**

Innovative approaches to cervical cancer screening in low- and middle-income countries.

*Climacteric* 2018 Jun;21(3):235-238. doi: 10.1080/13697137.2018.1439917. Epub 2018 Feb 28.

The estimated cervical cancer burden is over ten-fold greater in low- and middle-income countries (LMICs) than in high-income countries. This health



gap is thought to be primarily due to limited access to effective screening and treatment programs for cervical pre-cancer and cancer in such settings. The World Health Organization advocates a policy of 'screen and treat' approach to cervical screening in LMICs and recommends visual inspection of the cervix with acetic acid (VIA) or Lugo's iodine (VILI), followed by ablative cervical cryotherapy if indicated, and this policy has been implemented in many high-burden settings. The performance of VIA/VILI as a primary screening tool for the detection of cervical pre-cancer and cancer has, however, been inconsistent. Recently, many high-income countries have integrated HPV-DNA testing into their cervical cancer screening programs. The comparatively high cost and resource requirements of HPV-based screening have to date prevented many LMICs from doing the same. A significant development has been the entrance of innovative, easy-to-use and highly accurate HPV tests that can be provided at point of care; these could enable LMICs to implement 'test and treat' approaches for cervical cancer screening.

**137 Tosif S, Nasi T, Gray A, Sadr-Azodi N, Ogaoga D, Duke T.**

Assessment of the quality of neonatal care in the Solomon Islands.

*J Paediatr Child Health* 2018 Feb;54(2):165-171. doi: 10.1111/jpc.13686. Epub 2017 Sep 14.

**AIM:** To identify strengths and obstacles for improving the quality of newborn care in the Solomon Islands. Improving the quality of newborn care is a priority in the Sustainable Development Goals and the Action Plan for Healthy Newborns in the Western Pacific. The neonatal mortality rate in the Solomon Islands, a lower-middle-income country, has improved slower than overall child mortality. In 2013, neonatal mortality (13.2/1000) constituted 44% of under-5 deaths (30.1/1000). **METHODS:** A cross-sectional study of newborn care in five provincial hospitals using a World Health Organization assessment tool for hospital quality of care. Twelve months of neonatal records of the National Referral Hospital (NRH) labour ward and nursery were audited. **RESULTS:** Essential medications and basic equipment were generally available. Challenges included workforce shortages and lack of expertise, high costs, organisation and maintenance of equipment, infection control and high rates of stillbirth. Over 12 months at the NRH labour ward, there were 5412 live births, 65 (1.2%) 'fresh' stillbirths and 96 (1.8%) 'macerated' stillbirths. Over the same period, there were an associated 779 nursery admissions, and the main causes of mortality were complications of prematurity, birth asphyxia, congenital abnormalities and sepsis. Total neonatal mortality at NRH was 16 per 1000 live births, and 77% of deaths occurred in the first 3 days of life. **CONCLUSIONS:** Infrastructure limitations, technical maintenance and equipment organisation were obstacles to newborn care. Greater health-care worker knowledge and skills for early essential newborn care, infection control and management of newborn complications is needed.

**138 Tsukahara T, Sugahara T, Furusawa T, Hombhanje FW.**

Comparison of health service utilization for febrile children before and after introduction of malaria rapid diagnostic tests and artemisinin-based combination therapy in rural Papua New Guinea.

*Front Public Health* 2018 Mar 13;6:75. doi: 10.3389/fpubh.2018.00075. eCollection 2018.

**Background:** In Papua New Guinea (PNG), a malaria treatment policy using rapid diagnostic tests (RDTs) plus artemisinin-based combination therapy (ACT) was widely introduced to rural communities in 2012. The objectives of the study were to evaluate the effect of this RDT/ACT introduction to a rural PNG population on health service utilization and to compare factors associated with health service utilization before and after the RDT/ACT introduction. **Methods:** Household surveys with structured questionnaires were conducted before and after the introduction of RDT/ACT in a catchment area of a health center in East Sepik Province, PNG. We interviewed caregivers with children less than 15 years of age and collected data on fever episodes in the preceding 2 weeks. Using propensity score matching, febrile children before the introduction of RDT/ACT were matched to febrile children after the introduction. Then, the adjusted difference in the proportion of health service utilization [ie, the average treatment effect (ATE) of the introduction of RDT/ACT on health service utilization] was estimated. We also employed a multilevel Poisson regression model to investigate factors influencing the use of health services. **Results:** Of 4,690 children, 911 (19%) were reported to have a fever episode. The unadjusted proportion of health service utilization was 51.7 and 57.2% before and after the RDT/ACT introduction, respectively. After matching, no significant difference in the health service utilization was observed before and after the introduction of RDT/ACT (ATE: 0.063, 95% confidence interval -0.024 to 0.150). Multilevel regression analysis showed that the consistent factors associated with a higher utilization of health services were severe illness and being female. **Conclusion:** The utilization of health services was not significantly different before and after the introduction of RDT/ACT. Villagers may have neither sufficient information on the new protocol nor high acceptance of RDT/ACT. The observed gender bias in health service utilization could be due to female caregivers' preferences toward girls.

**139 Tucci JD, Pumuye PP, Helsby NA, Barratt DT, Pokeya PP, Hombhanje F, Somogyi AA.**

Pharmacogenomics in Papua New Guineans: unique profiles and implications for enhancing drug efficacy while improving drug safety.

*Pharmacogenet Genomics* 2018 Jun;28(6):153-164. doi: 10.1097/FPC.0000000000000335.

Papua New Guinea (PNG) can be roughly divided into highland, coastal and island peoples with significant mitochondrial DNA differentiation reflecting early and recent distinct migrations from Africa and East Asia, respectively. Infectious diseases such as tuberculosis, malaria and HIV severely impact on the health of its peoples for which drug therapy is the major treatment and pharmacogenetics has clinical relevance for many of these drugs. Although there is generally little information about known single nucleotide polymorphisms in the population, in some instances, their frequencies have been shown to be higher than anywhere worldwide. For example, CYP2B6\*6 is over 50%, and CYP2C19\*2 and \*3 are over 40 and 25%, respectively. Conversely, CYP2A6\*9, 2B6\*2, \*3, \*4 and \*18, and 2C8\*3 appear to be much lower than in Whites. CYP2D6 known variants are



unclear, and for phase II enzymes, only UGT2B7 and UGT1A9 data are available, with variant frequencies either slightly lower than or similar to Whites. Although almost all PNG people tested are rapid acetylators, which variant(s) define this phenotype are not known. For HLA-B\*13:01, HLA-B\*35:05 and HLA-C\*04:01, the frequencies show some regioselectivity, but the clinical implications with respect to adverse drug reactions are not known. There are minimal phenotype data for the CYPs and nothing is known about drug transporter or receptor genetics. Determination of genetic variants that are rare in Whites or Asians but common in PNG people is a topic of both scientific and clinical importance, and further research needs to be carried out. Optimizing the safety and efficacy of infectious disease drug therapy through pharmacogenetic studies that have translation potential is a priority.

- 140 **Tynan A, Vallely L, Kupul M, Neo R, Fiya V, Worth H, Kariwiga G, Mola GDL, Kaldor J, Kelly-Hanku A.**

Programmes for the prevention of parent-to-child transmission of HIV in Papua New Guinea: health system challenges and opportunities.

*Int J Health Plann Manage* 2018 Jan;33(1):e367-e377. doi: 10.1002/hpm.2450. Epub 2017 Sep 27.

**BACKGROUND:** Prevention of parent-to-child transmission (PPTCT) of HIV is a highly complex package of interventions, which spans services in both maternal and child health programmes. In Papua New Guinea (PNG), a commitment to ensure that all pregnant women and their partners have access to the full range of PPTCT interventions exists; however, efforts to increase access and utilisation of PPTCT remain far from optimal. The aim of this paper is to examine health care worker (HCW) perception of health system factors impacting on the performance of PPTCT programmes. **METHOD:** Sixteen interviews were undertaken with HCWs involved in the PPTCT programme. Application of the WHO 6 building blocks of a health system was applied, and further thematic analysis was conducted on the data with assistance from the analysis software NVivo. **RESULTS:** Broken equipment, problems with access to medication and supplies, and poorly supported workforce were reported as barriers for implementing a successful PPTCT programme. The absence of central coordination of this complex, multistaged programme was also recognised as a key issue. **CONCLUSION:** The study findings highlight an important need for investment in appropriately trained and supported HCWs and integration of services at each stage of the PPTCT programme. Lessons from the PPTCT experience in PNG may inform policy discussions and considerations in other similar contexts.

- 141 **Ubillos I, Campo JJ, Requena P, Ome-Kaius M, Hanieh S, Rose H, Samol P, Barrios D, Jiménez A, Bardaji A, Mueller I, Menéndez C, Rogerson S, Moncunill G, Dobaño C.**

Chronic exposure to malaria is associated with inhibitory and activation markers on atypical memory B cells and marginal zone-like B cells.

*Front Immunol* 2017 Aug 21;8:966. doi: 10.3389/fimmu.2017.00966. eCollection 2017.

In persistent infections that are accompanied by chronic immune activation, such as human immunodeficiency virus, hepatitis C virus, and malaria, there is an increased frequency of a

phenotypically distinct subset of memory B cells lacking the classic memory marker CD27 and showing a reduced capacity to produce antibodies. However, critical knowledge gaps remain on specific B cell changes and immune adaptation in chronic infections. We hypothesized that expansion of atypical memory B cells (aMBCs) and reduction of activated peripheral marginal zone (MZ)-like B cells in constantly exposed individuals might be accompanied by phenotypic changes that would confer a tolerogenic profile, helping to establish tolerance to infections. To better understand malaria-associated phenotypic abnormalities on B cells, we analyzed peripheral blood mononuclear cells from 55 pregnant women living in a malaria-endemic area of Papua New Guinea and 9 Spanish malaria-naïve individuals using four 11-color flow cytometry panels. We assessed the expression of markers of B cell specificity (IgG and IgM), activation (CD40, CD80, CD86, b220, TACI, and CD150), inhibition (PD1, CD95, and CD71), and migration (CCR3, CXCR3, and CD62L). We found higher frequencies of active and resting aMBC and marked reduction of MZ-like B cells, although changes in absolute cell counts could not be assessed. Highly exposed women had higher PD1+, CD95+, CD40+, CD71+, and CD80+-activated aMBC frequencies than non-exposed subjects. Malaria exposure increased frequencies of b220 and proapoptotic markers PD1 and CD95, and decreased expression of the activation marker TACI on MZ-like B cells. The increased frequencies of inhibitory and apoptotic markers on activated aMBCs and MZ-like B cells in malaria-exposed adults suggest an immune-homeostatic mechanism for maintaining B cell development and function while simultaneously downregulating hyperreactive B cells. This mechanism would keep the B cell activation threshold high enough to control infection but impaired enough to tolerate it, preventing systemic inflammation.

- 142 **Urlacher SS, Liebert MA, Konečná M.**

Global variation in diurnal cortisol rhythms: evidence from Garisakang forager-horticulturalists of lowland Papua New Guinea.

*Stress* 2018 Mar;21(2):101-109. doi: 10.1080/10253890.2017.1414798. Epub 2017 Dec 13.

The hypothalamic-pituitary-adrenal (HPA) axis represents an important and evolutionarily ancient biological pathway linking physical and psychological stressors with human health. Despite considerable research exploring the physiological stress response among developed populations, few studies have examined HPA activity in non-industrialized contexts, restricting understanding of variation in human stress reactivity across global socio-ecological diversity. The present study addresses this shortcoming by investigating diurnal cortisol rhythms among Garisakang forager-horticulturalists of remote, lowland Papua New Guinea. Using a large sample of repeated salivary cortisol measurements from 169 participants (age 4-70 years), multilevel growth curve models were constructed to assess Garisakang waking cortisol concentrations and diurnal cortisol slopes. As predicted, results demonstrate identifiable but substantially diminished diurnal cortisol rhythms relative to those of industrialized populations. Sample-wide, Garisakang cortisol concentrations are highest upon waking (mean=4.86nmol/L) and decrease throughout the day at a mean rate

of only  $-0.18 \text{ nmol/L/h}$  or  $-6.20\%/h$ . Age and sex significantly predict evaluated cortisol parameters in ways not consistently reported among industrialized populations, suggesting that Garisakang diurnal cortisol rhythms are defined by distinct ontogenetic trajectories across the lifespan. These findings highlight cross-cultural diversity in HPA activity and have important implications for understanding basic mechanisms of the physiological stress response in contexts of chronic physical stressors such as limited nutrition, heavy burden of infectious disease, and high levels of physical activity.

- 143 **Vallely LM, Toliman P, Ryan C, Rai G, Wapling J, Gabuzzi J, Allen J, Opa C, Munnall G, Kaima P, Kombuk B, Kumbia A, Kombati Z, Law G, Kelly-Hanku A, Wand H, Siba PM, Mola GDL, Kaldor JM, Vallely AJ.**

Performance of syndromic management for the detection and treatment of genital *Chlamydia trachomatis*, *Neisseria gonorrhoeae* and *Trichomonas vaginalis* among women attending antenatal, well woman and sexual health clinics in Papua New Guinea: a cross-sectional study.

*BMJ Open* 2017 Dec 29;7(12):e018630. doi: 10.1136/bmjopen-2017-018630.

**OBJECTIVE:** Papua New Guinea (PNG) has among the highest estimated prevalences of genital *Chlamydia trachomatis* (CT), *Neisseria gonorrhoeae* (NG) and *Trichomonas vaginalis* (TV) of any country in the Asia-Pacific region. Diagnosis and treatment of these infections have relied on the WHO-endorsed syndromic management strategy that uses clinical presentation without laboratory confirmation to make treatment decisions. We evaluated the performance of this strategy in clinical settings in PNG. **DESIGN:** Women attending antenatal (ANC), well woman (WWC) and sexual health (SHC) clinics in four provinces were invited to participate, completed a face-to-face interview and clinical examination, and provided genital specimens for laboratory testing. We estimated the performance characteristics of syndromic diagnoses against combined laboratory diagnoses. **RESULTS:** 1764 women were enrolled (ANC = 765; WWC = 614; SHC = 385). The prevalences of CT, NG and TV were highest among women attending ANC and SHC. Among antenatal women, syndromic diagnosis of sexually transmitted infection had low sensitivity (9%-21%) and positive predictive value (PPV) (7%-37%), but high specificity (76%-89%) and moderate negative predictive value (NPV) (55%-86%) for the combined endpoint of laboratory-confirmed CT, NG or TV. Among women attending WWC and SHC, 'vaginal discharge syndrome' had moderate to high sensitivity (72%-78%) and NPV (62%-94%), but low specificity (26%-33%) and PPV (8%-38%). 'Lower abdominal pain syndrome' had low sensitivity (26%-41%) and PPV (8%-23%) but moderate specificity (66%-68%) and high NPV (74%-93%) among women attending WWC, and moderate-high sensitivity (67%-79%) and NPV (62%-86%) but low specificity (26%-28%) and PPV (14%-33%) among SHC attendees. **CONCLUSION:** The performance of syndromic management for the detection and treatment of genital chlamydia, gonorrhoea and trichomonas was poor among women in different clinical settings in PNG. New diagnostic strategies are needed to control these infections and to prevent their adverse health outcomes in PNG and other high-burden

countries.

- 144 **van den Biggelaar AHJ, Richmond PC, Fuery A, Anderson D, Opa C, Saleu G, Lai M, Francis JP, Alpers MP, Pomat WS, Lehmann D.**

Pneumococcal responses are similar in Papua New Guinean children aged 3-5 years vaccinated in infancy with pneumococcal polysaccharide vaccine with or without prior pneumococcal conjugate vaccine, or without pneumococcal vaccination.

*PLoS One* 2017 Oct 13;12(10):e0185877. doi: 10.1371/journal.pone.0185877. eCollection 2017.

**TRIAL DESIGN:** In an earlier trial, Papua New Guinean (PNG) children at high risk of pneumococcal disease were randomized to receive 0 or 3 doses of 7-valent pneumococcal conjugate vaccine (PCV7), followed by a single dose of 23-valent pneumococcal polysaccharide vaccine (PPV23) at 9 months of age. We here studied in a non-randomized follow-up trial the persistence of pneumococcal immunity in these children at 3-5 years of age ( $n = 132$ ), and in 121 community controls of a similar age with no prior pneumococcal vaccination. **METHODS:** Circulating IgG antibody titers to all PCV7 and PPV23-only serotypes 2, 5 and 7F were measured before and after challenge with 1/5th of a normal PPV23 dose. Serotype-specific memory B-cells were enumerated at 10 months and 3-5 years of age for a subgroup of study children. **RESULTS:** Serotype-specific IgG antibody titers before and after challenge were similar for children who received PCV7/PPV23, PPV23 only, or no pneumococcal vaccines. Before challenge, at least 89% and 59% of children in all groups had serotype-specific titers  $\geq 0.35 \mu\text{g/ml}$  and  $\geq 1.0 \mu\text{g/ml}$ , respectively. Post-challenge antibody titers were higher or similar to pre-challenge titers for most children independent of pneumococcal vaccination history. The rise in antibody titers was significantly lower when pre-challenge titers were higher. Overall the relative number of serotype-specific memory B-cells remained the same or increased between 10 months and 3-5 years of age, and there were no differences in serotype-specific memory B-cell numbers at 3-5 years of age between the three groups. **CONCLUSIONS:** Immunity induced by PCV7 and/or PPV23 immunization in infancy does not exceed that of naturally acquired immunity in 3-5-year-old children living in a highly endemic area. Also, there was no evidence that PPV23 immunization in the first year of life following PCV7 priming induces longer-term hypo-responsiveness.

- 145 **van der Meulen Rodgers Y, Kassens AL.**

Women's asset ownership and children's nutritional status: evidence from Papua New Guinea.

*Soc Sci Med* 2018 May;204:100-107. doi: 10.1016/j.socscimed.2018.03.026. Epub 2018 Mar 21.

This study examines how women's asset ownership is associated with children's nutritional status in Papua New Guinea, a country with some of the most severe child malnutrition in the world. The 2009-2010 Household Income and Expenditure Survey is employed, but restricted to children under the age of 72 months living with married mothers, leaving a final analytic sample of 1651. Asset ownership is expected to strengthen mothers' income-generating capacity and their bargaining power within the home, which increases investments in children's health. Women's ownership of fishing and agricultural equipment (important for meeting

subsistence needs and for generating cash earnings) appears to be driving most of the results. OLS regression results point to beneficial effects of maternal asset ownership for children's height-for-age, weight-for-height, and weight-for-age Z-scores, and results from detailed quantile regressions indicate that these effects occur at various parts of the distribution, especially for children's WAZ scores.

- 146 **Vasileva H, Butcher R, Pickering H, Sokana O, Jack K, Solomon AW, Holland MJ, Roberts CH.**

Conjunctival transcriptome profiling of Solomon Islanders with active trachoma in the absence of *Chlamydia trachomatis* infection.

*Parasit Vectors* 2018 Feb 21;11(1):104. doi: 10.1186/s13071-018-2682-2.

**BACKGROUND:** Clinical signs of active (inflammatory) trachoma are found in many children in the Solomon Islands, but the majority of these individuals have no serological evidence of previous infection with *Chlamydia trachomatis*. In Temotu and Rennell and Bellona provinces, ocular infections with *C. trachomatis* were seldom detected among children with active trachoma; a similar lack of association was seen between active trachoma and other common bacterial and viral causes of follicular conjunctivitis. Here, we set out to characterise patterns of gene expression at the conjunctivae of children in these provinces with and without clinical signs of trachomatous inflammation-follicular (TF) and *C. trachomatis* infection. **METHODS:** Purified RNA from children with and without active trachoma was run on Affymetrix GeneChip Human Transcriptome Array 2.0 microarrays. Profiles were compared between individuals with ocular *C. trachomatis* infection and TF (group D; n=6), individuals with TF but no *C. trachomatis* infection (group I; n=7), and individuals without TF or *C. trachomatis* infection (group N; n=7). Differential gene expression and gene set enrichment for pathway membership were assessed. **RESULTS:** Conjunctival gene expression profiles were more similar within-group than between-group. Principal components analysis indicated that the first and second principal components combined explained almost 50% of the variance in the dataset. When comparing the D group to the N group, genes involved in T-cell proliferation, B-cell signalling and CD8+ T cell signalling pathways were differentially regulated. When comparing the D group to the I group, CD8+ T-cell regulation, interferon-gamma and IL17 production pathways were enriched. Genes involved in RNA transcription and translation pathways were upregulated when comparing the D group to the N group. **CONCLUSIONS:** Gene expression profiles in children in the Solomon Islands indicate immune responses consistent with bacterial infection when TF and *C. trachomatis* infection are concurrent. The transcriptomes of children with TF but without identified infection were not consistent with allergic or viral conjunctivitis.

- 147 **Venketasubramanian N, Yoon BW, Pandian J, Navarro JC.**

Stroke epidemiology in South, East, and South-East Asia: a review.

*J Stroke* 2017 Sep;19(3):286-294. doi: 10.5853/jos.2017.00234. Epub 2017 Sep 29.

Asia, which holds 60% of the world's population, comprises some developing countries which are in economic transition. This paper reviews the

epidemiology of stroke in South, East and South-East Asia. Data on the epidemiology of stroke in South, East, and South-East Asia were derived from the Global Burden of Disease study (mortality, disability-adjusted life-years [DALYs] lost because of stroke), World Health Organization (vascular risk factors in the community), and publications in PubMed (incidence, prevalence, subtypes, vascular risk factors among hospitalized stroke patients). Age- and sex-standardized mortality is the lowest in Japan, and highest in Mongolia. Community-based incidence data of only a few countries are available, with the lowest rates being observed in Malaysia, and the highest in Japan and Taiwan. The availability of prevalence data is higher than incidence data, but different study methods were used for case-finding, with different age bands. For DALYs, Japan has the lowest rates, and Mongolia the highest. For community, a high prevalence of hypertension is seen in Mongolia and Pakistan; diabetes mellitus in Papua New Guinea, Pakistan, and Mongolia; hypercholesterolemia in Japan, Singapore, and Brunei; inactivity in Malaysia; obesity in Brunei, Papua New Guinea, and Mongolia; tobacco smoking in Indonesia. Hypertension is the most frequent risk factor, followed by diabetes mellitus and smoking. Ischemic stroke occurs more frequently than hemorrhagic stroke, and subarachnoid hemorrhages are uncommon. There are variations in the stroke epidemiology between countries in South, East, and South-East Asia. Further research on stroke burden is required.

- 148 **Waltmann A, Koepfli C, Tessier N, Karl S, Fola A, Darcy AW, Wini L, Harrison GLA, Barnadas C, Jennison C, Karunajeewa H, Boyd S, Whittaker M, Kazura J, Bahlo M, Mueller I, Barry AE.**

Increasingly inbred and fragmented populations of *Plasmodium vivax* associated with the eastward decline in malaria transmission across the Southwest Pacific.

*PLoS Negl Trop Dis* 2018 Jan 26;12(1):e0006146. doi: 10.1371/journal.pntd.0006146. eCollection 2018 Jan.

The human malaria parasite *Plasmodium vivax* is more resistant to malaria control strategies than *Plasmodium falciparum*, and maintains high genetic diversity even when transmission is low. To investigate whether declining *P. vivax* transmission leads to increasing population structure that would facilitate elimination, we genotyped samples from across the Southwest Pacific region, which experiences an eastward decline in malaria transmission, as well as samples from two time points at one site (Tetere, Solomon Islands) during intensified malaria control. Analysis of 887 *P. vivax* microsatellite haplotypes from hyperendemic Papua New Guinea (PNG, n = 443), meso-hyperendemic Solomon Islands (n = 420), and hypoendemic Vanuatu (n = 24) revealed increasing population structure and multilocus linkage disequilibrium yet a modest decline in diversity as transmission decreases over space and time. In Solomon Islands, which has had sustained control efforts for 20 years, and Vanuatu, which has experienced sustained low transmission for many years, significant population structure was observed at different spatial scales. We conclude that control efforts will eventually impact *P. vivax* population structure and with sustained pressure, populations may eventually fragment into a limited number of clustered foci that could be targeted for elimination.

- 149 **Wampfler R, Hofmann NE, Karl S, Betuela I, Kiniboro B, Lorry L, Silkey M, Robinson LJ, Mueller I, Felger I.**

Effects of liver-stage clearance by primaquine on gametocyte carriage of *Plasmodium vivax* and *P. falciparum*.

*PLoS Negl Trop Dis* 2017 Jul 21;11(7):e0005753. doi: 10.1371/journal.pntd.0005753. eCollection 2017 Jul.

**BACKGROUND:** Primaquine (PQ) is the only currently licensed antimalarial that prevents *Plasmodium vivax* (Pv) relapses. It also clears mature *P. falciparum* (Pf) gametocytes, thereby reducing post-treatment transmission. Randomized PQ treatment in a treatment-to-reinfection cohort in Papua New Guinean children permitted the study of Pv and Pf gametocyte carriage after radical cure and to investigate the contribution of Pv relapses. **METHODS:** Children received radical cure with chloroquine, artemether-lumefantrine plus either PQ or placebo. Blood samples were subsequently collected in 2-to 4-weekly intervals over 8 months. Gametocytes were detected by quantitative reverse transcription-PCR targeting *pvs25* and *pfs25*. **RESULTS:** PQ treatment reduced the incidence of Pv gametocytes by 73%, which was comparable to the effect of PQ on incidence of blood-stage infections. 92% of Pv and 79% of Pf gametocyte-positive infections were asymptomatic. Pv and to a lesser extent Pf gametocyte positivity and density were associated with high blood-stage parasite densities. Multivariate analysis revealed that the odds of gametocytes were significantly reduced in mixed-species infections compared to single-species infections for both species (ORPv = 0.39 [95% CI 0.25-0.62], ORPf = 0.33 [95% CI 0.18-0.60],  $p < 0.001$ ). No difference between the PQ and placebo treatment arms was observed in density of Pv gametocytes or in the proportion of Pv infections that carried gametocytes. First infections after blood-stage and placebo treatment, likely caused by a relapsing hypnozoite, were equally likely to carry gametocytes as first infections after PQ treatment, likely caused by an infective mosquito bite. **CONCLUSION:** Pv relapses and new infections are associated with similar levels of gametocytaemia. Relapses thus contribute considerably to the Pv reservoir highlighting the importance of effective anti-hypnozoite treatment for efficient control of Pv.

- 150 **Warner JM, Currie BJ.**

Melioidosis in Papua New Guinea and Oceania.

*Trop Med Infect Dis* 2018 Mar 15;3(1). pii: E34. doi: 10.3390/tropicalmed3010034.

Melioidosis has only been sporadically reported throughout Melanesia and the Pacific region since the first report from Guam in 1946; therefore, its contribution to the disease burden in this region is largely unknown. However, the outcome of a small number of active surveillance programs, serological surveys, and presumptive imported cases identified elsewhere provide an insight into its epidemiology and potential significance throughout the region. Both clinical cases and environmental reservoirs have been described from the rural district of Balimo in the Western Province of Papua New Guinea and from the Northern Province of New Caledonia. In both these locations the incidence of disease is similar to that described in tropical Australia and *Burkholderia pseudomallei* isolates are also phylogenetically linked to Australian isolates.

Serological evidence and presumptive imported cases identified elsewhere suggest that melioidosis exists in other countries throughout the Pacific. However, the lack of laboratory facilities and clinical awareness, and the burden of other infections of public health importance such as tuberculosis, contribute to the under-recognition of melioidosis in this region.

- 151 **Watch V, Aipit J, Kote-Yarong T, Rero A, Bolnga JW, Lufele E, Laman M.**

The burden of presumed tuberculosis in hospitalized children in a resource-limited setting in Papua New Guinea: a prospective observational study.

*Int Health* 2017 Nov 1;9(6):374-378. doi: 10.1093/inthealth/ihx043.

**Background:** In Papua New Guinea, TB is considered to be a major public health problem, but little is known about the prevalence and prognosis of presumed TB in children. **Methods:** As part of a prospective hospital-based surveillance on the northern coast of mainland Papua New Guinea, the authors investigated the admission prevalence and case fatality rate associated with presumed TB over a 6-year period (2011-2016). All children admitted who were diagnosed with TB were followed-up until discharge or death. **Results:** Of 8992 paediatric admissions, 734 patients (8.2%) were diagnosed with presumed TB and there were 825 deaths, with TB accounting for 102 (12.4%). Extrapulmonary TB was the final diagnosis in 384 admissions {prevalence 4.3% [384/8992 (95% CI 3.9-4.7)]} with a case fatality rate of 21.4% [82/384 (95% CI 17.4-25.9)]. TB meningitis, disseminated TB and pericardial TB had high case fatality rates of 29.0% (53/183), 28.9% (11/38) and 25% (4/16), respectively. Severe malnutrition was more common in patients with pulmonary compared with extrapulmonary TB (25.4% vs 15.6%;  $p < 0.01$ ). **Conclusions:** Improved community-based case detection strategies, routine BCG vaccinations and other effective forms of TB control need revitalization and sustainability to reduce the high case fatality rates associated with childhood TB in Papua New Guinea.

- 152 **Weber A, Darmstadt GL, Rao N.**

Gender disparities in child development in the east Asia-Pacific region: a cross-sectional, population-based, multicountry observational study.

*Lancet Child Adolesc Health* 2017 Nov;1(3):213-224. doi: 10.1016/S2352-4642(17)30073-1. Epub 2017 Sep 13.

**BACKGROUND:** Gender differences in child development have been extensively studied in high-income countries, but few data are available from low-income and middle-income countries. Our objective was to assess gender disparities in child development that might arise from differential investment in child health, nutrition, and education in six countries across the east Asia-Pacific region. **METHODS:** In this cross-sectional, population-based study we quantified the magnitude of gender differences in child development using the East Asia-Pacific Early Child Development Scales (EAP-ECDS) in six countries (Cambodia, China, Mongolia, Papua New Guinea, Timor-Leste, and Vanuatu). We used stratified random sampling (according to age, residence [urban vs rural], and sex) in all countries to recruit eligible children aged 3-5 years from non-ethnic minority populations with no identified or suspected special educational needs for whom EAP-



ECDS scores for five or more of seven domains and urban-rural residence information were available. Gender differences in development associated with four national indicators of gender equality (sex ratio at birth, Gender Development Index, Gender Inequality Index, and Gender Parity Index for primary school enrolment) were also examined. We used generalised estimating equation regression to study moderation of differences by family socioeconomic status and wealth, and structural equation models with maximum likelihood to test mediation through health, nutrition, and education. **FINDINGS:** Between June 1, 2013, and Dec 13, 2013, 7582 eligible children were included from Cambodia ( $n = 1189$ ), China ( $n = 1618$ ), Mongolia ( $n = 1230$ ), Papua New Guinea ( $n = 1639$ ), Timor-Leste ( $n = 1176$ ), and Vanuatu ( $n = 730$ ). Girls had significantly higher development scores than boys in Cambodia (difference in composite score:  $\beta = 1.87$  points, 95% CI 0.29 to 3.45;  $p = 0.747$ ), China (2.66 points, 1.20 to 4.13;  $p = 0.0004$ ), Vanuatu (3.10 points, 1.65 to 4.55;  $p < 0.0001$ ), and Mongolia (3.94 points, 2.67 to 5.21;  $p < 0.0001$ ), but not Papua New Guinea (-0.43 points, -1.19 to 0.33;  $p = 0.272$ ) or Timor-Leste (0.09 points, -0.96 to 1.14;  $p = 0.861$ ). Differences in favour of girls were the largest for language skills in Mongolia (5.30 points, 95% CI 4.45 to 6.15); differences in language skills were smallest in the two poorest countries, Timor-Leste (-0.07 points, -1.03 to 0.88) and Papua New Guinea (0.05 points, -1.02 to 1.12). Greater differences in composite scores for girls compared with boys – in favour of girls – were associated with higher national Gender Development Index values ( $R^2 = 0.790$ ). In Mongolia, smaller gender differences in development were associated with increased household wealth (6.07 points [95% CI 3.22 to 8.92] in the lowest wealth quartile vs 2.27 points [1.38 to 3.15] in the highest wealth quartile), whereas in Timor-Leste, girls only outperformed boys when living in households with higher socioeconomic status (2.87 points [0.27 to 5.47] in the highest wealth quartile and 3.74 points [2.17 to 5.31] in the highest quartile of parental socioeconomic status). Mediating pathways explained up to 37% (in Vanuatu) of the association between gender and development, controlling for family socioeconomic status. **INTERPRETATION:** Girls aged 3-5 years generally outperformed boys on tests of development, and increasing levels of gender equality across six countries in the east Asia-Pacific region were associated with improved performance of young girls relative to boys. Greater opportunities for economic development are anticipated to result from improvements in gender equality and in the development of girls. Further study is warranted to understand family-level processes and societal norms that lead to gender differences in child development in the early years.

#### 153 Wentworth C.

Good food, bad food, and white rice: understanding child feeding using visual-narrative elicitation. *Med Anthropol* 2017 Aug-Sep;36(6):602-614. doi: 10.1080/01459740.2017.1336621. Epub 2017 Jun 6.

Visual-narrative elicitation, a process combining photo elicitation and pile sorting in applied medical anthropology, sheds light on food consumption patterns in urban areas of Vanuatu where childhood malnutrition is a persistent problem. Groups of participants took photographs of the foods they feed

their children, and the resources and barriers they encounter in accessing foodstuffs. This revealed how imported and local foods are assigned value as 'good' or 'bad' foods when contributing to dietary diversity and creating appropriate meals for children, particularly in the context of consuming white rice. The process of gathering and working with photographs illuminated the complex negotiations in which caregivers engaged when making food and nutritional choices for their children. At the nexus of visual and medical anthropology, the visual-narrative elicitation process yielded nuanced, comprehensive understandings of how caregivers value the various foods they feed their children.

#### 154 West F, Dawson A, Homer CSE.

Building midwifery educator capacity using international partnerships: findings from a qualitative study.

*Nurse Educ Pract* 2017 Jul;25:66-73. doi: 10.1016/j.nepr.2017.05.003. Epub 2017 May 8.

Midwifery educators play a critical role in strengthening the midwifery workforce globally, including in low and lower-middle income countries (LMIC) to ensure that midwives are adequately prepared to deliver quality midwifery care. The most effective approach to building midwifery educator capacity is not always clear. The aim of this study was to determine how one capacity building approach in Papua New Guinea (PNG) used international partnerships to improve teaching and learning. A qualitative exploratory case study design was used to explore the perspectives of 26 midwifery educators working in midwifery education institutions in PNG. Seven themes were identified which provide insights into the factors that enable and constrain midwifery educator capacity building. The study provides insights into strategies which may aid institutions and individuals better plan and implement international midwifery partnerships to strengthen context-specific knowledge and skills in teaching. Further research is necessary to assess how these findings can be transferred to other contexts.

#### 155 White MT, Karl S, Koepfli C, Longley RJ, Hofmann NE, Wampfler R, Felger I, Smith T, Nguitragool W, Sattabongkot J, Robinson L, Ghani A, Mueller I.

*Plasmodium vivax* and *Plasmodium falciparum* infection dynamics: re-infections, recrudescences and relapses.

*Malar J* 2018 Apr 17;17(1):170. doi: 10.1186/s12936-018-2318-1.

**BACKGROUND:** In malaria endemic populations, complex patterns of *Plasmodium vivax* and *Plasmodium falciparum* blood-stage infection dynamics may be observed. Genotyping samples from longitudinal cohort studies for merozoite surface protein (msp) variants increases the information available in the data, allowing multiple infecting parasite clones in a single individual to be identified. msp genotyped samples from two longitudinal cohorts in Papua New Guinea (PNG) and Thailand were analysed using a statistical model where the times of acquisition and clearance of each clone in every individual were estimated using a process of data augmentation. **RESULTS:** For the populations analysed, the duration of blood-stage *P. falciparum* infection was estimated as 36 (95% Credible Interval (CrI): 29-44) days in PNG, and 135 (95% CrI 94-191) days in Thailand. Experiments



on simulated data indicated that it was not possible to accurately estimate the duration of blood-stage *P. vivax* infections due to the lack of identifiability between a single blood-stage infection and multiple, sequential blood-stage infections caused by relapses. Despite this limitation, the method and data point towards short duration of blood-stage *P. vivax* infection with a lower bound of 24 days in PNG, and 29 days in Thailand. On an individual level, *P. vivax* recurrences cannot be definitively classified into re-infections, recrudescences or relapses, but a probabilistic relapse phenotype can be assigned to each *P. vivax* sample, allowing investigation of the association between epidemiological covariates and the incidence of relapses. **CONCLUSION:** The statistical model developed here provides a useful new tool for in-depth analysis of malaria data from longitudinal cohort studies, and future application to data sets with multi-locus genotyping will allow more detailed investigation of infection dynamics.

- 156 **Wirth JP, Woodruff BA, Engle-Stone R, Namaste SM, Temple VJ, Petry N, Macdonald B, Suchdev PS, Rohner F, Aaron GJ.**

Predictors of anemia in women of reproductive age: Biomarkers Reflecting Inflammation and Nutritional Determinants of Anemia (BRINDA) project. *Am J Clin Nutr* 2017 Jul;106(Suppl 1):416S-427S. doi: 10.3945/ajcn.116.143073. Epub 2017 Jun 14.

**Background:** Anemia in women of reproductive age (WRA) (age range: 15-49 y) remains a public health problem globally, and reducing anemia in women by 50% by 2025 is a goal of the World Health Assembly. **Objective:** We assessed the associations between anemia and multiple proximal risk factors (eg, iron and vitamin A deficiencies, inflammation, malaria, and body mass index) and distal risk factors (eg, education status, household sanitation and hygiene, and urban or rural residence) in nonpregnant WRA. **Design:** Cross-sectional, nationally representative data from 10 surveys (n = 27,018) from the Biomarkers Reflecting Inflammation and Nutritional Determinants of Anemia (BRINDA) project were analyzed individually and pooled by the infection burden and risk in the country. We examined the severity of anemia and measured the bivariate associations between anemia and factors at the country level and by infection burden, which we classified with the use of the national prevalences of malaria, HIV, schistosomiasis, sanitation, and water-quality indicators. Pooled multivariate logistic regression models were constructed for each infection-burden category to identify independent determinants of anemia (hemoglobin concentration <120 g/L). **Results:** Anemia prevalence was ~40% in countries with a high infection burden and 12% and 7% in countries with moderate and low infection burdens, respectively. Iron deficiency was consistently associated with anemia in multivariate models, but the proportion of anemic women who were iron deficient was considerably lower in the high-infection group (35%) than in the moderate- and low-infection groups (65% and 71%, respectively). In the multivariate analysis, inflammation, vitamin A insufficiency, socioeconomic status, and age were also significantly associated with anemia, but malaria and vitamin B-12 and folate deficiencies were not. **Conclusions:** The contribution of iron deficiency to anemia varies according to a country's infection burden. Anemia-reduction programs for WRA can be improved by considering the underlying

infection burden of the population and by assessing the overlap of micronutrient deficiencies and anemia.

- 157 **Yorston D, Duncalfe M.**

Managing emergencies: lessons from aviation. *Community Eye Health* 2018;31(103):58-59.

- 158 **Yoshikawa M, Ougi Y, Hirai N, Nakamura-Uchiyama F, Yamada M, Arizono N, Akamatsu N, Yoh T, Kaya D, Nakatani T, Kikuchi E, Katanami Y, Satoh K, Maki R, Miyazato Y, Oba Y, Kasahara K, Mikasa K.**

*Ancylostoma ceylanicum*, novel etiological agent for traveler's diarrhea – report of four Japanese patients who returned from Southeast Asia and Papua New Guinea.

*Trop Med Health* 2018 Mar 13;46:6. doi: 10.1186/s41182-018-0087-8. eCollection 2018.

**Background:** Countries in the Southeast Asia region have a high prevalence of soil-transmitted helminths, such as roundworm, whipworm, and hookworms [*Ancylostoma duodenale*, *Necator americanus*, *Ancylostoma ceylanicum*]. Recent molecular-based surveys have revealed that *A. ceylanicum*, a zoonotic hookworm, is likely the second most prevalent hookworm species infecting humans in that part of the world, while others have noted that this infection is an emerging public health risk not only for indigenous people but also for visitors from other countries. **Case presentation:** We recently encountered four cases of *A. ceylanicum* infection in Japanese individuals who returned from Southeast Asia and Papua New Guinea. Case 1 was a 25-year-old male who stayed in a rainforest in Malaysia for 4 weeks, where he developed abdominal pain and diarrhea in the third week. Eleven adult worms (five males, six females) were expelled after treatment with pyrantel pamoate and identified as *A. ceylanicum* based on morphological characteristics and DNA sequences of the mitochondrial cytochrome c oxidase subunit 1 (cox1) gene. Case 2 was a 26-year-old male who spent 2 years as an overseas cooperation volunteer for agriculture in Papua New Guinea. He did not note any symptoms at that time, though eggs were detected in feces samples at a medical check-up examination after returning. Although collection of adult worms was unsuccessful, DNA analysis of the eggs for cox1 and the ribosomal internal transcribed spacer (ITS)-1 and ITS-2 genes demonstrated that they were *A. ceylanicum*. Case 3 was a 47-year-old male who spent 1 month in a rural village in Lao People's Democratic Republic and began suffering from watery diarrhea from the third week. A total of nine adult worms (three males, six females) were collected by endoscopic procedures and following treatment with pyrantel pamoate. Morphological examination and molecular analyses of the cox1 gene showed that they were *A. ceylanicum*. Case 4 was a 27-year-old male who participated in group travel to India for 5 days. Three weeks after returning, he developed abdominal pain and diarrhea. Hookworm eggs were found in feces samples and developed into larvae in culture, which were identified as *A. ceylanicum* based on molecular analysis of the cox1 gene. Eosinophilia was observed in all of the cases prior to treatment. **Conclusions:** *A. ceylanicum* should be recognized as an important etiologic pathogen of hookworm diseases in travelers to countries in the Southeast Asia and West Pacific Ocean regions.

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## REFEREES 2015-2017

To maintain its standards the Journal is dependent on the willingness and dedication of its referees, colleagues who review all papers submitted to the Editor for publication and make the Journal's peer review system a reality.

We on the editorial staff recognize that we could not function without our referees (or reviewers). Their linked functions are to review and make constructive criticisms and, as referees, to make recommendations to the Editor for acceptance or rejection. Some papers submitted to the Journal are accepted with little change and some are rejected (but only after 2 referees have independently concurred in this opinion). However, the majority of papers are made acceptable only after considerable revision, following the reports of the reviewers, and in many cases this entails a great deal of work by the reviewer.

We acknowledge the help of the following colleagues who have contributed reports on papers which were published in the Journal - or rejected - during the period 2015-2017. Many have undertaken this task more than once, some many times. We thank them all for their essential contribution to the Journal. We apologize for any omissions: since we frequently have a focus issue with a guest editor, the work of some referees/reviewers may not have come to our attention.

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