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PUBLICATIONS OF RELEVANCE TO PAPUA NEW GUINEA AND MELANESIA

Bibliographic Citation List generated from MEDLARS

- 1 **Adisa A, Albano FR, Reeder J, Foley M, Tilley L.**
Evidence for a role for a *Plasmodium falciparum* homologue of Sec31p in the export of proteins to the surface of malaria parasite-infected erythrocytes.
J Cell Sci 2001 Sep;114(Pt 18):3377-3386.
The malaria parasite, *Plasmodium falciparum*, spends part of its life cycle inside the enucleated erythrocytes of its human host. The parasite modifies the cytoplasm and plasma membrane of its host cell by exporting proteins beyond the confines of its own plasma membrane. We have previously provided evidence that a plasmodial homologue of the COPII protein, Sar1p, is involved in the trafficking of proteins across the erythrocyte cytoplasm. We have now characterised an additional plasmodial COPII protein homologue, namely Sec31p. Recombinant proteins corresponding to the WD-40 and the intervening domains of the PfSec31p sequence were used to raise antibodies. The affinity-purified antisera recognised a protein with an apparent relative molecular mass of 1.6×10^5 on western blots of malaria parasite-infected erythrocytes but not on blots of uninfected erythrocytes. PfSec31p was shown to be largely insoluble in nonionic detergent, suggesting cytoskeletal attachment. Confocal immunofluorescence microscopy of malaria parasite-infected erythrocytes was used to show that PfSec31p is partly located within the parasite and partly exported to structures outside the parasite in the erythrocyte cytoplasm. We have also shown that PfSec31p and PfSar1p occupy overlapping locations. Furthermore, the location of PfSec31p overlaps that of the cytoadherence-mediating protein PfEMP1. These data support the suggestion that the malaria parasite establishes a vesicle-mediated trafficking pathway outside the boundaries of its own plasma membrane – a novel paradigm in eukaryotic biology.
- 2 **Alpers J.**
Papua and New Guinea medical experiences.
Intern Med J 2001 Jul;31(5):304-307.
- 3 **Burley DV, Dickinson WR.**
Origin and significance of a founding settlement in Polynesia.
Proc Natl Acad Sci USA 2001 Sep 25;98(20):11829-11831.
Selected prehistoric potsherds from the deepest cultural level of the oldest known archaeological site in the Kingdom of Tonga, within the Eastern Lapita province of western Polynesia, display decorative motifs characteristic of the Western Lapita province of modern-day Island Melanesia, to the west. Most of the stylistically anomalous sherds contain temper sands exotic to Tonga but, in one case, petrographically indistinguishable from temper in a Lapita sherd recovered from the Santa Cruz Islands of Melanesia, and are inferred to record maritime transport of Lapita ceramics into Tonga from Melanesia far to the west. The non-Tongan sherds found on Tongatapu provide direct physical evidence for interisland transfer of earthenware ceramics between Western and Eastern Lapita provinces, and the Nukuleka site, where they occur, is interpreted as one of the founding settlements of Polynesia.
- 4 **Duke T, Mgone J, Frank D.**
Hypoxaemia in children with severe pneumonia in Papua New Guinea.
Int J Tuberc Lung Dis 2001 Jun;5(6):511-519.
OBJECTIVES: To investigate the severity and duration of hypoxaemia in 703 children with severe or very severe pneumonia presenting to Goroka Hospital in the Papua New Guinea highlands; to study the predictive value of clinical signs for the severity of hypoxaemia, the predictive value of transcutaneous oxygen saturation (SpO₂) and other variables for mortality. DESIGN: Prospective evaluation of children with severe or very severe pneumonia. SpO₂ was measured at the time of presentation and every day until hypoxaemia resolved. Children with an SpO₂ less than 85% received supplemental oxygen. By comparing with a retrospective control group for whom oxygen administration was guided by clinical signs, we evaluated whether there was a survival advantage from using a protocol for the administration of oxygen based on pulse oximetry. We determined normal values for oxygen saturation in children living in the highlands. RESULTS: In 151 well, normal highland children, the mean SpO₂ was 95.7% (SD 2.7%). The median SpO₂ among children with severe or very severe pneumonia was 70% (56-77); 376 (53.5%) had moderate hypoxaemia (SpO₂ 70-84%); 202 (28.7%) had severe hypoxaemia (SpO₂ 50-69%); and 125 (17.8%) had very severe hypoxaemia (SpO₂ < 50%). Longer duration of cough or the presence of hepatomegaly or cyanosis predicted more severe degrees of hypoxaemia. After 10, 20 and 30 days from the beginning of treatment, respectively 102 (14.5%), 38 (5.4%) and 19 (2.7%) of children had persistent hypoxaemia; 46 children (6.5%) died. Predictors of death were low SpO₂ on presentation, severe malnutrition, measles and history of cough for more than 7 days. The mortality risk ratio between the 703 children managed whose oxygen administration was guided by the use of pulse oximetry and the retrospective control group who received supplemental oxygen based on clinical signs was 0.65 (95% CI 0.41-1.02,

two-sided Fisher's exact test, $p = 0.07$).
CONCLUSION: There is a need to increase the availability of supplemental oxygen in smaller health facilities in developing countries, and to train health workers to recognise the clinical signs and risk factors for hypoxaemia. In moderate sized hospitals a protocol for the administration of oxygen based on pulse oximetry may improve survival.

5 **Forster P, Torroni A, Renfrew C, Rohl A.**

Phylogenetic star contraction applied to Asian and Papuan mtDNA evolution.

Mol Biol Evol 2001 Oct;18(10):1864-1881.

In the past decade, mitochondrial DNA (mtDNA) of 826 representative East Asians and Papuans has been typed by high-resolution (14-enzyme) restriction fragment length polymorphism (RFLP) analysis. Compared with mtDNA control region sequencing, RFLP typing of the complete human mitochondrial DNA generally yields a cleaner phylogeny, the nodes of which can be dated assuming a molecular clock. We present here a novel star contraction algorithm which rigorously identifies starlike nodes (clusters) diagnostic of prehistoric demographic expansions. Applied to the Asian and Papuan data, we date the out-of-Africa migration of the ancestral mtDNA types that founded all Eurasian (including Papuan) lineages at 54,000 years. While the proto-Papuan mtDNA continued expanding at this time along a southern route to Papua New Guinea, the proto-Eurasian mtDNA appears to have drifted genetically and does not show any comparable demographic expansion until 30,000 years ago. By this time, the East Asian, Indian, and European mtDNA pools seem to have separated from each other, as postulated by the weak Garden of Eden model. The east Asian expansion entered America about 25,000 years ago, but was then restricted on both sides of the Pacific to more southerly latitudes during the Last Glacial Maximum around 20,000 years ago, coinciding with a chronological gap in our expansion dates. Repopulation of northern Asian latitudes occurred after the Last Glacial Maximum, obscuring the ancestral Asian gene pool of Amerinds.

6 **Garap JP, Dubey SP.**

Canal-down mastoidectomy: experience in 81 cases.

Otol Neurotol 2001 Jul;22(4):451-456.

OBJECTIVES: To identify the common presentation(s) and the clinical and operative finding(s) in patients with cholesteatomatous and long-term noncholesteatomatous chronic suppurative otitis media and to adapt a surgical management best suited to ensure long-term safety in these Papua New Guinean patients for whom postoperative follow-up is minimal. **DESIGN:** Retrospective case series. **SETTING:** Port Moresby General Hospital, the tertiary referral center for otolaryngologic services. **PATIENTS:** Eighty-one patients in all age groups who received a clinical diagnosis of chronic suppurative otitis media, with or without cholesteatoma, with or

without its associated complications. **INTERVENTION:** Canal-down (modified radical) mastoidectomy with wide meatoplasty. **MAIN OUTCOME MEASURE AND RESULTS:** Adults were more commonly affected than adolescent or pediatric cases, and there was a male preponderance. The median age was 24 years (range, 13 months to 73 years). Otorrhea remained the most common presentation in all age groups. Postauricular abscesses and fistulae were seen frequently. Cholesteatoma and granulation with polypoidal mucosa were frequent operative findings; a high incidence involved both the attic space and the antrum. Five (6%) patients had preoperative facial paralysis; in addition, postoperative facial paralysis developed in three (4%) patients. The incidence of postoperative 'wet ear' was high in all age groups. Meningitis was the most common intracranial complication, followed by lateral sinus thrombosis. There were seven (9%) deaths altogether, and all the deaths occurred as a direct result of otogenic intracranial complication. **CONCLUSION:** Lack of health consciousness, poor socioeconomic status, and lack of health care delivery system resulted in late presentations and poor postoperative follow-up. Hence, the canal-wall-down technique with wide meatoplasty is recommended to ensure a best possible one-time treatment in Papua New Guinean patients with cholesteatomatous or long-term 'dangerous' chronic suppurative otitis media with or without complications.

7 **Halder A, Morewaya J, Watters DA.**

Rising incidence of breast cancer in Papua New Guinea.

Aust NZ J Surg 2001 Oct;71(10):590-593.

BACKGROUND: Three previous reports have shown the incidence of breast cancer in Papua New Guinea (PNG) to have risen in the 30 years between 1958 and 1987. In the present report the incidence and pathology of breast cancer in the decade 1989-1998 are described. **METHODS:** This was a retrospective review of all histopathology specimens in PNG from 1989 to 1998. During this period the female population grew from 1 640 000 to more than 2 000 000. **RESULTS:** There were 790 cases of breast cancer. The age of the patient was not known in 221 cases (26%). The age-standardized incidence was 6.9 per 100 000. The incidence of breast cancer has been steadily rising in the 40 years since cancers were recorded in PNG. The incidence has risen in all four regions, most notably in the islands. The peak incidence was in the 45-54-year-old age group (18.4/100 000); 83.9% of women with breast cancer were aged 54 or less. Fifteen per cent were under 35 years old and 55.7% were under 45. The incidence fell in the elderly. The tumours tended to be advanced. The actual size was recorded in only 163 cases (20.7%) but there were only three T1 tumours in this group. Clinical signs of advanced breast cancer were recorded in 206 cases: ulceration of skin (91 cases), peau d' orange (69 cases), nipple retraction (43 cases) and lymphoedema of the upper extremity (three cases).

Axillary nodes were positive in 185 of 247 patients (75%) in whom they were sampled. CONCLUSIONS: The incidence of breast cancer in PNG women has steadily risen over the past 40 years and the highest age-specific incidence occurs in the 35-54 year age group. Tumours present late at an advanced stage. Clinical information on pathology request forms is poor and a prospective clinical audit is needed. Strategies need to be developed to detect breast cancer earlier in this population of women.

8 **Harley D, Sleight A, Ritchie S.**

Ross river virus transmission, infection, and disease: a cross-disciplinary review.

Clin Microbiol Rev 2001 Oct;14(4):909-932.

Ross River virus (RRV) is a fascinating, important arbovirus that is endemic and enzootic in Australia and Papua New Guinea and was epidemic in the South Pacific in 1979 and 1980. Infection with RRV may cause disease in humans, typically presenting as peripheral polyarthralgia or arthritis, sometimes with fever and rash. RRV disease notifications in Australia average 5,000 per year. The first well-described outbreak occurred in 1928. During World War II there were more outbreaks, and the name epidemic polyarthritis was applied. During a 1956 outbreak, epidemic polyarthritis was linked serologically to a group A arbovirus (Alphavirus). The virus was subsequently isolated from *Aedes vigilax* mosquitoes in 1963 and then from epidemic polyarthritis patients. We review the literature on the evolutionary biology of RRV, immune response to infection, pathogenesis, serologic diagnosis, disease manifestations, the extraordinary variety of vertebrate hosts, mosquito vectors, and transmission cycles, antibody prevalence, epidemiology of asymptomatic and symptomatic human infection, infection risks, and public health impact. RRV arthritis is due to joint infection, and treatment is currently based on empirical anti-inflammatory regimens. Further research on pathogenesis may improve understanding of the natural history of this disease and lead to new treatment strategies. The burden of morbidity is considerable, and the virus could spread to other countries. To justify and design preventive programs, we need accurate data on economic costs and better understanding of transmission and behavioral and environmental risks.

9 **Huoponen K, Schurr TG, Chen Y, Wallace DC.** Mitochondrial DNA variation in an Aboriginal Australian population: evidence for genetic isolation and regional differentiation.

Hum Immunol 2001 Sep;62(9):954-969.

The mitochondrial DNA (mt-DNA) variation in the Walbiri tribe of the Northern Territory, Australia, was characterized by high resolution restriction fragment length polymorphism (HR-RFLP) analysis and control region sequencing. Surveying each mt-DNA for RFLPs with 14 different restriction enzymes detected 24 distinct haplotypes, whereas direct sequencing of the control region hypervariable segment I (HVS-I) of these mt-DNAs revealed 34 distinct sequences.

Phylogenetic analysis of the RFLP haplotype and HVS-I sequence data depicted that the Walbiri have ten distinct haplotype groups (haplogroups), or mt-DNA lineages. The majority of the Walbiri RFLP haplotypes lacked polymorphisms common to Asian populations. In fact, most of the Walbiri haplogroups were unique to this population, although a few appeared to be subbranches of larger clusters of mt-DNAs that included other Aboriginal Australian and/or Papua New Guinea haplotypes. The similarity of these haplotypes suggested that Aboriginal Australian and Papua New Guinea populations may have once shared an ancient ancestral population(s), and then rapidly diverged from each other once geographically separated. Overall, the mt-DNA data corroborate the genetic uniqueness of Aboriginal Australian populations.

10 **Johansen CA, van den Hurk AF, Pyke AT, Zborowski P, Phillips DA, Mackenzie JS, Ritchie SA.**

Entomological investigations of an outbreak of Japanese encephalitis virus in the Torres Strait, Australia, in 1998.

J Med Entomol 2001 Jul;38(4):581-588.

Japanese encephalitis (JE) virus first appeared in Australia in 1995, when three clinical cases (two fatal) were diagnosed in residents on Badu Island in the Torres Strait, northern Queensland. More recently, two confirmed human JE cases were reported in the Torres Strait Islands and Cape York Peninsula, in northern Queensland in 1998. Shortly after JE virus activity was detected in humans and sentinel pigs on Badu Island in 1998, adult mosquitoes were collected using CO₂ and octenol-baited CDC light traps; 43 isolates of JE virus were recovered. Although *Culex sitiens* group mosquitoes yielded the majority of JE isolates (42), one isolate was also obtained from *Ochlerotatus vigilax* (Skuse). Four isolates of Ross River virus and nine isolates of Sindbis (SIN) virus were also recovered from members of the *Culex sitiens* group collected on Badu Island in 1998. In addition, 3,240 mosquitoes were speciated and pooled after being anesthetized with triethylamine (TEA). There was no significant difference in the minimum infection rate of mosquitoes anesthetized with TEA compared with those sorted on refrigerated tables (2.8 and 1.6 per 1,000 mosquitoes, respectively). Nucleotide analysis of the pre-membrane region and an overlapping region of the fifth nonstructural protein and 3' untranslated regions of representative 1998 Badu Island isolates of JE virus revealed they were identical to each other. Between 99.1% and 100% identity was observed between 1995 and 1998 isolates of JE from Badu Island, as well as isolates of JE from mosquitoes collected in Papua New Guinea (PNG) in 1997 and 1998. This suggests that the New Guinea mainland is the likely source of incursions of JE virus in Australia.

11 **Khan MR, Kihara M, Omoloso AD.** Antimicrobial activity of *Cassia alata*.

Fitoterapia 2001 Jun;72(5):561-564.

- The methanol extracts of leaves, flowers, stem and root barks of *Cassia alata* showed a broad spectrum of antibacterial activity. The activity was increased on fractionation (petrol, dichloromethane, ethyl acetate), the dichloromethane fraction of the flower extract being the most effective. No activity was shown against tested moulds.
- 12 **Khan MR, Kihara M, Omoloso AD.** Antimicrobial activity of *Clematis papuasica* and *Nauclea obversifolia*. *Fitoterapia* 2001 Jun;72(5):575-578.
The methanol extracts of *Clematis papuasica* leaves and stem bark and of *Nauclea obversifolia* leaves, stem and root barks showed a wide spectrum of antibacterial activity which was increased on fractionation (petrol, dichloromethane, ethyl acetate), the ethyl acetate fractions being in all cases the most effective. None of the extractives was active against tested moulds.
- 13 **Khan MR, Kihara M, Omoloso AD.** Antimicrobial activity of *Bidens pilosa*, *Bischofia javanica*, *Elmerillia papuana* and *Sigesbekia orientalis*. *Fitoterapia* 2001 Aug;72(6):662-665.
The ethanolic extracts of *Bidens pilosa* (whole plant), *Bischofia javanica* (leaves), *Elmerillia papuana* (root bark) and *Sigesbekia orientalis* (whole plant) were partitioned (petrol, dichloromethane, ethyl acetate). The crude ethanolic extracts and all the obtained fractions showed a broad spectrum of antibacterial activity, the ethyl acetate fractions and the petrol fraction of *E. papuana* being the most effective. No activity was observed against the tested moulds.
- 14 **Khan MR, Kihara M, Omoloso AD.** Antimicrobial activity of *Lithocarpus celebicus*. *Fitoterapia* 2001 Aug;72(6):703-705.
The methanol extracts of leaves, stem and root barks of *Lithocarpus celebicus* showed a broad spectrum of antibacterial activity which was increased on fractionation (petrol, chloromethane, ethylacetate), particularly in the ethyl acetate fraction of the stem bark and petrol fraction of the root bark. None of the extractives was active against tested moulds.
- 15 **Kun JF, Mordmuller B, Perkins DJ, May J, Mercereau-Puijalon O, Alpers M, Weinberg JB, Kreamsner PG.** Nitric oxide synthase 2(Lambarene) (G-954C), increased nitric oxide production, and protection against malaria. *J Infect Dis* 2001 Aug 1;184(3):330-336.
A point mutation in the promoter of the nitric oxide synthase 2 gene (NOS2), termed NOS2(Lambarene) (NOS2-G954C), protects heterozygous carriers against severe malaria as effectively as the sickle cell trait. In a prospective longitudinal study, 841 individual infections of initially 200 children (151 wild-type vs. 49 NOS2(Lambarene) carriers) were monitored for 4 years, to assess the rates of malarial attacks in the 2 groups; carriers of the NOS2(Lambarene) polymorphism were significantly less likely to experience malarial attacks than were others (p=0.002). The distribution of the NOS2(Lambarene) polymorphism was investigated in malaria-endemic areas. It was found to be present with the highest frequency in Africa and at a lower frequency in Asia. Ex vivo studies showed that cells isolated from people with this polymorphism have a 7-fold higher baseline NOS activity, compared with the levels detected in cells from subjects with the wild-type gene (p=0.003).
- 16 **Lindeberg S, Soderberg S, Ahren B, Olsson T.** Large differences in serum leptin levels between nonwesternized and westernized populations: the Kitava study. *J Intern Med* 2001 Jun;249(6):553-558.
OBJECTIVES: To compare serum leptin between nonwesternized and westernized populations. SETTING: (i) The tropical island of Kitava, Trobriand Islands, Papua New Guinea and (ii) the Northern Sweden MONICA study population. DESIGN: Cross-sectional survey. METHODS: Fasting levels of serum leptin were analysed in 163 randomly selected Kitavans aged 20-86 years and in 224 Swedes aged 25-74. MAIN OUTCOME MEASURE: Mean and determinants of serum leptin. RESULTS: Geometric means of serum leptin in Kitavan males and females were 1.5 and 4.0 vs. 4.9 and 13.8 ng/mL in Swedish males and females (p < 0.0001 for both sexes). In Kitavans, observed geometric means were close to predicted levels (1.8 ng/mL for males and 4.5 ng/mL for females) based on multiple linear regression equations including body mass index (BMI), triceps skinfolds (TSF) and age from the Swedish population-based sample. In Kitavans serum leptin was positively related to TSF amongst both sexes and, amongst females, to BMI. In Kitavans leptin was not related to fasting serum insulin. TSF explained 55% of the variation of leptin amongst females. There was a slight age-related increase of leptin amongst males. In Kitava leptin was not related to fasting serum insulin which was substantially lower than in Sweden. CONCLUSION: The low concentrations of serum leptin amongst Kitavans probably relates to the absence of overweight and hyperinsulinaemia. At a population level serum leptin can apparently be predicted from simple measures of adiposity.
- 17 **Maguire JD, Susanti AI, Krisin, Sismadi P, Fryauff DJ, Baird JK.** The T76 mutation in the *pfert* gene of *Plasmodium falciparum* and clinical chloroquine resistance phenotypes in Papua, Indonesia. *Ann Trop Med Parasitol* 2001 Sep;95(6):559-572.
The T76 mutation in the *pfert* gene has been linked to chloroquine (CQ) resistance in *Plasmodium falciparum*. PCR-based analysis of *pfert* alleles was performed on pre-treatment samples from 107 individuals who had *P. falciparum* infections and lived in Papua, Indonesia. The results of a 28-day, in-vivo test

- revealed clinical resistance to CQ in 79 (74%) of the samples. The crude sensitivity of the *pfcr* T76 assay for detecting the CQ-resistant infections in the samples was 96% and the crude specificity 52%. Discordance between *pfcr* genotype and in-vivo phenotype was analysed either by genotyping of the merozoite surface protein-2 (to distinguish re-infection from recrudescence) or by amplification of the *P. falciparum*-specific small-subunit ribosomal RNA (ssrRNA) gene, using nested PCR (to detect any subpatent but resistant parasites in infections misclassified as sensitive by the in-vivo test). When adjusting for the results of these analyses, the sensitivity and specificity of the *pfcr* T76 assay for detecting the CQ-resistant infections became 93% and 82%, respectively. Overall, the present results indicate that the *pfcr* T76 assay may be used to forecast therapeutic failure caused by CQ resistance. Validation requires exploration of the phenotype classifications based on the results of in-vivo tests, using genetic analyses that distinguish re-infection from recrudescence and detect microscopically subpatent parasitaemias.
- 18 **Main P, Attenborough R, Chelvanayagam G, Gao X.**
The peopling of New Guinea: evidence from class I human leukocyte antigen.
Hum Biol 2001 Jun;73(3):365-383.
This study utilizes newly developed direct DNA typing methods for human leukocyte antigens (HLA) to provide new information about the peopling of New Guinea. The complete polymorphism of eight Melanesian populations was examined. The groups included were highlanders, northern and southern highlands fringe populations, a Sepik population, northern and southern coastal New Guinea populations, and populations from the Bismarck Archipelago and New Caledonia. The study concluded that, based on HLA and other evidence, Melanesians are likely to have evolved largely from the same ancestral stock as Aboriginal Australians but to have since differentiated. Highlanders are likely to be descendants of earlier migrations who have been isolated for a long period of time. Northern highlands fringe and Sepik populations are likely to share a closer common ancestry but to have differentiated due to long term isolation and the relative proximity to the coast of the Sepik. Southern fringe populations are likely to have a different origin, possibly from the Gulf region, although there may be some admixture with neighboring groups. Coastal populations have a wider range of polymorphisms because of the genetic trail left by later population movement along the coast from Asia that did not reach Australia or remote Oceania. Other polymorphisms found in these populations may have been introduced by the movement of Austronesian-speaking and other more recent groups of people into the Pacific, because they share many polymorphisms with contemporary southeast Asians, Polynesians, and Micronesians that are not found in highlanders or Aboriginal
- Australians. There is evidence suggestive of later migration to Melanesia from Polynesia and Micronesia.
- 19 **McMaster P, Ezeilo N, Freisen H, Pomat N, Vince JD.**
Ten-year experience with paediatric lymph node tuberculosis in Port Moresby.
J Trop Pediatr 2001 Jun;47(3):160-164.
This is a descriptive study of short-course chemotherapy in children with nodal tuberculosis at Port Moresby General Hospital (PMGH). Between 1 August 1989 and 31 December 1997 5248 children were started on TB treatment. In the retrospective study 427 children were treated for lymph node TB up to 31 December 1996. Of these, 207 definitely completed the treatment and 24 (11.6%) of them were known to have relapsed up to the end of 1997. In the prospective study 179 children with lymph node TB were enrolled between 1 January 1997 and 31 December 1997. Of these, 97 definitely completed the treatment and 10 (10.6%) were known to have relapsed during a follow-up period of between 1 and 2 years.
- 20 **Tisch DJ, Hazlett FE, Kastens W, Alpers MP, Bockarie MJ, Kazura JW.**
Ecologic and biologic determinants of filarial antigenemia in bancroftian filariasis in Papua New Guinea.
J Infect Dis 2001 Oct 1;184(7):898-904.
The relationship between filarial antigenemia and lymphatic pathology was investigated in residents of 11 villages in an area of Papua New Guinea where *Wuchereria bancrofti* is endemic. Antigenemia was determined in 1322 persons by means of the Og4C3 antibody capture assay. Prevalence of antigenemia by village ranged from 61.7% to 98.2% and did not vary by sex. Antigen level increased with transmission potential among the 4 villages with measured transmission potential ($r^2=0.945$; $p=0.028$). Antigenemia was associated positively with age in villages with the lowest annual transmission potentials (45 and 404 infective larvae/year; $p<0.001$), but was distributed evenly across age groups in villages with increased transmission (1485 and 2518 infective larvae/year). These data suggest that children and adults have similar worm burdens in areas of high transmission, whereas worm burdens in areas of lower transmission increase with age. These results may be useful in the design and evaluation of programs aimed at eliminating lymphatic filariasis.
- 21 **Tjitra E, Suprianto S, Currie BJ, Morris PS, Saunders JR, Anstey NM.**
Therapy of uncomplicated falciparum malaria: a randomized trial comparing artesunate plus sulfadoxine-pyrimethamine versus sulfadoxine-pyrimethamine alone in Irian Jaya, Indonesia.
Am J Trop Med Hyg 2001 Oct;65(4):309-317.
Combining artesunate with existing antimalarial drugs may improve cure rates, delay emergence of resistance, and reduce transmission. We performed a randomized comparative trial to

quantify the effect of adding artesunate to sulfadoxine-pyrimethamine in the treatment of uncomplicated falciparum malaria in Indonesia. Using a modified 1997 World Health Organization protocol for assessment of therapeutic efficacy of antimalarial drugs, 105 patients (stratified by age/ethnic group) were randomized: 53 received artesunate orally, 4 mg/kg of body weight, a single daily dose for three days, plus sulfadoxine-pyrimethamine orally (1.25 mg of pyrimethamine/kg of body weight), a single dose on day 0, and 52 patients received sulfadoxine-pyrimethamine alone. Six from the combination group were withdrawn from analysis, as were six of the sulfadoxine-pyrimethamine group. Treatment failure rates on day 14 were 0% in the artesunate plus sulfadoxine-pyrimethamine group and 8.7% in the sulfadoxine-pyrimethamine group ($p = 0.12$). Treatment failure rates on day 28 were 4.4% and 15.2%, respectively ($p = 0.16$). Relative risk of treatment failure at 28 days was 0.3 (95% confidence interval [CI] = 0.1-1.3). Mean fever clearance time (1.3 versus 1.7 days) and mean parasite clearance time (1.4 versus 2.0 days) were both faster in the artesunate plus sulfadoxine-pyrimethamine group than in the sulfadoxine-pyrimethamine group ($p = 0.08$ and $p < 0.0001$, respectively). Only 20 (39.2%) of 51 patients treated with artesunate plus sulfadoxine-pyrimethamine were still parasitemic on day 1 compared with 45 (86.5%) of 52 patients treated with sulfadoxine-pyrimethamine alone ($p = 0.000001$, relative risk [RR] = 0.4, 95% CI = 0.3-0.6). Gametocyte carriage was lower following artesunate plus sulfadoxine-pyrimethamine than following sulfadoxine-pyrimethamine (RR = 0.5, 95% CI = 0.2-1.0 on day 7 and RR = 0.5, 95% CI = 0.2-1.1 on day 14). Mild diarrhea, rash, and itching resolved without treatment. Combined artesunate plus sulfadoxine-pyrimethamine resulted in more rapid fever and parasite clearance, was well tolerated, reduced risk of treatment failure, and lowered gametocyte carriage.

- 22 **Ulett GC, Currie BJ, Clair TW, Mayo M, Ketheesan N, Labrooy J, Gal D, Norton R, Smith CA, Barnes J, Warner J, Hirst RG.** *Burkholderia pseudomallei* virulence: definition, stability and association with clonality. *Microbes Infect* 2001 Jul;3(8):621-631.

Clinical presentations of melioidosis, caused by *Burkholderia pseudomallei*, are protean, but the mechanisms underlying development of the different forms of disease remain poorly understood. In murine melioidosis, the level of virulence of *B. pseudomallei* is important in disease pathogenesis and progression. In this study, we used *B. pseudomallei*-susceptible BALB/c mice to determine the virulence of a library of clinical and environmental *B. pseudomallei* isolates from Australia and Papua New Guinea. Among 42 non-arabinose-assimilating (ara(-)) isolates, LD(50) ranged from 10 to $> 10^6$ CFU. There were numerous

correlations between virulence and disease presentation in patients; however, this was not a consistent observation. Virulence did not correlate with isolate origin (i.e. clinical vs environmental), since numerous ara(-) environmental isolates were highly virulent. The least virulent isolate was a soil isolate from Papua New Guinea, which was arabinose assimilating (ara(+)). Stability of *B. pseudomallei* virulence was investigated by in vivo passage of isolates through mice and repetitive in vitro subculture. Virulence increased following in vivo exposure in only one of eight isolates tested. In vitro subculture on ferric citrate-containing medium caused attenuation of virulence, and this correlated with changes in colony morphology. Pulsed-field gel electrophoresis and randomly amplified polymorphic DNA typing demonstrated that selected epidemiologically related isolates that had variable clinical outcomes and different in vivo virulence were clonal strains. No molecular changes were observed in isolates after in vivo or in vitro exposure despite changes in virulence. These results indicate that virulence of selected *B. pseudomallei* isolates is variable, being dependent on factors such as iron bioavailability. They also support the importance of other variables such as inoculum size and host risk factors in determining the clinical severity of melioidosis.

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Velickovic ZM, Carter JM.

HLA-DPA1 and DPB1 polymorphism in four Pacific Islands populations determined by sequencing based typing. *Tissue Antigens* 2001 Jun;57(6):493-501.

Class II HLA-DP antigens are heterodimers comprised of alpha and beta chains coded by HLA-DPA1 and HLA-DPB1 genes. Both genes are polymorphic with substantial variation between different populations world wide. This work describes DPA1 and DPB1 polymorphism in four Pacific Island populations of Cook Islands, Samoa, Tokelau and Tonga, living in New Zealand. Using sequencing based typing four DPA1 alleles and twelve DPB1 alleles were observed in total among the four populations. There are two predominant DPA1 alleles DPA1*01031 and DPA1*02022 and three predominant DPB1 alleles DPB1*02012, DPB1*0401 and DPB1*0501. Fourteen DPA1-DPB1 haplotypes in total are present in these four populations with three predominant haplotypes: DPA1*02022-DPB1*0501, DPA1*01031-DPB1*02012, and DPA1*01031-DPB1*0401. Strong positive and negative disequilibrium was observed for individual DPA1-DPB1 haplotypes. Significant differences in DPA1 and DPB1 allele and haplotype frequencies were observed between Tokelauan and the other three populations. Phylogenetic analysis of genetic distances between the four Pacific Island populations and other Asian Oceanian populations have shown that Cook Islanders, Samoans and Tongans are more closely related to Asian populations whereas Tokelauans cluster towards non-Austronesian populations of Papua New Guinea Highlanders and Australian Aborigines.

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