Strategies to control Yaws and other Neglected Tropical Diseases in the South Pacific Islands

Estrategias para el control del Pián y otras Enfermedades Tropicales Desatendidas en Islas del Pacífico Sur

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TESIS DOCTORAL

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Universitat de Barcelona

Als meus pares
que m’han donat tot el que tenen

En recuerdo de Julia y a Rafi
quienes me han dado mucho más de lo que tienen

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1. Glossary

ADA	Antigen Detection Assays
ADL	Acute adenolymphangitis
AFL	Acute filarial lymphangitis
CFA	Circulating filarial antigenaemia
DEC	Diethylcarbamazine citrate
DOT	Directly observed therapy
EIR	Entomological inoculation rate
ICT	Immunochromatographic test
LF	Lymphatic filariasis
LLITN	Long-lasting insecticide-treated nets
LMC	Lihir Medical Centre
MDA	Mass drug administration
MBR	Monthly biting rate
Mf	Microfilaraemia
NTD	Neglected tropical disease
PCR	Polymerase chain reaction
PacELF	Pacific program for elimination of lymphatic filariasis
PELF	Program for elimination of lymphatic filariasis
PCT	Preventive chemotherapy
PNG	Papua New Guinea
SPI	South Pacific Islands
STH	Soil-transmitted-helminthiases
RPR	Rapid plasma reagin
TPHA	Treponema pallidum hemagglutination
VDRL	Venereal disease research laboratory
UNICEF	United Nations Children's Fund
WHO	World Health Organization

2. Summary (English)

Every year, through mass drug administration (MDA), hundreds of millions of the world's poorest people receive a single annual dose of one or more drugs to eliminate certain parasitic worm or bacterial infections. Some of these infections, mostly prevalent in tropical areas, have traditionally been neglected from the public health and research point of view. These conditions, collectively known as the neglected tropical diseases (NTDs), still cause, at the cusp of the second decade of the 21st century, a significant amount of morbidity and mortality. The existing control measures for NTD have an enormous potential, although there are still some challenges that require further investigation. For some diseases, alternative strategies may be needed, including longer duration of MDA programmes or modified drug regimens. For other diseases, such as yaws, the work must start almost from scratch, since little has been achieved in terms of control of this disease in the past 50 years. Although eight NTDs affect the region, two diseases pose a major public health problem in the South Pacific Islands, namely yaws and lymphatic filariasis and are the basis for his thesis. These two infections were selected for a number of reasons. First, they affect the South Pacific region disproportionately. Secondly, little research has been conducted in the past years. And third, but more importantly, several epidemiological, technological and historical factors make these two diseases amenable to elimination. Safe and effective tools and interventions to achieve these targets are available and concerted efforts to scale them up are likely to lead to success.

Yaws is one of the most neglected of the NTDs. Yaws was one of the first diseases to be targeted for eradication on a global scale, efforts which almost led to the disease disappearance as a result of a massive treatment program started in the 1950s. After the successful eradication campaigns the primary health care systems were supposed to give the last push towards eradication of yaws. However a combination of various factors including poor political commitment and limited funding resulted in a progressive abandonment of efforts and the resurgence of the disease. Every new case of yaws was the disappointing confirmation that the public health world had missed a great opportunity.

Today yaws has resurged in many tropical areas and presents new challenges including its unknown epidemiological situation, the attenuated clinical forms of the disease, a poor awareness and knowledge among health care workers, the lack of knowledge about the effectiveness of classic treatment with penicillin and, an obvious

need for research into simplified administration schemes or new antibiotic treatments, particularly oral ones.

There is an enormous knowledge gap regarding current reliable epidemiological information about the disease. Certainly we know little about the burden in the three Melanesian countries where the disease is highly endemic, Papua New Guinea, Solomon Islands and, Vanuatu. In Solomon Islands and Vanuatu there are indications that Yaws is widespread and prevalent, but we know that the diagnosis is unreliable. This takes us to the next point, what does a diagnosis of yaws mean?

Overall the natural history of the disease in this era, where it is often subject to inadequate antibiotic pressure, is very unclear. Some authors have suggested that yaws appears to be attenuated in both Solomon Islands and Vanuatu. They state that bone involvement in yaws is now rare and implies that yaws is a mild disease not requiring efforts for elimination. However, the first paper of this thesis describes the epidemiology of yaws in Lihir Island (Papua New Guinea, PNG) and shows a high rate of classical primary ulcers (almost 60%) and significant bone and periosteal involvement (more than 15%), suggesting that “attenuation” is not an important issue.

When we look at the diagnostic criteria for yaws, signs and symptoms alone are still used often in many areas to diagnose the disease. This reliance on clinical findings was the result of the difficulty of performing serological tests in remote areas. Today, available rapid serological tests are simple, rapid, inexpensive and useful for guiding confirmation of cases, making them adequate tools for the diagnosis and monitoring of the disease. The clinical diagnosis of yaws is complicated because its clinical manifestations may be unspecific. Thus, it is possible that a significant proportion of yaws cases may in fact have been falsely diagnosed. We show, in the first article, that in our experience only 60% of the cases with a clinical suspicion of yaws were finally confirmed by serologic tests. Therefore, a proper diagnosis of yaws requires the interpretation of clinical findings with reference to laboratory results and the epidemiologic history of the patient.

Serological testing in yaws is not only important for diagnostic accuracy, but also is very helpful in defining the disease’s evolution and eventual cure after treatment. Rapid plasma regain (RPR) titres should decline within 6-12 months, becoming negative in less than 2 years. The second article of this thesis combines a clinical and serological approach to assess the response after treatment with benzathine benzylpenicillin, and it identifies an overall 20% treatment failure. This could be related to resistance to the antimicrobial drug used or to re-infection caused. The distinction between re-infection

and true resistance to antibiotic treatment is difficult to make but these failures are worrisome. This article also proposes a multivariate model performed to identify independent determinants of failure that affected the outcome after treatment. The risk for reinfection caused by repeated contact with infected children seems to be a pivotal predictor of failure. Low baseline titters (<1:32) of RPR are also an important and independent predictor of failure, possibly as a result of the greater difficulty in resolving chronic infections which are usually accompanied by low titters.

With yaws re-emerging, the development of new strategies against this infection aimed at simplifying its treatment and potentially re-focussing strategies towards its eradication seems essential. Injectable penicillin is still effective but management with an oral drug that can be easily administered on a large scale should be the preferred method for treatment. To date, there had been no studies that directly compared the efficacy of penicillin with any of the potentially alternative agents shown to work in the treatment of the non-venereal treponematoses. The fourth paper in this thesis has shown that a single-dose of oral azithromycin is non-inferior to benzathine benzylpenicillin for the treatment of yaws in children in PNG. In an open-label randomised trial, at 6-month follow-up, 96% of patients treated with azithromycin were cured, as were 93% in the benzathine benzylpenicillin group.

The prospects of eliminating and eventually eradicating yaws may now be enhanced by the use of a single-dose of oral azithromycin in mass drug administration campaigns. Community based mass administration of azithromycin has been widely used in many locations for the control of trachoma, which, like yaws, is a disease of poor rural communities in developing countries, and has been used in a more limited way to control granuloma inguinale and outbreaks of venereal syphilis.

Elimination of yaws and lymphatic filariasis in the South-Pacific Islands is now considered biologically feasible and programmatically attainable. The Global Programme to Eliminate Lymphatic Filariasis (GPELF) has expanded quickly to reach the target of elimination by 2020. On the other hand the strategy to eliminate yaws is again at the centre of discussions and given that infected humans are the only source of disease, its eradication could be achieved within a very relatively short time. The fifth article of the thesis comprehensively reviews antimicrobial treatments and elimination strategies against yaws. In order to control yaws and push it towards elimination, we propose to move away from penicillin to azithromycin and use mass treatment campaigns of the entire population in endemic communities irrespective of the prevalence. Also, to make sure all cases are tracked down and treated, strict follow-up

measures and selective mass treatment will be required until zero case prevalence is reached. Importantly, we suggest testing the principle of interrupting transmission in pilot implementation studies, including prevalence surveys to assess the impact of the intervention and macrolide resistance monitoring which in our opinion will be essential evaluation tools to guide us towards a sustainable elimination.

Lymphatic filariasis (LF), caused by the mosquito-borne nematode Wuchereria Bancrofti, is a major public-health problem in the Melanesian countries. Annual MDA over five years is currently the WHO's recommended strategy to eliminate lymphatic filariasis. This approach aims to suppress microfilaraemia in infected individuals and bring the infection below a threshold that leads to interruption of transmission. However theoretical work and clinical field experience has highlighted how the ecological diversity between different endemic regions can result in elimination thresholds that vary between local communities. This means that the duration required might be different for different areas. Other variables have also been previously identified as potentially having an influence on the outcome of the program, including baseline prevalence of infection, vector density or the treatment coverage. The last article of this thesis provides data about the impact of a five-year filariasis control program in Papua New Guinea. The findings reported support this strategy for areas with low-to-moderate rates of transmission in regions where anopheline mosquitoes transmit this infectious disease. Additional measures or longer periods of treatment may be necessary in areas with a high rate of transmission.

The experience acquired on Lihir Island in MDA programs during the campaigns for the elimination of filariasis, will be very valuable when implementing a pilot strategy for yaws control. Also, in the near future it might be important to link yaws mass treatment with other mass programmes to increase efficiency. The plan for elimination of lymphatic filariasis in PNG was approved as a pilot project in 2005 but the program still needs to be extended to the total of 20 provinces in the country where filariasis is endemic. In this context, an integrated approach to NTD control could represent an important global public health solution in PNG and other South Pacific Islands.

Little has been achieved in the past decade in NTDs. We are now in a good position to translate into policies the results of our research projects. A new elimination policy for yaws around the azithromycin pillar has been sketched a WHO consultation meeting held in Morges, Switzerland last March. In the intentions of the organization, a last global mass campaign to tackle yaws should permit to reach zero cases in 2017, and the subsequent certification of worldwide interruption of transmission by 2020.

3. Resumen (Castellano)

Cada año, a través de la administración masiva de medicamentos (MDA), cientos de millones de personas, las más pobres del mundo, reciben una dosis única de uno o más medicamentos para eliminar ciertas infecciones, parasitarias o bacterianas. Algunas de estas infecciones, frecuentes sobre todo en las zonas tropicales, han sido tradicionalmente desatendidas desde el punto de vista de salud pública e investigación. Estas enfermedades, conocidas comúnmente como las enfermedades tropicales desatendidas (ETD), aún causan, en el inicio de la segunda década del siglo 21, una cantidad significativa de morbilidad y mortalidad.

Las medidas de control actuales para ETDs tienen un enorme potencial, pero todavía existen algunas cuestiones que requieren investigación. Para algunas de estas infecciones, son necesarias estrategias alternativas, incluyendo una mayor duración de los programas de MDA o regímenes modificados de medicamentos. Para otras enfermedades, como la enfermedad de pián, el trabajo debe comenzar casi desde cero, ya que poco se ha logrado, en términos de control de esta enfermedad, en los últimos 50 años.

Aunque ocho ETDs afectan a la región, dos enfermedades constituyen un problema importante de salud pública en las Islas del Pacífico Sur, a saber: el pián y la filariasis linfática y son la base de esta tesis. Estas dos infecciones fueron elegidas por muchas razones. En primer lugar, afectan a la región del Pacífico Sur de forma desproporcionada. En segundo lugar, pocas investigaciones se han llevado a cabo en los últimos años. Y en tercer lugar, pero lo más importante, varios factores epidemiológicos, tecnológicos e históricos hacen que estas dos enfermedades sean susceptibles de eliminación. Existen armas terapéuticas seguras y eficaces para lograr este objetivo, y esfuerzos coordinados para ejecutar los programas de control pueden conducir al éxito.

El pián es una de las más olvidadas de las ETDs. Ésta fue una de las primeras enfermedades en ser objetivo de erradicación a escala global. Los esfuerzos de un programa de tratamiento masivo que se inició en la década de 1950, casi llevaron a la desaparición de la enfermedad. Después de las exitosas campañas de erradicación, los sistemas de salud de atención primaria debían dar el último empujón hacia la erradicación del pián. Sin embargo, una combinación de varios factores, incluyendo un pobre compromiso político y una financiación limitada, dieron como resultado el abandono progresivo de los esfuerzos y el resurgimiento de la enfermedad. Cada

nuevo caso de pián era la decepcionante confirmación de que el mundo de la salud pública había perdido una gran oportunidad.

Hoy la enfermedad de pián ha resurgido en muchas áreas tropicales con nuevos desafíos: una situación epidemiológica desconocida, formas clínicas atípicas o atenuadas, poco conocimiento de la enfermedad entre el personal sanitario, la falta de datos acerca de la eficacia del tratamiento clásico con penicilina inyectable y la necesidad de desarrollar esquemas terapéuticos simplificados o investigar en nuevos tratamientos antibióticos, en especial de administración oral.

Actualmente hay una enorme brecha de conocimiento entorno a la información epidemiológica fiable sobre la enfermedad. Ciertamente, sabemos poco acerca de la incidencia en los tres países melanesios, donde la enfermedad es altamente endémica, Papúa Nueva Guinea (PNG), Islas Salomón y Vanuatu. En las Islas Salomón y Vanuatu, las cifras de incidencia son muy altas lo que demuestra que el pián es una enfermedad frecuente y ampliamente extendida, pero sabemos que el diagnóstico no es muy fiable. Esto nos lleva al siguiente punto: ¿Cuáles son los criterios diagnósticos del pián?

En general, la historia natural de la enfermedad en la época actual, donde la bacteria es objeto de presión antibiótica inadecuada, no es muy clara. Algunos autores han escrito que el pián parece presentar manifestaciones “atenuadas” en las Islas Salomón y Vanuatu. Afirman que la afectación ósea en el pián es poco frecuente, lo que implica que el pián es una enfermedad leve que no requeriría esfuerzos para su eliminación. Sin embargo, el primer trabajo de esta tesis describe la epidemiología del pián en la Isla de Lihir (Papúa Nueva Guinea) y muestra una alta tasa de úlceras primarias clásicas (casi el 60% de casos) y una afectación significativa del hueso y periostio (más del 15%) que sugiere que la "atenuación" no es un tema importante.

Cuando nos fijamos en los criterios diagnósticos, únicamente signos y síntomas todavía se utilizan en muchas áreas para el diagnóstico de la enfermedad. Esta confianza en los hallazgos clínicos fue el resultado de la dificultad de realizar pruebas serológicas en las zonas remotas. Hoy en día, las pruebas serológicas rápidas son simples, rápidas, económicas y útiles para orientar la confirmación de los casos. El diagnóstico clínico del pián es complicado debido a que sus manifestaciones pueden ser inespecíficas. Así, es posible, que una proporción significativa de los casos de pián puedan haber sido falsamente diagnosticados. En el primer artículo, presentamos que, en nuestra experiencia, sólo el 60% de los casos con sospecha clínica de pián fueron finalmente confirmados por pruebas serológicas. Por lo tanto, un diagnóstico adecuado

del pián requiere la interpretación de los hallazgos clínicos con referencia a los resultados de laboratorio y la historia epidemiológica de los pacientes.

Las pruebas serológicas en el pián no sólo son importantes para el diagnóstico de la enfermedad, también son muy útiles en la definición de curación después del tratamiento. En la prueba de la Reagina plasmática rápida (RPR) los títulos deben descender a los 6-12 meses, llegando a ser negativa en menos de 2 años. El segundo artículo de esta tesis combina un enfoque clínico / serológico para evaluar la respuesta a bencilpenicilina benzatina, e identifica una tasa de fracaso terapéutico del 20% a los 12 meses del tratamiento. Esto podría estar relacionado con resistencia al fármaco antimicrobiano, o bien indicar una re-infección por re-exposición. La distinción entre la re-infección y la resistencia verdadera al tratamiento es difícil, pero estos fracasos terapéuticos son preocupantes. En este artículo se describe un modelo multivariante realizado para identificar los factores determinantes del fracaso terapéutico. El riesgo de re-infección causado por el contacto repetido con otros niños infectados parece ser un predictor fundamental de fracaso. También es un factor de riesgo, los títulos basales bajos (< 1:32) de RPR. Este último factor podría estar relacionado con la mayor dificultad para resolver infecciones crónicas (en estadio secundario), habitualmente acompañadas de títulos bajos.

Con la enfermedad de pián re-emergiendo, el desarrollo de nuevas estrategias contra la infección para hacer más fácil los esfuerzos de erradicación, es esencial. La penicilina inyectable sigue siendo eficaz, pero el tratamiento con un fármaco por vía oral que pueda ser fácilmente administrado a gran escala es el método preferido para el tratamiento, prevención y finalmente eliminación en todas las regiones endémicas del mundo. Hasta la fecha, no ha habido estudios que comparen directamente la eficacia de la penicilina con cualquiera de los agentes alternativos en el tratamiento de las treponematosis no venéreas.

El cuarto artículo de esta tesis ha demostrado que una dosis única de azitromicina por vía oral no es inferior a la bencilpenicilina benzatina intramuscular, para el tratamiento del pián en niños en Papúa Nueva Guinea. En un ensayo abierto, aleatorio, el 96% de los pacientes tratados con azitromicina estaban curados a los 6 meses de seguimiento, al igual que el 93% en el grupo de bencilpenicilina benzatina. Las perspectivas de finalmente erradicar el pián son ahora mayores, mediante el uso de una dosis única de azitromicina oral en campañas masivas de tratamiento. El tratamiento masivo con azitromicina ha sido ampliamente utilizado para el control del tracoma, que, al igual que el pián es una enfermedad de comunidades rurales pobres

de países en desarrollo. También se ha utilizado de una manera más limitada para controlar el granuloma inguinal y brotes de sífilis venérea. En general, el uso de azitromicina ha demostrado ser seguro, y de hecho ha habido beneficios inesperados de salud en algunos programas.

La eliminación del pián y la filariasis linfática en las Islas del Pacífico Sur se considera ahora biológicamente factible y operacionalmente alcanzable. El Programa Global para Eliminar la Filariasis Linfática (GPELF) se ha expandido rápidamente para alcanzar la meta de eliminación en el año 2020. Por otro lado la estrategia para eliminar el pián es nuevamente centro de atención. Además, dado que los seres humanos infectados son la única fuente de la enfermedad, su eliminación podría lograrse en un plazo relativamente corto.

El quinto artículo de la tesis revisa de forma integral el tratamiento con antimicrobianos y las estrategias de eliminación contra el pián. Con el fin de controlar el pián hasta la erradicación, se propone pasar de la penicilina a la azitromicina, y el uso de campañas de tratamiento masivo de toda la población en todas las comunidades endémicas. Además, para asegurar que todos los casos son encontrados y tratados, serán necesarias medidas estrictas de seguimiento y tratamiento masivo selectivo hasta llegar al objetivo de cero casos clínicos. Es importante destacar que el principio de interrupción de la transmisión se debe probar en estudios piloto, incluyendo estudios de prevalencia, para monitorizar el impacto de la intervención, y también la valoración de resistencia a macrolidos, que en nuestra opinión, serán herramientas fundamentales que nos guíen en el camino hacia una eliminación sostenible

La filariasis linfática (FL), causada por el nematodo Wuchereria bancrofti, es otro de los grandes problemas de salud pública en los países de la Melanesia. Un curso de MDA anual, durante cinco años, es la estrategia que la OMS recomienda para eliminar la FL. Este enfoque tiene como objetivo suprimir la microfilaremia en los individuos infectados y disminuir los niveles de infección por debajo de un umbral que conduzca a la interrupción de la transmisión. Sin embargo, trabajo teórico y experiencia práctica clínica han puesto de relieve cómo la diversidad ecológica, entre diferentes regiones endémicas, puede resultar en que los umbrales de eliminación varíen en diferentes comunidades. Esto significa que la duración requerida podría ser diferente para diferentes áreas. Algunas variables que han sido previamente identificadas como potenciales determinantes en el resultado de un Programa para la eliminación de FL (PELF) son la prevalencia basal de infección por filariasis, la densidad de vectores (mosquitos) o la cobertura del tratamiento en la población.

El último artículo de esta tesis, proporciona datos sobre el impacto de un PELF de cinco años en PNG. Los resultados obtenidos apoyan la estrategia descrita para las zonas con baja a moderada tasas de transmisión en regiones donde mosquitos anofelinos transmiten la infección (pe. Melanesia, África). Medidas adicionales o períodos más largos de tratamiento pueden ser necesarios en áreas con una alta tasa de transmisión.

La experiencia adquirida en la Isla de Lihir en los programas de tratamiento masivo durante las campañas para la eliminación de la filariasis, será muy valiosa en la aplicación de una estrategia piloto para el control del pián. Además, en un futuro próximo podría ser importante vincular los programas para el control del pián con otros programas de tratamiento masivo (por ejemplo, filariasis) para aumentar la eficiencia y reducir los costos. El plan para la eliminación de la filariasis linfática en PNG fue aprobado como proyecto piloto en 2005 en la provincia de Milne Bay. El programa todavía tiene que ser extendido a un total de 20 provincias en el país, donde la filariasis es endémica. En este contexto, un enfoque integrado para el control de enfermedades tropicales olvidadas podría representar una importante solución global de salud pública en PNG.

Poco se ha logrado en la última década en enfermedades tropicales desatendidas. Ahora estamos en una buena posición para traducir los frutos de nuestra investigación en políticas de salud. Durante una consulta celebrada en la sede de la OMS en Ginebra el pasado mes de marzo, ya se ha esbozado una nueva política de eliminación para el pián que toma como pilar el tratamiento con azitromicina. La intención de la OMS es que una última campaña global debe permitir llegar a cero casos de pián en 2017, y la posterior certificación de la interrupción de la transmisión en todo el mundo en el año 2020.

4. General Introduction

4.1 NTDs amenable to eradication

The neglected tropical diseases (NTDs) are a group of conditions causing significant morbidity and mortality worldwide but which until recently received only minimal attention from most of the world, largely because they affect the poorest, most vulnerable and most disenfranchised members of society (1). Afflicting more than one billion persons, one-sixth of the world's population, these diseases cause severe morbidity, including disfigurement, disability, and blindness (Table 1).

The most important neglected tropical diseases include six helminth infections— lymphatic filariasis, onchocerciasis, schistosomiasis and, soil-transmitted helminthiases; three vector-borne protozoan infections— leishmaniasis, human african trypanosomiasis, and Chagas disease; and four bacterial infections—endemic treponematoses, trachoma, leprosy, and Buruli ulcer.

The main focus of this thesis is the generation of data that may be of help to the design, execution and evaluation of large-scale population-based massive preventive chemotherapy campaigns as the main strategy to control these infections in the South Pacific Islands (2). Other recommended strategies for the prevention and control of NTDs are intensified case-management; vector control; the provision of safe water, sanitation and hygiene; and veterinary public health. The World Health Organization (WHO) recommends, whenever possible, the integration of the control activities for the different NTDs to contain costs and increase efficiency (3).

The treatment and diagnostic tools currently available for this group of diseases are sufficiently effective for these NTDs to be targeted either for elimination or for reduction to such low levels that they no longer constitute a significant public health problem (4). The active involvement of the pharmaceutical industry in the fight against NTDs, which has included important donations to support their control, has allowed an increased access to high-quality medicines free of charge for hundreds of millions of poor people. The increasing awareness, willingness and commitment of local and global communities of partners to work with endemic countries have resulted in a boost of resources, innovation, expertise and advocacy to control and elimination efforts to overcome NTDs using preventive chemotherapy.

Table 1. Neglected tropical diseases (5).

Disease	Major etiologic agent	Estimated global prevalence	Main route of transmission	Main strategy of epidemiological control
Soil-transmitted helminthiases	*Ascaris lumbricoides; Trichuris trichiura; Necator americanus*	1200 million	Fecal-oral	Albendazole MDA
Schistosomiasis	*Schistosoma haematobium; Schistosoma mansoni*	200 million	Soil-skin	Praziquantel MDA
Lymphatic filariasis	*Wuchereria bancrofti*	120 million	Vector borne	DEC or ivermectine MDA
Trachoma	*Chlamydia trachomatis*	84 million	Person-to-person	Azithromycin MDA
Onchocerciasis	*Onchocerca volvulus*	37 million	Vector borne	Ivermectin MDA
Leishmaniasis	*Leishmania sp.*	12 million	Vector borne	Intensified case-management
Chagas disease	*Tripanosoma cruzi*	10 million	Vector borne	Vector control
Yaws	*Treponema pallidum subs pertenue*	2.5 million	Person-to-person	Benzathine penicillin MDA
Leprosy	*Micobacterium leprae*	224,000	Person-to-person	Intensified case-management
Human African trypanosomiasis	*Tripanosoma brucei*	70,000	Vector borne	Intensified case-management
Buruli Ulcer	*Micobacterium ulcerans*	Unknown	Under investigation	Intensified case-management

4.2 The high-prevalence NTDs in South Pacific Islands (SPI)

Two diseases continue to represent a major public health problem in the South Pacific Islands (Figure 1) namely yaws and lymphatic filariasis. Their endemicity and burden of disease are summarized in tables 2 and 3.

Yaws was highly prevalent in the South Pacific prior to mass treatment campaigns carried out in the late 1950s and early 1960s. Following mass treatment campaigns the number of reported cases dramatically declined and yaws was considered eliminated in most areas (6)(7). This was confirmed by surveys conducted in the 1960s and 1970s that showed successful reduction of yaws below detectable levels. For example, Geizer reported that only six cases were found in Niue in 1957 where the disease was previously widespread (8). Only three cases were diagnosed between 1964 and 1984 in Fiji, the last one being in 1983, and in Tonga the last seven cases were reported in 1976 compared to the 7,452 cases which were reported in 1962 when the eradication campaign was launched. Since the late 1970s, however, suspected cases of yaws were reported in various areas of Papua New Guinea (PNG) (7)(9)(10)(11)(12), the Solomon Islands (13)(14)(15)(16), and Vanuatu (5)(17)(18). While available records suggest that these countries remain endemic to this date; the extent of the current burden due to yaws is not well established (19) (table 2).

Filariasis remains endemic in 14 Pacific countries. The total population at risk in 2006 was estimated at 6.55 million (20). Eleven countries completed the currently recommended five rounds of MDA for filariasis in 2006 (American Samoa, Cook Islands, Fiji, French Polynesia, Kiribati, Niue, Samoa, Tonga, Tuvalu, Vanuatu, and Wallis and Fortuna). In the remaining three endemic countries of the area (Papua New Guinea, Marshall Islands, and Federates States of Micronesia) with an eligible population of over 4.2 million individuals, between one and three MDA rounds have been administered (20). The annual distribution of albendazole (in the context of the MDA for the program for elimination of LF [PELF]) has also significantly lowered the prevalence of soil-transmitted helminths (STH) as in other countries using this antihelminthic agent (21).

4.3 Mass Drug administration to eliminate the high-prevalence NTDs in SPI

Currently, several factors make eliminating both lymphatic filariasis, and yaws from the South Pacific Region attainable goals: (i) they are endemic only in limited areas, (ii) simple diagnostic tests are available, (iii) safe and effective interventions and treatment

are available for the control of each of these diseases. These treatments include, for yaws, the use of a single intra-muscular injection of long-acting benzathine penicillin to cases and their contacts to cure the disease and interrupt transmission; and for lymphatic filariasis, mass drug administration of diethylcarbamazine and albendazole to reduce microfilaraemia levels and transmission rates.

Table 2. Countries in the South Pacific and Their Endemicity for Neglected Tropical Diseases

Pacific Islands	LF	STH	Yaws	
	2006	2006	1950	2010
American Samoa	*E*	*E*	*	*
Cook Islands	*E*	*E*	*	*N-E*
Fiji	*E*	*E*	*E*	*N-E*
French Polynesia	*E*	*E*	*	*
Guam	*N-E*	*	*	*
Kiribati	*E*	*E*	*	*
Marshall Islands	*E*	*E*	*	*
Micronesia, Federated States of	*E*	*E*	*	*
Nauru	*N-E*	*E*	*	*
New Caledonia	*N-E*	*	*	*
Niue	*E*	*N-E*	*E*	*N-E*
Northern Mariana Islands, Commonwealth of the	*N-E*	*N-E*	*	*
Palau	*N-E*	*	*	*
Papua New Guinea (PNG)	*E*	*E*	*E*	*E*
Pitcairn Islands	*N-E*	*N-E*	*	*
Samoa	*N-E*	*	*E*	*N-E*
Solomon Islands	*N-E*	*E*	*E*	*E*
Tokelau	*N-E*	*	*	*
Tonga	*E*	*N-E*	*E*	*N-E*
Tuvalu	*E*	*E*	*	*
Vanuatu	*E*	*E*	*E*	*E*
Wallis and Fortuna	*E*	*	*	*

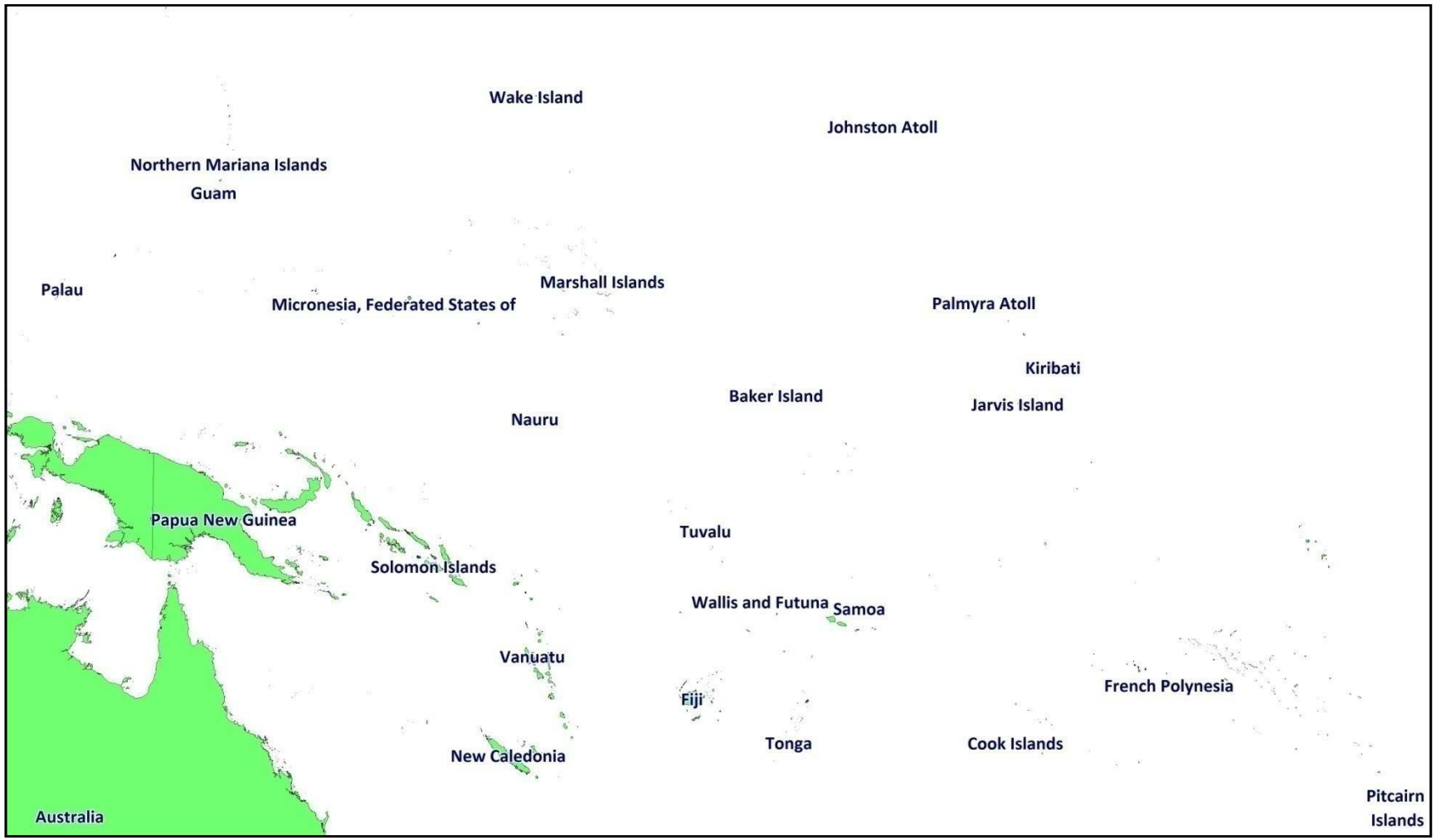
LF = lymphatic filariasis; STH = soil–transmitted helminthiases.
E = endemic; N-E = non-endemic; * No survey carried out or considered necessary.

Table 3. Number of Individuals at Risk for Diseases Requiring Large-Scale Preventive Chemotherapy in the South Pacific Islands in 2006 (22).

Pacific Islands	Yaws		LF		STH	
	Entire population		Entire population in coastal endemic areas		School-children in endemic areas	
	At risk (000)	Treated (%)	At risk (000)	Treated (%)	At risk (000)	Treated (%)
PNG	6,187	0	4,266	591 (14%)	1,574	0
Other Pacific Islands	747 *	0	2,285	965 (42%)	34	0

**** Includes populations in endemic areas of Solomon Islands and Vanuatu***

Figure 1. Map of South pacific Islands



4.4 Yaws

Panel 1. Key facts

- ***Yaws is a neglected skin and bones disease caused by Treponema pallidum subsp. pertenue.***
- ***Mass campaigns in the 1950s-1960s in 46 countries reduced the prevalence by 95%.***
- ***Yaws still occurs in poor communities in a number of countries.***
- ***The majority of those affected are children below 15 years of age.***
- ***A single dose treatment with injection of benzathine penicillin can cure the disease.***
- ***Yaws can be eliminated and eventually eradicated because humans are the only source of infection.***

4.4.1 Biology of *T. pallidum subsp. pertenue*

Yaws (also known as buba, framboesia, parangi and pian) is a non-venereal infectious disease caused by the bacterium *Treponema pallidum* subspecies *pertenue.* This organism belongs to the family of spiral shaped bacteria, the *Spirochaetaceae* (spirochetes), and is related to other pathogenic treponemes. It is morphologically and serologically indistinguishable from the organism that causes venereal syphilis (*T. pallidum* subspecies *pallidum*), although it is mainly transmitted through direct contact with exudates from the early skin lesions of infected people (23)(19).

T. pallidum subsp. pertenue varies from 6 to 15 µm in length and is 0.2 µm in diameter. The spiral-shaped body of *T. pallidum* is surrounded by a cytoplasmic membrane which is enclosed by a loosely associated outer membrane. The outer membrane is non-antigenic, which allows the organism to survive in infected hosts despite the presence of strongly reactive antibodies directed against a number of *T. pallidum* proteins. The bacterium is highly motile and is able to rapidly invade and survive in deep tissues. Endoflagella, organelles that allow for the characteristic corkscrew motility, are located in the periplasmic space. After invasion, *T. pallidum* readily causes chronic infection in the host, though little is known about how the bacterium causes the clinical manifestations in the absence of obvious classical virulence factors (24).

Genetic variations among subspecies and strains

Recent molecular genetic studies indicate that *T. pallidum, subsp. pallidum, subsp. pertenue and, subsp. endemicum* strains can be differentiated through subspecies-specific genetic signatures in multiple genes (12)(14).

A phylogenetic analysis indicates *that T. pallidum subsp. pertenue* arose first in history causing yaws in our anthropoid ancestors in the tropical belt of the Old World; it spread as yaws to the New World and as endemic syphilis to North Africa, Eastern Europe and the Middle East (through divergence of *subsp. pertenue* to *subsp. endemicum*); finally evolved in the Americas the modern *subsp. pallidum* strain (or a progenitor) which was introduced into the Old World as a result of the European exploration of the Americas, and disseminated as venereal syphilis all over the world (25).

4.4.2 Epidemiology

Geographic distribution

Yaws is encountered mainly in humid rural tropical regions and crowded environments and poor hygiene are considered as factors facilitating transmission (26). About 75% of people affected are younger than 15 years (the peak incidence of clinical manifestations is 2 to 10 years), who serve as the primary reservoir of the disease.

Recently an alarming resurgence of yaws has been observed in several countries in the tropics The main reservoir can be found in parts of West and Central Africa where the incidence is again increasing (27). In Southeast Asia and the Pacific Islands residual foci of infection persist in many countries (28). Only a few countries in The Americas report sporadic cases, specifically Suriname, Guyana, Colombia, Venezuela, Brazil, and Haiti.

Prevalence and incidence

The last estimate by WHO in 1995 yielded a global prevalence of 2.5 million cases, including 460,000 infectious cases (Table 4). The global prevalence today is not known. Only a few countries have kept yaws on their health agenda. Data available from six countries are as follows: Cameroon (167; 2010); Congo (646; 2009); DRC (383; 2005); Ghana (20,525; 2010); Indonesia (6,031; 2010) and Papua New Guinea (23,000; 2008). However these figures may only reflect the tip of the ice-berg.

Table 4: Endemic Treponematoses estimates in 1995 (29).

Regions	New cases*	Population at risk
Africa	400,000	20,000,000
America	2,000	2,000,000
Eastern Mediterranean	4,000	1,000,000
Europe	-	-
South-East Asia	50,000	10,000,000
Western Pacific	4,000	1,000,000
Total	460,000	34,000,000

**New cases: prevalence of infectious cases (used for planning and evaluation of control programmes)*

Table 5: List of known endemic countries for yaws in 2011(30).

Region (number of countries)	Endemic country
Africa (8)	Ghana, Benin, Togo, Central African Republic, Democratic Republic of Congo, Cameroon, Nigeria, Cote d'Ivoire, and Mali
Americas (unknown)	Unknown
South-East Asia (2)	Indonesia, Timor Leste (note: the last reported cases from India was in 2003)
Eastern Mediterranean (0)	--
Pacific (3)	Papua New Guinea, Solomon Islands and Vanuatu

4.4.3 Past and current yaws control strategies in South Pacific region

Historic perspective

The endemic treponematoses, because of the disfigurement and disability they cause, were a major public health problem in the pre-antibiotic era. In 1948, the World Health Organization (WHO) and the United Nations International Children's Emergency Fund (UNICEF) sponsored a global control program. This involved 46 countries (31) and brought this disease under control. The yaws elimination programme screened more than 160 million people, treated more than 50 million with intramuscular (IM) injections of benzathine penicillin, and reduced the prevalence of yaws by more than 95%. But yaws was not eliminated.

Yaws control during the 1950s and 1960s was based on initial surveys that often covered a large proportion of endemic populations, together with mass or selective treatment using long acting penicillin G (8). For example in the Cook Islands 99% of the

population was screened in 1960 and in Vanuatu an initial mass treatment survey conducted in 1958 covered 94% of the indigenous population (8).

Yaws surveillance and control activities subsequently became integrated into the primary health care systems of individual countries, where remaining cases were to be identified and treated (30). Yaws transmission persisted however, although at low levels, and the passive approach for yaws control under primary health care systems was not efficient in detecting and treating the cases remaining in remote and isolated areas of developing countries. In the 1970s resurgence was reported in many of the formally endemic areas (30). Despite efforts to renew the commitment to yaws control and to re-engage the international community (e.g., World Health Assembly Resolution 31.58 of 1978 on yaws; global and regional meetings in the early 1980s), yaws persisted in many parts of the world, with the largest number of cases found in west and central Africa and the Pacific Islands (6)(13).

Previous approaches to yaws treatment and control

The principles of prevention in yaws, are based on the interruption of transmission by mass or targeted treatment of affected population or community. It has been historically estimated that for each single case of yaws there might be five to ten sub-clinical cases (19). As both clinical and subclinical cases constitute the reservoir of infection, it is unlikely that identifying and treating active cases alone will have any effect on the prevalence of infection in highly endemic areas.

In 1984, the WHO recommendations were published in response to resurgence in the 1970s (27). According to the recommendations, a treatment strategy for yaws control should be based on the prevalence of clinically active yaws. Thus, the prevalence of active cases needed to be assessed in a representative sample of a population of interest, in order to determine an appropriate treatment policy for that population (Table 6).

Table 6. WHO recommended treatment strategy by disease prevalence (19).

Approximate prevalence of clinically active yaws in the community	Endemicity classification	Recommended treatment
High (>10%)	Hyperendemic	Entire population of the community (Total mass treatment)
Medium (5-10%)	Mesoendemic	All active cases, all children under 15, and obvious contacts (Juvenile mass treatment)
Low (<5%)	Hypoendemic	All active cases and all household and Other contacts (Selective mass treatment)

Table 6 summarizes the recommended policy for the treatment of yaws, based on the prevalence of active yaws in a village. With the exception of the total mass treatment (TMT) policy, which includes the treatment of the entire population it is difficult to envisage how the other two proposed schemes (Juvenile and Selective mass treatment) could be implemented in such a way to interrupt transmission. Indeed, contacts of the clinical case were defined as “people who have frequent, direct, person-to-person contact with a patient with active yaws lesions”(19). Such potential contacts are assumed either to be incubating yaws or to have latent disease. However, in practice it is difficult to identify all possible contacts and treat them; thus always leaving a pool of potentially infected people and infectious reservoirs.

Most yaws control activities implemented in the South Pacific since the 1990s have followed the above recommended strategies using an intramuscular treatment regimen with benzathine benzylpenicillin. The low cost of benzathine penicillin and its efficacy make it a valuable option for treating yaws in a population. De Noray et al. (9) estimated the cost of the 2001 mass treatment conducted in Vanuatu, to be USD 1.30 per person (19).

4.4.4 Yaws in Papua New Guinea

A nationwide mass treatment targeting the entire population of PNG took place between 1953 and 1958 under the Australian administration covering more than 90% of the population (15). Many of the untreated individuals were residents of remote and isolated areas of the country where the campaign reach was limited. The campaign was successful; with only 2,352 cases being reported in 1959 and fewer than 500 cases subsequently reported each year until 1973. A slight increase in the number of cases was recorded between 1973 and 1978, however it did not exceed 1,000 cases per year (16), and most of these occurred in the rural areas of Bougainville, New Britain and New Ireland Provinces (17). The disease was rare in the Highland districts and reported to be nonexistent in the Central Province and Port Moresby. Consequently, yaws was removed from the national list of reportable diseases. The clinical appearance of yaws observed during this time period was milder (fewer lesions, with plantar lesions and bone involvement rarely observed) than in the 1950s and these milder cases were described as “attenuated cases” (17).

In December 1978, a mass campaign targeting the entire population was carried out on Karkar Island, Madang Province, after a rapid increase in the number of yaws cases was recorded the previous year (17). Based on surveys carried out preceding the mass

treatment, the estimated prevalence varied from 0% to 27%. Although the mass treatment reported to have covered more than 90% of the island population, the island continued to report cases of yaws.

In the early 1980s, clusters of cases were reported in the Provinces of East and West Sepik, East and West New Britain, New Ireland, and Milne Bay. The outbreak, and subsequent mass treatments in Yilui village, West Sepik Province, is well documented (16). In Yilui village a survey in early 1984 found 193 clinical cases (35% of the population). A follow up MDA treatment conducted six months after the first still found 60 clinical cases. In addition, a large proportion of non-symptomatic individuals presented with a reactive VDRL.

In 1988, another outbreak was reported on Karkar Island (18). 39 children (6%) exhibited early yaws lesions, and all villagers were treated with benzathine penicillin. A 22 month serological follow-up showed that 13% of cases remained positive, suggesting that yaws had decreased sensitivity to penicillin in this area.

Between April 2000 and September 2001, the Nine Mile Clinic in Port Moresby identified 494 cases confirmed by serological tests (TPHA and VDRL) through clinic based case detection (11). The population in Port Moresby is young and rapidly growing, with continuous migration of people from throughout the country. With poor hygiene, crowded environments, and a large number of people previously unexposed to yaws, the population provides an ideal environment for yaws transmission (11).

Yaws is still a substantial cause of morbidity in Papua New Guinea. Monthly reports are currently being collected from hospitals, health centres, and aid posts throughout the country. The national health department estimated the number of yaws cases to be 17000 nationwide in 2003, and 29000 in 2008, of which 7300 were in New Ireland Province where Lihir Island is located and another 7200 in the neighbouring province of West New Britain (Table 7).

Table 7. Reported yaws cases in outpatient by province by years (2007-2011) in Papua New Guinea (32).

Province	**2007**	**2008**	**2009**	**2010**	**2011**
Western	291	67	70	57	49
Gulf	256	42	14	47	132
Central	86	334	327	407	258
National Capital District	109	139	665	432	335
Milne Bay	399	1.181	723	585	668
Northern	433	789	754	915	1.362
Southern Highlands	120	918	180	225	202
Enga	34	94	1	9	9
Western Highlands	57	140	50	33	27
Chimbu	93	64	63	16	309
Eastern Highlands	163	131	176	100	83
Morobe	692	211	236	490	637
Madang	1.835	2.657	2.357	2.538	2.671
East Sepik	1.845	1.399	1.066	773	651
West Sepik	712	1.077	1.254	1.755	1.652
Manus	76	13	40	30	29
New Ireland	3.336	5.306	5.668	7.573	7.322
East New Britain	2.286	2.654	3.478	4.271	4.446
West New Britain	2.512	5.386	7.906	7.089	7.262
North Solomons	601	859	794	1.716	885
Total	**15.936**	**23.461**	**25.822**	**29.061**	**28.989**

4.4.5 Clinical features

The disease has a natural history involving primary, secondary, and tertiary stages.

Primary stage

Infection is initiated when *T. pallidum subsp. pertenue* penetrates epidermal abrasions, typically resulting in a single chancre at the point of entry. The initial or primary lesion ('mother yaws') appears after 2–4 weeks of inoculation and is typically a painless, atraumatic ulcer with raised margins of 2–5cm in diameter. It may heal in 3–6 months with or without scarring (**Figure 2**) but, may still be discernible in a proportion of patients at the onset of secondary yaws. Primary chancres most commonly occur in the legs and arms.

Secondary stage

Within hours of inoculation, and during the evolution of the primary stage, *T. pallidum* disseminates widely via the lymphatic and blood vessels. Manifestations of secondary yaws usually occur a few weeks to 2 years after the primary lesion and are sometimes quite subtle. The most common manifestation of secondary yaws is polyarthralgia and osteoperiostitis of long bones, causing bone pains, affecting the fingers or toes (dactylitis), forearm, tibia, or fibula (Figure 2).

Concurrently with the appearance of bone pain, some patients develop secondary skin lesions consisting of multiple hyperkeratosic papules or multiple excrescences that can resemble the initial papilloma. The lesions may be irregular, crescentic or discoid in shape and on moist areas may mimic condylomata lata of venereal syphilis. Palmar and plantar lesions, which may be painful, have also been described. The patient may at any time enter latency, with only serologic evidence of the infection remaining, though infectious relapses may occur for 5 years and, rarely, for 10 years (23).

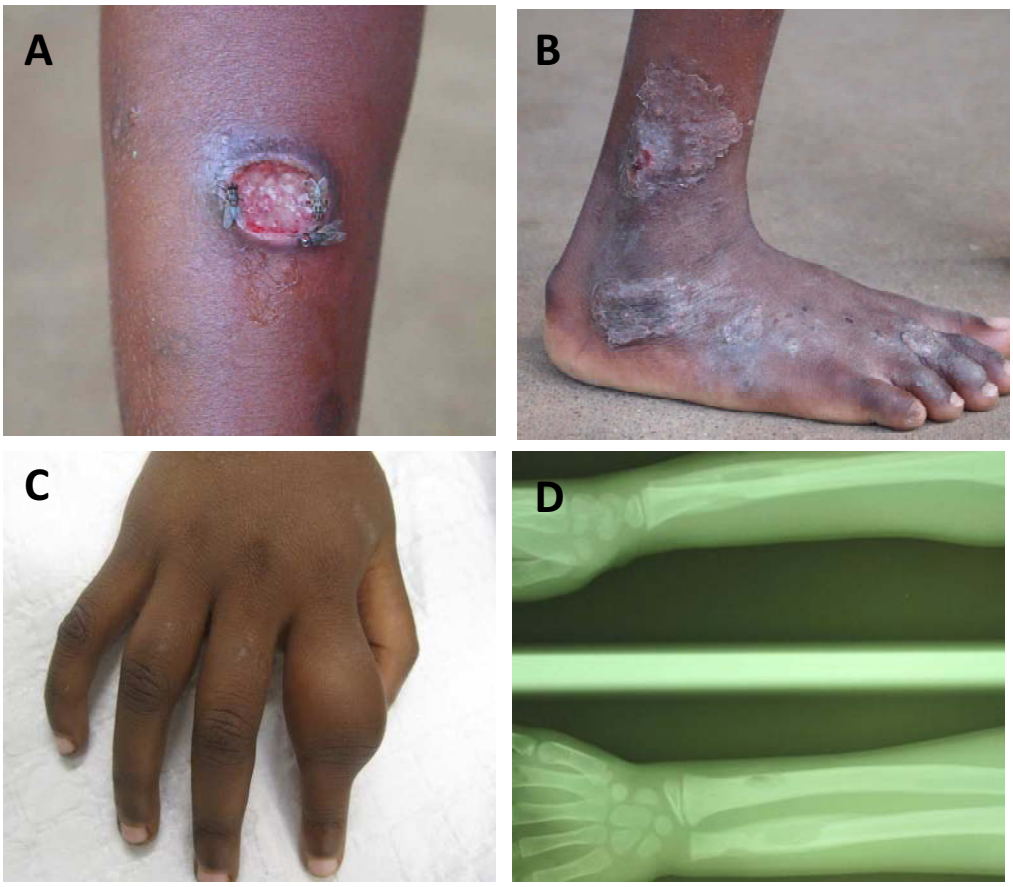
Tertiary stage

About 10% of patients develop late lesions after 5 years or more of untreated infection. The late stage is characterized by gummatous lesions of skin, bones and overlying tissues. The manifestations, some of which also occur in early stage but are now more destructive, include:

- hyperkeratosis of palms and soles with deep fissures;
- juxta-articular subcutaneous nodules;
- more extensive osteoperiostitis of long bones (e.g. sabre tibia);

- hyperostosis of the nasal processes of the maxillae (‘goundou’); and
- ulceration of the palate and nasopharynx (rhinopharyngitis mutilans) with secondary infection resulting in foul-smelling discharge (‘gangosa’).

Figure 2. Primary yaws’ skin lesion (ulcer with raised edges) on the leg of a patient (A) and secondary skin lesion (crustopapillomatous) on the ankle-foot (B). Fusiform swelling of the second digit in a patient with secondary yaws (C) and radiograph of a forearm showing osteo-periostitis (D).



Differential diagnosis

In endemic areas, an accurate clinical diagnosis can be made in the presence of classic lesions. This will, however, necessitate appropriate training of clinicians, especially in view of the rather milder forms being encountered. The difficulties arise when there are no clinical lesions (i.e. latent cases), when venereal syphilis is also locally prevalent and when the patient is an immigrant from an endemic area presenting at a clinic in a non-endemic country. The conditions to be considered for differential diagnosis include:

- anaerobic bacteria related ulcer (or tropical ulcer), cutaneous leishmaniasis, mycobacterial disease, in a patient who has early skin lesions;
- infected bites, psoriasis, excoriated chronic scabies or verrucae should be considered in a patient with secondary skin lesions;
- tuberculosis, bacterial osteomyelitis and sickle cell disease in a patient with dactylitis.

4.4.6 Diagnosis of yaws in South Pacific region

Clinical criteria

During the 1950s and 1960s in most cases diagnosis was based on clinical criteria (8). With the disappearance of yaws in a number of countries and the progressive retirement of those who were involved in the eradication campaigns in the 1950s and 1960s, some authors suggested that most health workers may have never encountered the disease and therefore may be incapable of clinically diagnosing it (11). However, yaws has continued to be detected clinically by primary health care workers, for example in Vanuatu in 2000 (9) and PNG in 1995 (10). Clinical diagnosis made in recent years may be less specific as the number of primary health care workers experienced in yaws diagnosis is declining. On the other hand, primary yaws is commonly confused with a number of conditions common in the tropics and thus it is possible that a significant proportion of cases may in fact be falsely diagnosed cases.

Dark-field microscopy

The Gold Standard for diagnosis of treponemal infection is the demonstration of treponemes in a wet preparation of the material from early lesions by dark-field microscopy or in the biopsy material stained by the silver impregnation technique. However, this method is impractical in the field. In practice dark-field microscopy is rarely used to diagnose treponemal infections because rapid serological tests are available.

Serologic tests

Serologic tests including the non-treponemal tests (rapid plasma reagin [RPR] or Venereal Disease Research Laboratory [VDRL]) and the treponemal tests (*T. pallidum* hemagglutination assay [TPHA] or fluorescent treponemal antibody absorption [FTA-Abs]) should be carried out in all cases, but their interpretation requires expertise. The treponemal tests are particularly useful to confirm a reactive non-treponemal test (exclusion of false positives) (19)(26). A reactive treponemal test may indicate a

current infection or a past infection ('serologic scar'). Simple and rapid treponemal tests recently became available in the form of immunochromatographic strips and as they can be used with whole blood and do not require refrigeration they are extremely useful in the field (33).

There is no test that can differentiate the treponematoses (including venereal syphilis) from one another. This reality can be of importance as it represents a particular challenge in countries where both yaws and syphilis are simultaneously endemic. For example, the lack of specificity of the RPR test raised questions in Vanuatu in 2000, where surveys found an unexpected, apparent 2.4% prevalence of syphilis in women attending antenatal clinics (RPR confirmed by TPHA), when in fact, in the absence of clinical symptoms it is not possible to differentiate between the two infections. Similarly, the inability to differentiate yaws and syphilis serologically can be an issue in countries where yaws was endemic in the past and the prevalence of syphilis is known to be high.

Molecular methods

New techniques such as the molecular methods reported by Centurion-Lara (12) and Pillai (14) to differentiate the three *T. pallidum* subspecies could be of great assistance in similar situations. However, such methods are expensive, complex, and they require more than the standard laboratory equipment found in the resource-limited countries still affected by yaws in the South Pacific. Thus, one can expect that in the South Pacific Region diagnosis of yaws will continue to require the assessment of test results together with clinical manifestations while carefully taking into account the epidemiologic characteristics of yaws. One of the purposes of this thesis is to explore the reliability of the diagnostic criteria for yaws.

4.4.7 Management of yaws

Antibiotic treatment

Injectable penicillin remains the drug of choice (30)(34). Long-acting benzathine penicillin G, given intramuscularly in a single dose, is preferred. The recommended dose is 600,0000 units for children under the age of 6 years; 1.2 million units for those aged 6–15 years; and 2.4 million units for those over 15 years. Oral penicillin V (50 mg/kg in 4 divided doses) for 10 days was used in rural Guyana and 16 out of 17 children with yaws were cured (35); but such a regimen with multiple doses has a potential compliance problem.

While it is recognized that treponematoses have remained exquisitely sensitive to penicillin, there is a report of penicillin treatment failures of yaws in Papua New Guinea (16). A few penicillin treatment failures have also been observed in Ecuador (30). The distinction between relapse, re-infection or true resistance is difficult to make but these clinical or serological failures are worrisome and this issue will be further researched in this thesis. In addition to this, mass campaigns using an injectable agent present logistical problems, with issues such as the need for trained staff, needles, syringes, waste disposal and infection control measures, and the possibility of adverse reactions all presenting a challenge in the isolated and resource poor areas where the disease is prevalent. Injections of penicillin cause anaphylactic reactions in a small proportion of cases. While the risk might be small (<1 in 50000), the consequences may be severe, and control programs need to train staff and equip them with the means to treat reactions. Importantly, past mass drug administration campaigns to control yaws using injectable agents have lead to the transmission of hepatitis C virus (36).

There is little information on the use of drugs other than penicillin to treat these conditions (i.e. in case of penicillin allergy), but regimens recommended for the treatment of venereal syphilis should be efficacious. Azithromycin in a single dose of 2 g orally was shown to be highly efficacious in adults with syphilis (37), but emergence of azithromycin-resistant *T. pallidum* should be monitored (38). The potential to use oral azithromycin for yaws is another important focus of this thesis**.** If a drug was to be shown effective as an oral single-dose treatment, its potential as a mass drug administration tool could be enormous and suitable for elimination campaigns.

Prognosis and follow-up

The lesions become non-infectious within 24 hours after the injection of penicillin. Whereas treatment in early stages should result in cure in almost 100% of patients, it will not reverse any destructive change in late stages. Rapid plasma reagin (or VDRL) titters should decline within 6–12 months, becoming negative in about 2 years. However, in a small proportion of cases, especially if treated in late stages, the RPR (or VDRL) may remain positive, albeit in low titter (below 1:8). The specific tests (i.e. TPHA, FTA-Abs, rapid treponemal tests) will remain positive throughout life.

4.5 Filariasis

Panel 2. Key facts

- ***More than 120 million people are currently infected by filariasis, with about 40 million disfigured and incapacitated by the disease.***
- ***Lymphatic filariasis can result in an altered lymphatic system and the abnormal enlargement of body parts.***
- ***Acute episodes of local inflammation involving the skin, lymph nodes and lymphatic vessels often accompany chronic lymphedema.***
- ***To interrupt transmission WHO recommends an annual mass drug administration of single doses of two medicines to all eligible people in endemic areas.***

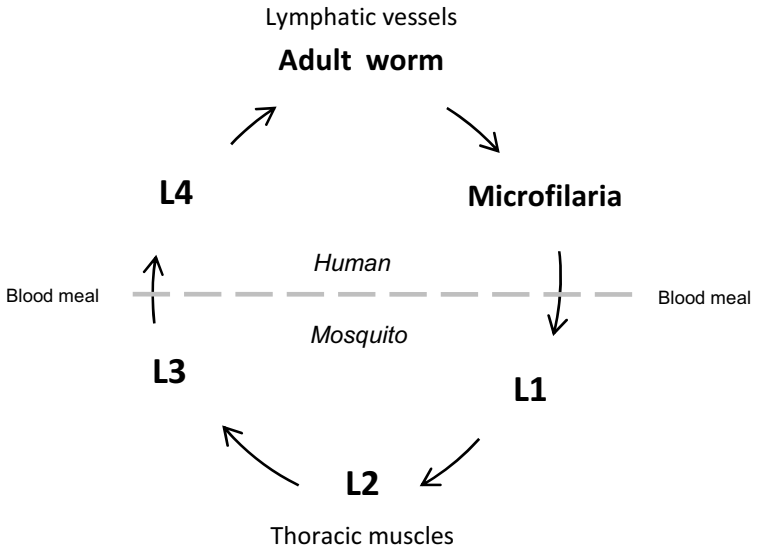
4.5.1 Biology of *Wuchereria bancrofti*

Lymphatic filariasis is a disease caused by the parasitic worm *Wuchereria bancrofti*. As with all nematodes, the filarial life cycle consists of 5 larval stages in a vertebral host (human) and an arthropod intermediate host (vector). Humans are the only definitive host for the parasite.

Life cycle

During a blood meal, an infected mosquito introduces third-stage filarial larvae onto the skin of the human host, where they penetrate into the bite wound. These larvae travel through the dermis and enter regional lymphatic vessels. During the next nine months, they develop into mature worms (20-100 mm in length), which can survive an average of about five years. Adult worms reside in lymph nodes and lymphatic vessels distal to the nodes and produce thousands of first-stage larvae, or microfilaria (244 to 296 μm), which are sheathed. The microfilariae migrate into lymph and blood channels moving actively. A mosquito ingests the microfilariae during a blood meal. Microfilariae then undergo two developmental changes within the insect (Figure 3). In the Pacific Islands filariasis is subperiodic. That is to say, microfilariae are present in peripheral blood at all times and reach maximal levels in the afternoon. Natural vectors for *W. bancrofti* include *Culex fatigans* mosquitoes in urban settings and *anopheline* mosquitoes in rural areas.

Figure 3. Life cycle of Wuchereria bancrofti in humans and the mosquito vectors (Aedes, Anopheles, Culex, and Mansonia species).



4.5.2 Epidemiology

Lymphatic filariasis widespread in Asia, Africa, the Pacific, and Latin America, with an estimated 43 million people having overt lymphatic pathology including hydrocele and lymphoedema and 1300 million at-risk population (table 8)(39). Papua New Guinea represents one of the biggest remaining foci of transmission and thus an important challenge for elimination of the disease in the South Pacific (40).

Table 8. Lymphatic filariasis estimates, 2009 (39)

Region	Number of endemic countries	At-risk population (in millions)
Africa	39	394
America	7	8.87
Eastern Mediterranean	3	14.9
Europe	-	-
South-East Asia	9	851
Western Pacific	23	31.6
Total	**81**	**1300**

Extensive medical, social, and economic benefits are expected to result from decreasing or eliminating infection (41). Population based control strategies became practical with the discovery that single administration of a drug could result in long lasting suppression of microfilaria similar to that seen with extended administration (42).

4.5.3 Clinical features

Four factors are currently thought to be central to the pathogenesis of lymphatic filariasis: microfilariae, the living adult worm, death of the adult worm and secondary bacterial infections.

- Microfilariae are associated with microscopic haematuria in otherwise asymptomatic infected persons; they are also central to the pathogenesis of tropical pulmonary eosinophilia.
- Living adult worms cause extensive lymphangiectasia through release of diffusible toxic substances.
- Death of the adult worm causes an acute inflammatory response that is manifested clinically as adenitis and lymphangitis
- Secondary bacterial infections cause an acute syndrome of adenolymphangitis.

The clinical expression of lymphatic filariasis varies considerably. The most common presentations are asymptomatic microfilaremia, acute adenolymphangitis, and chronic lymphatic disease (43) (44).

Asymptomatic (adult worm carriers and microfilaria-positive persons)

In areas where lymphatic filariasis is endemic, most infected persons are asymptomatic despite the presence of up to millions of microfilaria circulating in the peripheral blood. Thus, the diagnosis of microfilaraemia is often made incidentally in a “routine” blood examination. However, virtually all persons with *W. bancrofti* infection have some degree of subclinical disease that includes microscopic haematuria and/or proteinuria associated with microfilaria, and dilated lymphatics related to the adult worm.

Acute adenolymphangitis (ADL) and acute filarial adenolymphangitis (AFL)

ADL is characterized by a reticular pattern lymphangitis, including transient local oedema, pain, fever and chills (45). The aetiology of these “acute attacks” has been attributed to recurrent bacterial infections secondary to lymphatic dysfunction and accumulation of protein-rich fluid in the tissues. The lower limbs, in particular, become predisposed to recurrent bacterial infections. Trauma, interdigital fungal infections, and onychomycosis provide entry sites for Beta-haemolytic streptococci (46). Recurrent ADL is a major risk factor for the development of elephantiasis.

A different entity is the acute filarial adenolymphangitis (AFL) which is caused by death of the adult worm, either spontaneously or as a result of treatment with a

macrofilaricidal drug (47). The initial inflammatory response is manifested as adenitis or lymphangitis, depending on whether the worm is located in the lymph node or lymphatic vessel, respectively. The lymphangitis is retrograde producing a palpable cord, and is frequently accompanied by headache and malaise. When genital lymphatics are involved may present as funiculitis, epididymitis, or orchitis (48).

Chronic lymphatic disease

The chronic manifestations of lymphoedema and/or hydrocele will develop in approximately 30% of LF infected persons. Repeated ADL episodes are responsible for the progression of chronic lymphatic disease. Lymphoedema mostly affects the legs, but can also occur in the arms, breasts, and genitalia. Most people develop these symptoms years after being infected (49). This is a long-term consequence of lymphatic dysfunction resulting from dilatation of the lymphatic vessels due to ADL and AFL. Repeated bacterial infections hasten the progression of lymphoedema to elephantiasis, but fibrosis and sclerosis may occur even without these secondary infections (50).

The chronic urogenital manifestations of lymphatic filariasis include lymph scrotum, hydrocele, chylocele, and chyluria. Hydrocele is the most frequent chronic manifestation of bancroftian filariasis and the prevalence in men increases with age. Hydrocele is thought to be the consequence of lymphatic damage caused by adult worms (49). Chyluria occurs when dilated lymphatic vessels of the urinary excretory system rupture, causing leaking of lymphatic fluid and chyle into the urine. The urine may be milky white in colour, particularly after a fatty meal.

4.5.4 Diagnosis of LF in the South Pacific

Detection of Microfilariae

The standard method for diagnosing active infection is the identification of microfilaria in a blood smear by microscopic examination. For epidemiologic screening, 20–60 ml of capillary (“finger stick”) blood can be dried on a slide, stained with Giemsa, and examined under a microscope. A more sensitive method is to filter at least 1 ml of venous blood through a 3–5 mm Nuclepore™ filter (43).

Antigen Detection Assays (ADA)

While the visualization of microfilariae in peripheral blood by light microscopy is the gold standard for monitoring filarial infection, the Pacific program for elimination of LF (PacELF) activities are based on the use of antigen detection tests for diagnosis.

Commercial kits are available to test venous blood and can be quantitative (enzyme-linked immunoassay [ELISA]) Og4C3 monoclonal antibody–based assay) or qualitative (immunochromatographic). Both ADA have a high reported sensitivity (approaching 100%) and specificity (98.6% to 100%) (51)(52). The sensitivity of these assays appears to be higher than detection of microfilaria in 1 ml of filtered blood.

A major advantage of both these assays is that circulating filarial antigen remains diurnally constant; therefore, blood for diagnosis can be collected anytime during the day. Also these ADA permit the diagnosis of both microfilaraemic and amicrofilaraemic infections. A positive test result should be interpreted as evidence for the presence of live adult *W. bancrofti* (52).

4.5.5 Community-based treatment of LF in the South Pacific

In a community-based intervention the main goal is to profoundly suppress microfilaraemia in each individual and thereby interrupt transmission in the community. This treatment goal is usually compatible with the individual goal to prevent, reverse, or halt the progression of disease.

There are currently three drugs effective against *W. bancrofti* microfilaria that can be administered as single doses, in two-drug combinations—diethylcarbamazine, ivermectin, and albendazole. Recent studies have validated the use of single-dose regimens of DEC and albendazole for large-scale control and elimination programs to reduce *W. bancrofti* microfilaraemia, antigenaemia, and clinical manifestations in the South Pacific (53)(54).

When given in conventional doses, DEC is active against the microfilaria and only partially against the adult worms of *W. bancrofti*. Microfilariae are usually rapidly cleared from the peripheral blood, but the degree to which DEC kills adult *W. bancrofti* is variable (55). This drug has only a temporary effect in reducing the production of microfilaria by adult worms, probably due to sterilization. After some months renewed production occurs but at a reduced intensity (56). In the absence of macrofilaricidal activity, current programs rely on the interruption of transmission through sustained suppression of microfilaraemia over 5 years program of annual mass drug administration to the entire population.

4.5.6 Programs for the elimination of LF in the South Pacific

Lymphatic Filariasis Control Strategy

The Global Program to Eliminate Lymphatic Filariasis (GPELF) was launched in 1997. In the Pacific, the World Health Organization (WHO) has implemented from 1999, the Pacific Program to Eliminate Lymphatic Filariasis (PacELF) bringing together 22 countries and territories in a common effort to eliminate the disease (57).

The PacELF strategy is based on mass drug administration (MDA) with an annual single dose of a combination of two drugs (diethylcarbamazine plus albendazole) administered for five or six consecutive years to the entire eligible population living in the endemic area (58). The rationale of this approach is to reduce the mf reservoir of infected populations and bring the infection level down below a threshold that will break the transmission of *W. bancrofti* through the mosquito vectors (59). The program is monitored by a prevalence survey to assess the impact at completion of the last round of MDA (58)(60). Therefore, the assessment at the end of the MDA rounds should allow an evidence-based decision of whether to stop or to continue MDA after round 5. The current recommendation of the PacELF is that programs should reach an antigenaemia level below 1% and that less than 1 in 1000 children born since start of MDA should become newly infected (57). End-points for the GPELF have recently been changed to a level below 2% in areas where the main vector is an anopheline (60), such as in Papua New Guinea. Models have been created to predict the number of drug administrations needed to achieve this goal using existing estimates of drug efficacy (61). However, uncertainty remains regarding the effectiveness of this programme because of difficulties in estimating and comparing the overall relative effects of these interventions.

National Activities for Lymphatic Filariasis Control

During the past ten years most Pacific Island Countries and Territories (PICTs) have completed initial surveys to map the extent of LF infection. Of the 22 PICTs, 14 were found to be endemic for LF. The total population at risk was 6.55 million (20). Eleven countries in this region, completed the fifth round of Mass drug administration in 2006 (American Samoa, Cook Islands, Fiji, French Polynesia, Kiribati, Niue, Samoa, Tonga, Tuvalu, Vanuatu, and Wallis and Fortuna). In the remaining three endemic countries of the area, Papua New Guinea, Marshall Islands, and Federates States of Micronesia, with an eligible population of over 4.2 million individuals, between one and three MDA rounds have been administered (20).

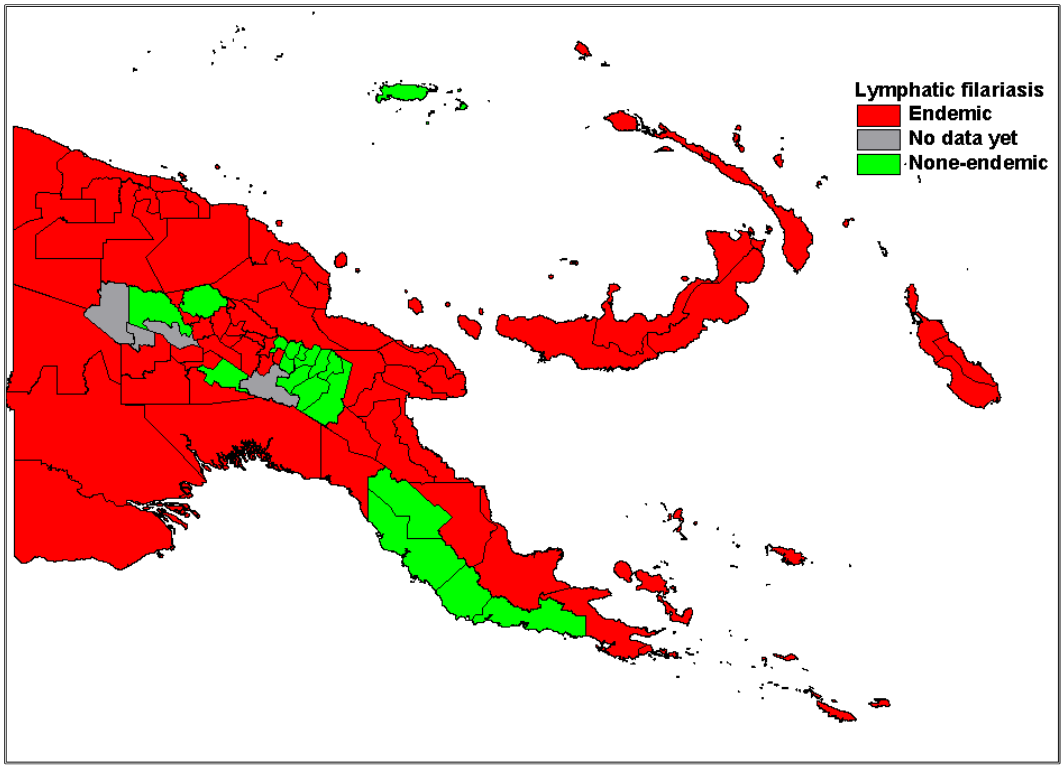
4.5.7 Update on the Papua New Guinea ELF programme

Lymphatic filariasis is endemic in 16 of the 21 provinces of Papua New Guinea (PNG). All infections are due to *W. bancrofti* and transmitted by *Anopheles punctulatus* and, less frequently, *An. koliensis* sibling species. More than 1 million persons in PNG are currently infected with *W. bancrofti*, and more than 3 million are at risk (total population ~6.6 million). Brugia infection has not been described in PNG or the Indonesian province of Papua in the western half of the island of New Guinea.

Lymphatic filariasis is mainly a problem in lowland coastal areas and the many small islands off the main island mass. Malaria infection that includes the four major species of human parasite co-exists in the lowland areas. The level of LF endemicity varies widely, with community mf+ rates ranging from ~10 to >70%. The high end of the range is typified by inland tropical rainforest areas of East and West Sepik Provinces, and the lower end in eastern coastal areas and parts of Milne Bay Province. The map in Figure 4 shows the estimated LF endemicity in various provinces of PNG. Darker shading indicates a higher prevalence of infection.

The programme for the elimination of LF was initiated in Papua New Guinea with support from the PacELF office in Fiji in 2004. After the preparatory phase in 2004, the first round of MDA was conducted in Milne Bay province in 2005. Baseline surveys for the provinces prior to MDA showed ICT-positivity rates ranging from 15% to 40%. The plan is to add several more provinces to the programme each year until the whole country is covered. There are 20 provinces in the country and each province is an implementation unit. To date, coverage has been variable in the implementation units conducting MDA, varying depending on the resources available. In its initial plan, Papua New Guinea opted for door-to-door delivery of the drugs for MDA using the existing health infrastructure. However, MDA implementation has taken a very long time due to use of this method by the health service in each village (62).

Figure 4. Distribution of Lymphatic filariasis in PNG, based on 2006 existing data (62) .



5. Specific introduction to this thesis

This thesis is based on work done in the Lihir Medical Centre in collaboration with Barcelona's Centre for International Health Research (CRESIB). The studies received support from the international gold mining company, Newcrest Mining. As part of its commitment to sustainable development on Lihir Island, Newcrest funds a community health plan which addresses existing and emerging health issues which incorporate curative and preventive health measures.

The first, second and third papers presented here report data obtained on patients examined in the outpatient medical department and suspected to have yaws. These are thorough analyses describing the burden of yaws in Lihir Island, the diagnostic challenges in the South Pacific, the standard treatment efficacy and the outcome predictors after treatment. Despite these data coming from a single hospital in Papua New Guinea, they may still be highly informative and relevant for other endemic areas.

The fourth paper presented in this thesis reports results from a rigorously conducted, randomised non-inferiority clinical trial, assessing the efficacy of an oral single-dose of azithromycin for the treatment of yaws. This study has been reported according to internationally accepted CONSORT guidelines (63). The fifth paper outlines a possible strategy for the eradication of yaws. Clearly, oral treatment is easier to give and, if the results of our study can be confirmed elsewhere, this could facilitate the eradication of yaws and other endemic treponematoses

The last paper reports the results of an ecological study conducted during a large scale intervention program in 27 villages on Lihir Island, involving more than 8000 people. The aim of the study was to identify and assess the factors determining success for Lymphatic filariasis elimination program

5.1 First paper

The first paper describes the clinical features of yaws and assesses the accuracy of the commonly used diagnostic procedures in Papua New Guinean children in an area of medium to high endemicity, such as the PNG northern islands. Previous case reports had suggested that yaws may have changed its pattern of presentation by manifesting as milder or atypical forms, and this paper confirms that the number of secondary stage forms is now more common. These data provide guidance to help identify children potentially having yaws. The paper highlights the importance of supporting laboratory

diagnostic techniques to confirm the clinical suspicion of yaws. Clinical diagnosis alone may be difficult even for experienced clinicians because yaws produces lesions which can resemble several other diseases in the tropics and because of the mentioned increasing number of atypical presentations.

5.2 Second paper

The second paper on this thesis is a descriptive analysis of yaws treatment failure on the island of Lihir. There are very few studies that measure treatment outcome for yaws, and it is generally recognized that treponematoses have remained exquisitely sensitive to penicillin. In this research study, an estimation of failure rates after treatment with benzathine penicillin was assessed during a long-term follow up. Particular attention is drawn to the distinction between relapse, re-infection or true resistance, which is generally difficult to make. The paper highlights the importance of risk of reinfection caused by repeated contact with infected children.

5.3 Third paper

The third paper is a case series of patients with osteoperiostitis in early yaws. The paper provides a detailed report of the clinical and radiological manifestations and outcome after treatment of this rare presentation of the disease. Since 1950s, clinical and radiographical descriptions of bone abnormalities in yaws had been described only in archaeologically based research. The paper shows that yaws alters the radiological appearance of bones in a highly specific manner and suggests that these specific signs can be used to support the clinical diagnosis of yaws.

5.4 Fourth paper

The fourth paper on this thesis reports the results of an open-label, non-inferiority randomised trial designed to assess the efficacy of azithromycin compared with intramuscular long-acting penicillin in the treatment of patients with yaws. The randomized trial involved 250 children aged between 6 months and 15 years. The motivation for this study was the realisation that a single dose oral treatment would have several advantages over the currently recommended injectable penicillin. Oral azithromycin is safe and easy to administer and avoids the need for injection equipment and medically trained personnel. The study shows that a single oral dose of azithromycin is as effective as IM benzathine penicillin in the treatment of yaws in Papua New Guinea. A change to the simpler azithromycin treatment regimen could enable yaws elimination through mass drug administration programmes.

5.5 Fifth paper

The fifth paper is a review of the past and future antibiotic treatments for yaws and its applicability in eradication programs. The strategy of the yaws elimination program in 1952 called for the screening of patients for clinical disease and their treatment with penicillin injections; however the goal of eradication remained elusive. There are very few published articles that provide information on why previous attempts to eliminate the disease were ultimately unsuccessful and more importantly what are the future perspectives to tackle yaws as a public health problem.

The paper describes the main features of azithromycin that make it an excellent candidate for an oral shortened course therapy for yaws and also to be used as a epidemiologic mass treatment tool. The article also explores what would be the path to a global eradication worldwide, taking into account the main lessons learned from the past.

5.6 Sixth paper

The last article describes a large scale intervention program to control filariasis implemented in Lihir Island. The paper explores the unresolved question about the appropriate duration for mass drug administration programs, and the factors determining success for this intervention. Previous theoretical work and clinical field experience has highlighted how the ecological diversity between different endemic regions hinders the decision making process of when to stop ongoing MDA programs.

The study shows that the five yearly cycles of MDA could neither eliminate the disease nor stop transmission in the high prevalence villages, demonstrating that high baseline lymphatic filariasis prevalence has a negative influence on the outcome of a program. The paper provides data supporting the recommendation that in certain high prevalence and transmission environments more sustained efforts may be necessary.

6. Hypotheses and objectives

6.1 Hypotheses

6.1.1. First paper

- Classical skin and bone lesions are a common presentation in patients with yaws in Papua New Guinea, implying that attenuated forms are less frequent than previously described.

- The diagnosis of yaws requires the support of laboratory techniques, plus a detailed clinical and epidemiological history. Clinical data by themselves are not very specific for the diagnosis of yaws.

6.1.2. Second paper

- Serologically defined treatment failures can occur after treatment with benzathine benzylpenicillin in Papua New Guinea.

- Re-infection due to continuous contact with infected hosts is the most important risk factor for serologically defined treatment failure in yaws.

6.1.4. Fourth paper

- A single oral dose of azithromycin is non-inferior to benzathine benzylpenicillin to induce serological cure, defined as a decrease in the rapid plasma regain titre by at least two dilutions at 6-months follow-up, and improvement of skin lesions within the first two weeks after treatment.

6.1.4. Fifth paper

- This paper is a summary review of the state of the art knowledge regarding the treatment of yaws and its eventual inclusion along other existing and ongoing MDA programs against NTDs.

6.1.6. Sixth paper

- Low baseline prevalence of filariasis in the population is an important factor predicting success in reducing infection rates in a elimination program.

6.2 General objectives

1. Describe yaws clinical presentation, recognition and diagnosis, and treatment outcome at a rural hospital setting in Papua New Guinea.

2. Evaluate the efficacy of new strategies to treat yaws and filariasis in Papua New Guinean population.

6.3 Specific objectives

1. Describe the clinical signs and symptoms of patients with yaws in Papua New Guinea

2. Determine the accuracy of the commonly used diagnostic procedures in yaws.

3. Estimate failure rates after treatment with benzathine benzylpenicillin in yaws.

4. Identify determinants of failure that affected the outcome after treatment for yaws.

5. Describe the clinical presentation of early yaws osteoperiostitis and review other cases reported in the English-language literature.

6. Assess the efficacy of a single oral dose of azithromycin compared with the standard single intramuscular dose of benzathine benzylpenicillin to treat yaws.

7. Outline a path towards the eradication of yaws and provide more information on why previous attempts to eliminate the disease were ultimately unsuccessful

8. Estimate success rates of a program to eliminate lymphatic filariasis in villages from different areas of Lihir Island.

9. Identify determinants of success affecting a program to eliminate lymphatic filariasis' outcome.

7. Materials and methods

7.1 Origin of patients in the different studies

Data for patients involved in the first 4 studies was obtained from the outpatient medical department records of individuals assessed by personnel working at Lihir Medical Centre. All patients suspected to have primary-stage or secondary-stage yaws were assessed for possible inclusion in the studies.

Studies number 1, 2 and 3 were performed by retrospective analysis of cases with yaws from January through September 2009. We included only case-patients with clear documentation of demographic, epidemiologic and clinical data.

Study number 4 was designed as non-inferiority, randomized trial to assess the efficacy of a single-dose azithromycin. 250 children aged between 6 months and 15 years were recruited from the outpatient medical department of LMC between September 1, 2010 and February 24, 2011.

Data for study number 6 were collected at a community level during the delivery of an MDA program in villages of Lihir Island. The program was closely monitored epidemiologically, entomologically and through laboratory studies. This ecological study followed up an average of 6,100 individuals during 5 years (around 70% of the total population determined by the yearly census from 2003 to 2008).

7.2 Study area and population

The study area is located in Lihir Island, New Ireland Province, Northern Islands of Papua New Guinea (Figure 5). The Lihir Island is mountainous with pristine tropical forest with numerous streams and rivers all around the island (Figure 6). The southern part of Lihir Island is dense with thick jungle due to high rainfall in that area. There are only two seasons, wet and dry. It rains most of the time between January and September and this has a lot of impact on diseases that are related to seasonal variations, like yaws and filariasis.

The population living in Lihir Island is approximately 18,353, 40% of which are under 15 years of age. This comprised of the Lihirian population 14,833 and non-Lihirians 3,520. This figure was obtained from the Lihir population data in December 2010 by the LGL-Social Research Monitoring. There are 27 villages in Lihir sub-district and this is the only sub-district in New Ireland that has implemented the National prioritized health

interventions by concentrating on: (1) fully immunized child 1 to 5 year old (>80% children immunized per month), (2) reduction of malaria incidence (from >1000 confirmed malaria cases per 1000 population-year in 1997 to 365 in 2007), and (3) reduction of maternal mortality due to high rates of supervised deliveries (<2% births in the village) (64). All population resident in the study area have a card with a permanent identification number issued by the LMC.

The five most common diseases/injuries diagnosed on the island, according to the morbidity surveillance system (unpublished data) are: Malaria, Pneumonia, Trauma, Tuberculosis and Ulcers –Yaws. Most of these diseases are caused by unhealthy living conditions such as many breeding sites for mosquitoes, overcrowding and general ignorance or lack of understanding on personal hygiene and sanitation practices.

Figure 5: Map of Papua New Guinea, and location of Lihir Island

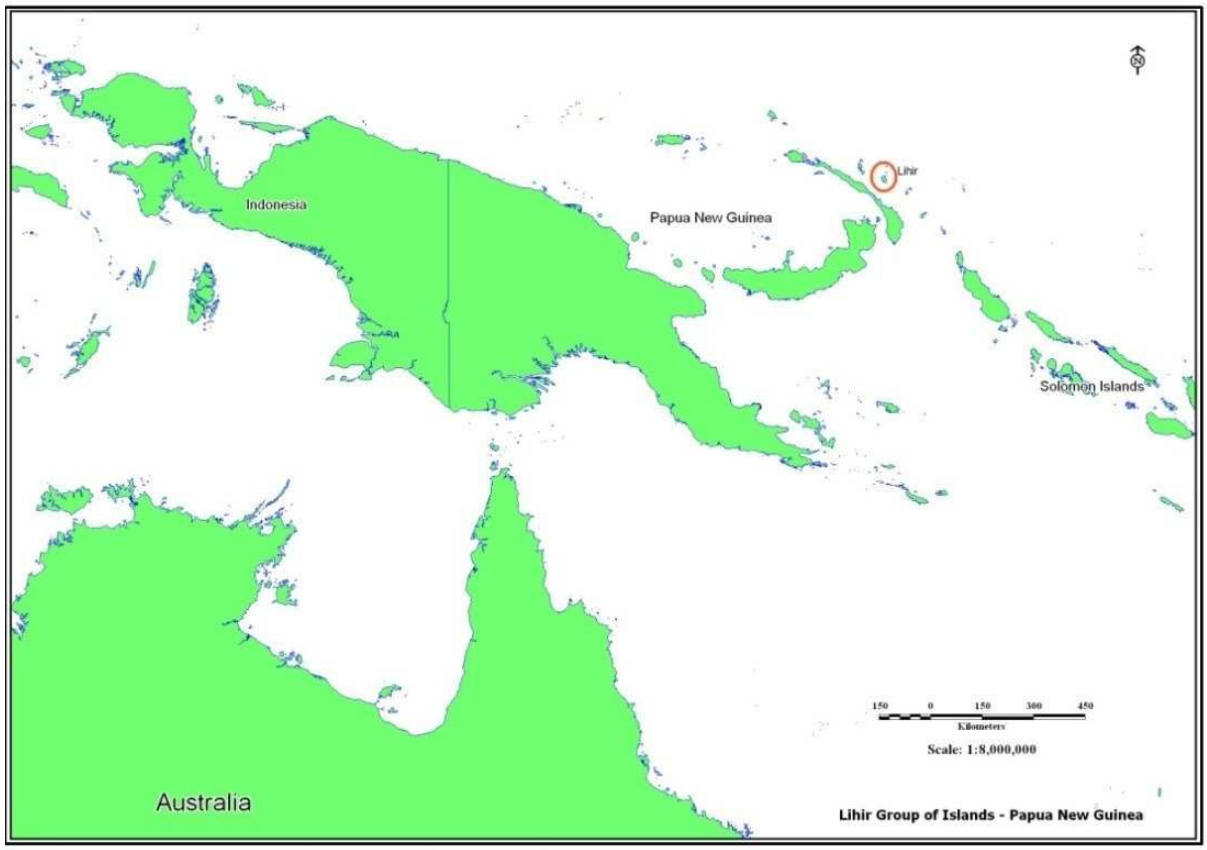


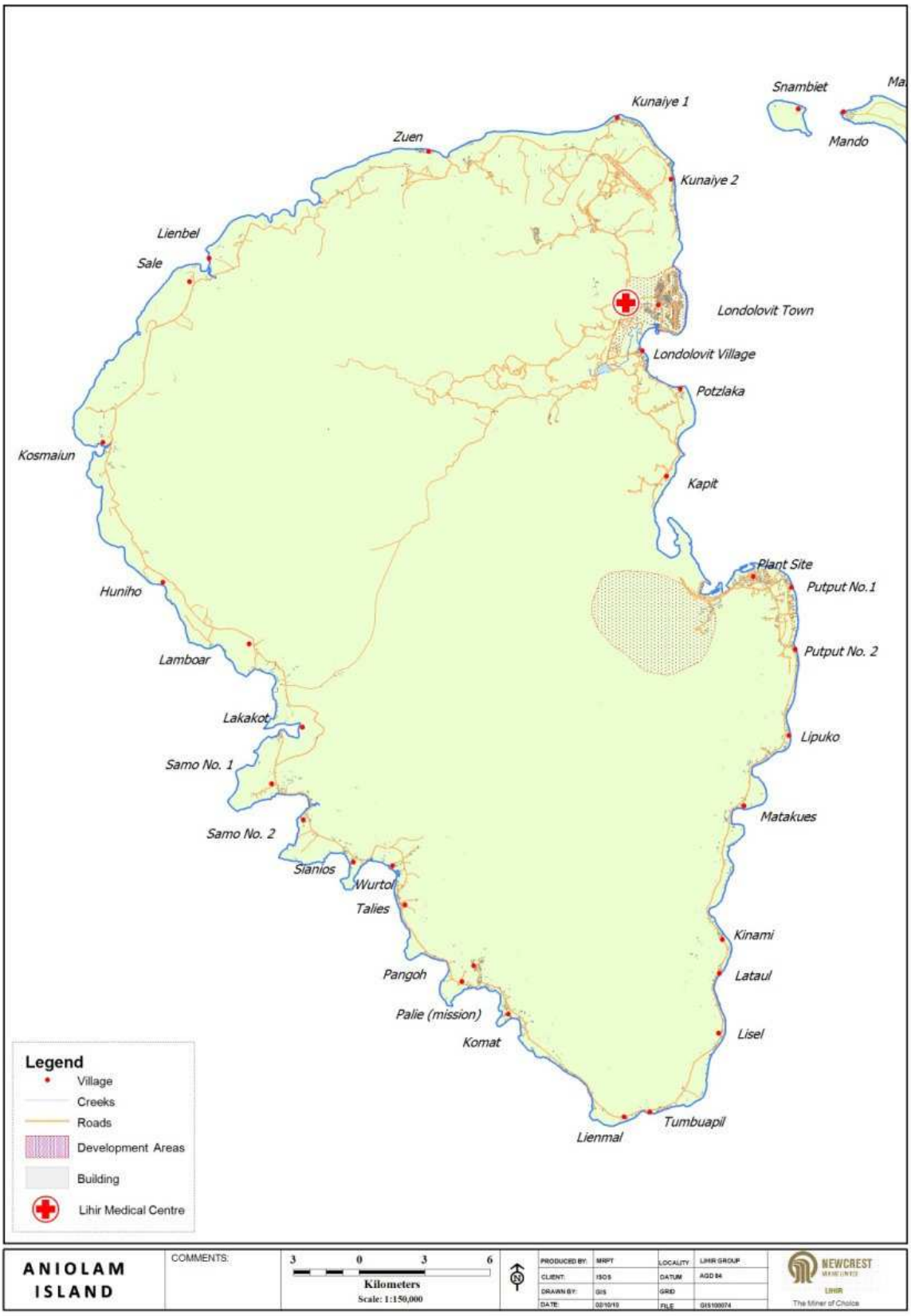
Figure 6: Aerial view of Lihir Island's tropical rain forest

7.3 Lihir Medical Centre

The Lihir Medical Centre (LMC) is located in Londolovit village, in the North-eastern part of the Island (Figure 7). It was developed with the mission of providing curative services to the Lihir Island population. It is sub contracted and managed by International SOS (ISOS) and funded by the LGL-mining operation that commenced on 1997, currently named Newcrest mining.

LMC has modern health facilities and provides services such as outpatients, inpatients, dispensary, medical laboratory, dental services, radio imaging, operating theatre, and labour ward. There is a definite increase in attendance from 50,000 cases in 2003 to above 80,000 in 2010. Apart from providing curative health services, the health staffs of ISOS provide supervisory visits to the other health facilities; do contact tracing and supervision of Tb patients and conduct public health programs including the malaria and filariasis control. LMC has run since 1997 a morbidity surveillance system for the Lihir sub-district that links with the Demographic Surveillance System run by the LGL-mining operation.

Figure 7: Map of Lihir Island showing the location of the Lihir Medical Centre



7.4 Ethical considerations

The study protocols for studies 2, 4 and 6 were examined and approved by the Medical Research Advisory Committee (MRAC) of Papua New Guinea. The MRAC act as the National Ethical Clearance Committee and as the Institutional Ethical Committee for the Papua New Guinea Institute of Medical Research. The randomized clinical trial (study number 4) was conducted under the provisions of the Declaration of Helsinki and in accordance with Good Clinical Practices guidelines set up by the International Conference on Harmonization. For the other two studies (number 1 and 3) no specific Ethical approval was sought, as they consisted mainly in retrospective analysis of clinical data.

7.5 Data management and statistical analysis

For the first and second studies we used the Electronic Data Capture system utilized in the Hospital of Lihir. The system includes a graphical user interface component for data entry that is utilized by administration staff, clinicians, laboratory technicians and pharmacists. For all patients visited in the outpatients department, demographic data, clinical data, laboratory results and treatment are entered into this centralized database. The data can be retrieved by a reporting tool for analysis of the collected data.

For the fourth study (clinical trial) Case Report Forms (CRFs) specifically designed for the study were manually filled in by the attending physician after the study team started enrolling patients. The data on forms were then monitored and transferred to a separate Clinical data management system through a double data entry system. The computer system used in the processing and management of this clinical trial data underwent validation testing

In all cases, statistical analyses were done with Stata 10.0 (Stata Corp., College Station, TX, USA).

8. Articles

Study 1

Short Report: Challenges in Recognition and Diagnosis of Yaws in Children in Papua New Guinea

Oriol Mitjà, Russell Hays, Francis Lelngei, Nedley Laban, Anthony Ipai, Slim Pakarui, and Quique Bassat

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Short Report: Challenges in Recognition and Diagnosis of Yaws in Children in Papua New Guinea

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Abstract. A global resurgence of yaws in developing countries highlights the need for reliable diagnostic criteria for this neglected infection. We conducted a clinical and serologic survey of 233 children less than 15 years of age who had clinically suspected yaws. A total of 138 (59%) cases were confirmed serologically, and 10 of 12 primary stage cases showed positive results for *Treponema pallidum* by a polymerase chain reaction assay that has not yet been validated for identification of yaws. A high proportion of cases (46%) were in the secondary stage; 92% of them had osteoarticular involvement, and only 24% had a Venereal Disease Research Laboratory titer greater than 1:32.

The etiologic agent of yaws, *Treponema pallidum* subsp. *pertenue*, causes a multistage infection transmitted by nonsexual contact with the exudates from active lesions.[1,2] Although a multinational mass eradication campaign in the 1950s greatly reduced its global incidence,[3–5] a resurgence of yaws has occurred during the past decade in western and central Africa, southeast Asia, and the Pacific Islands. This resurgence emphasizes the need for reliable diagnostic criteria.[6–9] Unless diagnosed and treated at an early stage, yaws can become a chronic, relapsing disease and can enter into a late stage characterized by severely deforming bone lesions.

The differential diagnosis of yaws is extensive. The clinical diagnosis may be difficult even for experienced clinicians because yaws produces lesions in the skin, bone, and cartilage, which can resemble several other diseases in the tropics.[1,2] It has been reported that the disease may show a milder form or an atypical form, with less florid skin lesions.[7] Moreover, laboratory diagnosis of yaws is based on serologic analysis, which may not be suitable in syphilis-endemic areas because of cross-reactivity. The aim of this study was to describe the clinical signs and symptoms of patients with yaws in Papua New Guinea and determine the accuracy of the commonly used diagnostic procedures.

This study was a descriptive cross-sectional study involving patients who came to Lihir Medical Center (Lihir Island, Papua New Guinea) during January–September 2009. Patients with clinical suspicion of yaws and positive results for the Venereal Disease Research Laboratory (VDRL) test and the *Treponema pallidum* hemagglutination test were eligible.

The study group was limited to children less than 15 years of age whose mothers had negative treponemal test results at antenatal screening to reduce the likelihood of syphilis-related positive results. We repeated the VDRL test after one week for all patients with an initial negative result and a disease duration less than two weeks to reduce the probability of initial false-negative results. A diagnosis of primary yaws was established by clinicians on the basis of chronic (> 2 weeks), painless, atraumatic ulcers with raised margins. Criteria for the diagnosis of secondary yaws included one of the following: 1) multiple hyperkeratotic papules, 2) polyarthalgia, and 3) bone pain and swelling affecting the fingers or toes, forearms, and tibia or fibula, irrespective of accompanying radiologic abnormalities.

For testing by using a *T. pallidum* PCR specific for the 47-kD membrane lipoprotein gene, not yet validated for yaws, a dry swab specimen was obtained from 12 exudates of primary ulcers and from skin scrapings from three secondary lesions randomly chosen. Histopathologic examination of biopsy specimens, including a margin of normal tissue, was also performed for four cases.

Because yaws is known to cluster in close communities and its prevalence can vary greatly between villages, we estimated the incidence rate derived from hospital-detected cases among the whole population for each of the 27 villages served by our hospital. We defined a high incidence as a rate greater than 1.5%.

In the 12-month study period, 233 patients with clinically suspected yaws were evaluated and 138 patients received a diagnosis of yaws on the basis of a correlation of clinical findings, epidemiologic history, and positive serologic results. The remaining 95 patients evaluated had a negative VDRL test result, including 61 (64.2%) patients with a skin ulcer and 34 (35.8%) patients with bone or joint pains. Patient demographic characteristics, clinical signs and symptoms, laboratory results, and outcome are shown in Table 1. Eighty one (58.7%) persons displayed active primary cutaneous yaws lesions; most exhibited either solitary lesions or a scanty number of papillomata, most commonly on the legs and ankles (85.2%), but also on the buttocks, arms, hands, and face.

Of the 138 patients evaluated, 63 (45.7%) exhibited signs of secondary stage yaws, including 58 (92%) with osteoarticular involvement (Figure 1). In some cases, the initial primary lesion persisted into the secondary stage (6 [9.5%] of 63); in some other cases healed primary lesions were noted. Arthralgias were the most common presentation of secondary stage yaws (48 [76.2%] of 63) and usually affected multiple large joints including the knees, ankles, elbows, and wrists. Marked pain in the long bones of extremities with or without visible bone or soft-tissue swelling or deformity on examination was present in 10 (15.9%) of secondary stage cases.

The association between the stage of infection and patient demographic features and laboratory results is shown in Table 2. There was a positive association between a high initial titer and primary stage disease; 36 (48.0%) of 75 persons with primary yaws compared with 15 (23.7%) of 63 persons with secondary yaws ($P = 0.004$) had a VDRL test titer > 1:32.

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Table 1
Demographic data, clinical presentation, laboratory results, and outcome after treatment of 138 patients with yaws, Papua New Guinea*

Characteristic	Global (n = 138)
Mean (SD) age, years	9.6 (4.4)
Male sex, no. (%)	81 (58.7)
VDRL test titer, no. (%)	
1:16	54 (39.1)
1:32	33 (23.9)
1:64	42 (30.4)
1:128	9 (6.5)
Primary lesion, no. (%)	81 (58.7)
Face	2/81 (2.5)
Upper limb	10/81 (12.3)
Lower limb	69/81 (85.2)
Secondary stage, no. (%)	63 (45.7)
Skin lesions	18/63 (28.6)
Arthralgias	48/63 (76.2)
Bone swelling or pain	10/63 (15.9)†
Family history, no. (%)	36 (26.1)

*VDRL = Venereal Disease Research Laboratory.
†Includes seven cases of radiologically confirmed yaws osteoperiostitis among three patients who had dactylilitis.

Among the secondary cases, 48 (76.2%) of 63 patients lived in a high prevalence village and only 42 (56.0%) of 75 patients had primary stage disease ($P = 0.014$).

The PCR results were positive for 10 (83.3%) of 12 children with primary ulcers, and 3 of 3 patients with secondary skin lesions had PCR-negative results. The latter negative results could be ultimately related to the scarce numbers of bacteria present in secondary stage lesions, which are mainly an inflammatory infiltrate.[10] The five patients with negative PCR results had positive serologic results and typical clinical signs and symptoms.

Microscopic study of biopsy specimens of four skin samples at the margin of primary ulcerative lesions showed parakeratosis containing neutrophils with epidermal erosion and an inflammatory cell infiltrate in the dermis comprising of lymphocytes. Furthermore, immunoperoxidase staining was positive for *Treponema* sp. and showed scattered spirochetes within the epidermis (Figure 2).

Yaws is endemic to areas of Papua New Guinea, but because this disease is not fatal and occurs primarily in remote areas among isolated communities, it does not receive adequate attention. The clinical and serologic survey we conducted highlights three issues. First, clinical diagnosis of yaws is not easy to determine and support for laboratory techniques is necessary. Second, yaws in Papua New Guinea may have changed its pattern of presentation by showing an increased number of secondary stage osteoarticular forms. Third, molecular biological techniques should be explored as an alternative to dark-field microscopy for direct diagnosis of ulcers of yaws.

In our experience, only 60% of the cases with a clinical suspicion of yaws were confirmed by serologic tests. The diagnosis of yaws is complicated because its clinical manifestations are diverse or may be totally unspecific. Primary yaws is commonly confused with anaerobic fusobacteria-related ulcer, cutaneous leishmaniasis, mycobacterial disease, *C. diphtheriae*, or *A. haemolyticum* skin infection. Similar secondary cutaneous manifestations might be caused by infected bites, psoriasis, excoriated chronic scabies or verrucae. Secondary stage bone lesions need to be differentiated from bacterial osteomyelitis, tuberculosis, and sickle cell disease. Arthralgias are also a common but nonspecific symptom of patients.[1,2]

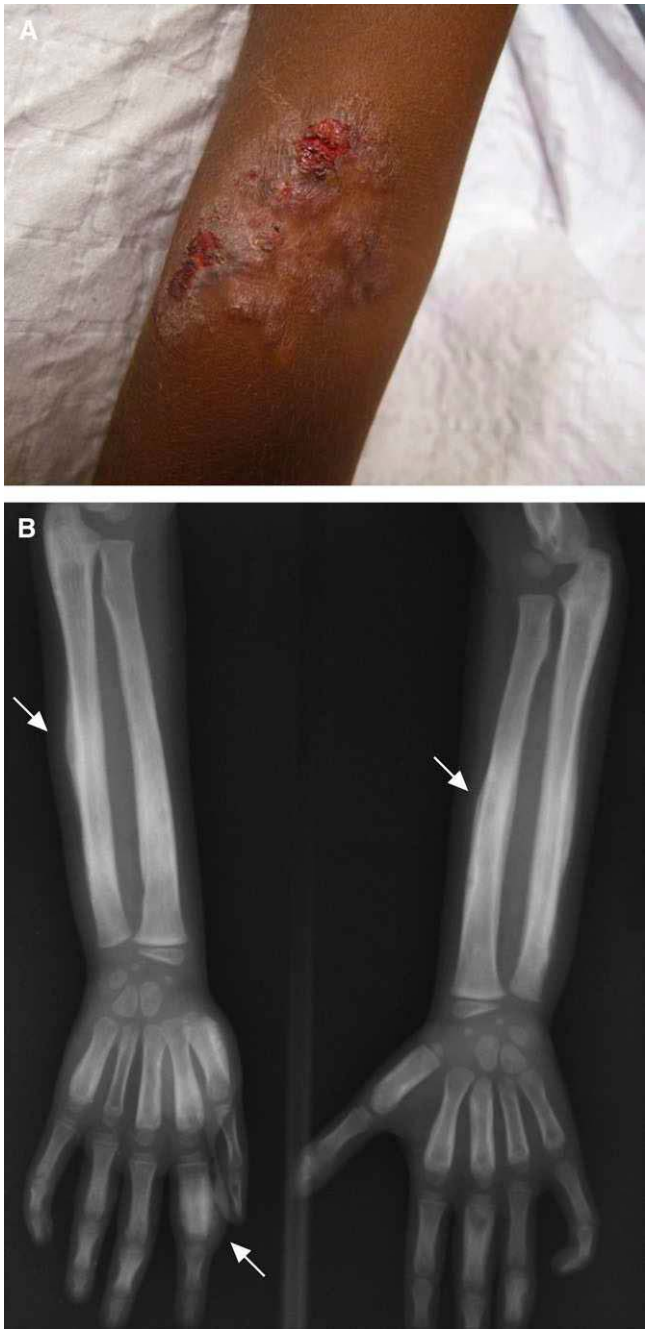

Figure 1. Secondary skin lesion (crustopapillomatous) on the left arm of a patient with yaws (**A**) and radiograph of her forearms and hands (**B**), Papua New Guinea. **Arrows** show dactilitis with thickening of the cortex and increase in width of the phalanx and bilateral periosteal reaction of the ulna and radius with widespread onion layering deposition of periosteal bone.

We believe that clinical findings alone, even for experienced clinicians, are not reliable in reaching a diagnosis of yaws. Conversely, serologic tests commonly used may not enable confident diagnosis of yaws from other treponemal infections. For persons greater than 15 years of age who are known to be sexually active, syphilis infection cannot be strictly excluded. Therefore, a proper diagnosis of yaws requires interpretation

TABLE 2

Association between stage of infection and demographic data, laboratory results, and outcome after treatment of patients with yaws, Papua New Guinea*

Characteristic	Primary stage (n = 75)	Secondary stage (n = 63)	OR (95% CI)	*P*
Mean (SD) age, years	10.0 (3.4)	9.3 (5.5)	0.72 (0.78–2.22)	0.34
Male sex, no. (%)	48 (64.0)	33 (52.4)	0.61 (0.31–1.23)	0.17
VDRL test titer > 1:32, no. (%)	36 (48.0)	15 (23.8)	0.34 (0.16–0.70)	0.004
High prevalence village, no. (%)	42 (56.0)	48 (76.2)	2.51 (1.20–5.26)	0.014
Family history, no. (%)	12 (16.0)	24 (38.1)	3.23 (1.45–7.19)	0.01

* OR, odds ratio, using primary stage cases as baseline; CI = confidence interval; VDRL = Venereal Disease Research Laboratory. A *P* value < 0.05 was considered statistically significant.

of clinical findings with reference to laboratory results and the epidemiologic history of the patient.

Manifestations of secondary yaws, particularly bone and joint involvement, are now more frequent and often subtle. In a community survey in the Democratic Republic of Congo, 80% of patients had lesions suggestive of secondary yaws.[6] On Lihir Island, 46% of case-patients had the secondary stage of yaws, and this feature was more pronounced in those villages with a high endemicity (ratio 2.5).

A factor that could have contributed to the change on clinical presentation is the widespread use of oral antibiotics. Low bioavailability of penicillin and its derivatives given as oral dosages likely prevented eradication of the causative bacteria from bone.[11] Also, these drugs could have had a specific effect on skin lesions.

Although there are no detailed data available for yaws in Papua New Guinea, VDRL test results seem to be similar to those for syphilis in which VDRL test results decrease over time.[12] In this study the longer-term infections in secondary stage were more commonly associated with a VDRL test titer < 1:32. A negative correlation between VDRL test titer and duration of syphilis was reported by McMillan and Young, in which test results were positive in 100% of patients in an early stage of syphilis, but decreased to 85% in patients in a latent stage.[13]

A PCR used in laboratory diagnosis of early syphilis that is specific for the 47-kD membrane lipoprotein gene showed positive results for most of the tested patients with primary ulcers.[14] To our knowledge, this PCR method has not been previously used with clinical specimens from patients with yaws. However, the 47-kD protein is involved in cell wall synthesis and would be expected to be conserved in related treponemes.

Treponema pallidum has historically been detected in clinical specimens by using dark-field microscopy, a method that has high specificity. However, if bacterial load is low or viability of the treponemes is reduced, the sensitivity of this method may be severely decreased.[15] In this context, potential use of the *T. pallidum* PCR specific for the 47-kD gene as a direct and fast test for diagnosis of primary yaws should be explored. However, its additional value for diagnosis of secondary yaws might be limited.

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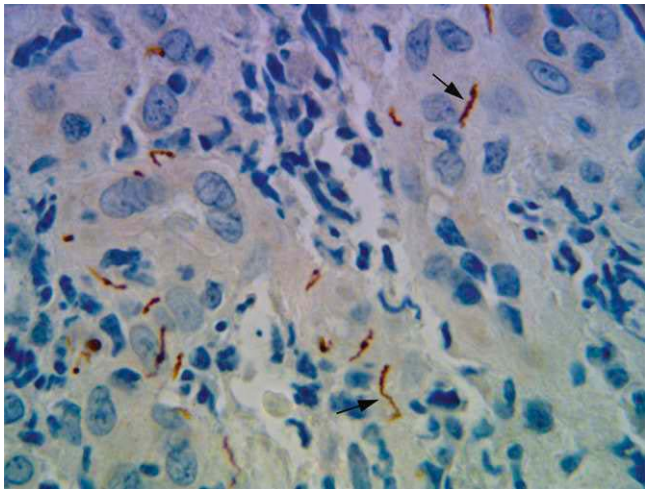

FIGURE 2. Immunoperoxidase staining of a skin biopsy specimen from a patient with yaws, showing scattered spirochetes within the epidermal lesion, Papua New Guinea. **Arrows** show the spiral-shaped body of *Treponema pallidum* that confers the bacteria a corkscrew-like motility. Photograph courtesy of Sullivan Nicolaides Pathology/Dr. Kevin Whitehead.

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Outcome Predictors in Treatment of Yaws

Oriol Mitjà, Russell Hays, Anthony Ipai, David Gubaila, Francis Lelngei, Martin Kiara, Raymond Paru, Quique Bassat

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Outcome Predictors in Treatment of Yaws

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To estimate failure rates after treatment with benzathine penicillin and to identify determinants of failure that affected outcomes for yaws, we conducted a cohort study of 138 patients; treatment failed in 24 (17.4%). Having low initial titers on Venereal Disease Research Laboratory test and living in a village where yaws baseline incidence was high were associated with increased likelihood of treatment failure.

Yaws is a tropical infection of the skin and bones caused by *Treponema pallidum* subsp. *pertenue* and is transmitted by direct, nonsexual contact with infectious lesions (*1,2*). Although a multinational mass eradication campaign in the 1950s greatly reduced the incidence of this disease (*3–5*), a resurgence of yaws has occurred in west and central Africa, Southeast Asia, and the Pacific Islands (*6–9*). The currently recommended drug therapy for yaws is penicillin G benzathine, administered intramuscularly as a single dose of 1.2 million units (*3,5*). *T. pallidum* is a primary human pathogen that has eluded in vitro cultivation (*10*). Hence, although penicillin treatment failure has been reported for yaws (*11*), to date penicillin resistance has not been proven. Most serologically defined treatment failures are thought to be caused by either reinfection after treatment or patient-to-patient variation in the rate of decline in nontreponemal test titers after treatment (i.e., ≥4-fold decrease), rather than by relapse (*10*). The aim of this study was to estimate failure rates after treatment with benzathine penicillin and to identify determinants of failure that affected the outcome.

The Study

We conducted a retrospective cohort study involving patients diagnosed with yaws at Lihir Medical Centre from January through September 2009. Ethics approval was obtained from the Papua New Guinea Ministry of Health Medical Research Advisory Committee. Diagnosis of yaws was based on correlation of the clinical findings, positive serologic results, and epidemiologic history. Patients <15 years of age whose mothers had negative treponemal test results at antenatal screening, with clinical evidence of early yaws (primary or secondary stage), and whose Venereal Disease Research Laboratory (VDRL) and *T. pallidum* hemagglutination test results were positive, were eligible to participate in the study. We included only case-patients with clear documentation of the village of residence, contact history, yaws clinical stage, clinical outcome, pretreatment titer, and at least 1 follow-up titer 12–15 months after treatment. We also estimated the minimum incidence rate for each of the 27 villages served by our hospital; a high incidence rate was defined as >1.5%. This percentage was calculated by dividing the number of new cases diagnosed at Lihir Medical Centre within the study period by the estimated population from each village, according to the local annual census. Treatment outcome was measured at a follow-up visit 12–15 months after treatment. Treatment failure was defined as the lack of a 4-fold decrease in VDRL titers at least 365 days after treatment.

A total of 138 patients were identified during enrollment. Table 1 summarizes patient demographic characteristics, clinical signs and symptoms, laboratory results, and outcomes. Eighty-one (58.7%) persons displayed active primary cutaneous yaws lesions (Figure 1), and 63 (45.7%) exhibited signs of secondary stage yaws (hyperkeratotic skin papules or bone involvement). All patients were administered 3 doses of intramuscular benzathine penicillin 1×/wk, and only 6 (4.4%) children

Table 1. Demographic data, clinical signs/symptoms, laboratory results, and outcome after treatment of yaws in 138 case-patients, Papua New Guinea, January–September, 2009*

Characteristic	Total no. (%) patients, N = 138
Mean age, y (SD)	9.6 (4.4)
Male sex	81 (58.7)
VDRL titer	
16	54 (39.1)
32	33 (23.9)
64	42 (30.4)
128	9 (6.5)
Primary skin lesion	81 (58.7)
Secondary stage	63 (45.7)†
Family history	36 (26.1)
Treatment with IM penicillin G benzathine	138 (100.0)
Clinical healing	132 (95.7)
Concurrent disease	7 (5.1)‡
Seroconversion	63 (45.7)
Serologically defined treatment failure	24 (17.4)

*VDRL, Venereal Disease Research Laboratory; IM, intramuscular.
†Includes 7 cases of early yaws osteoperiostitis, among whom were 3 patients with dactylilitis.
‡Includes 3 cases of *Plasmodium falciparum* malaria, 1 case of *P. vivax* malaria, 1 case of acute diarrhea diagnosed at the 12-month follow-up visit, and 2 case-patients with a chronic underlying disease (1 case of congenital heart disease and 1 case of chronic asthma).

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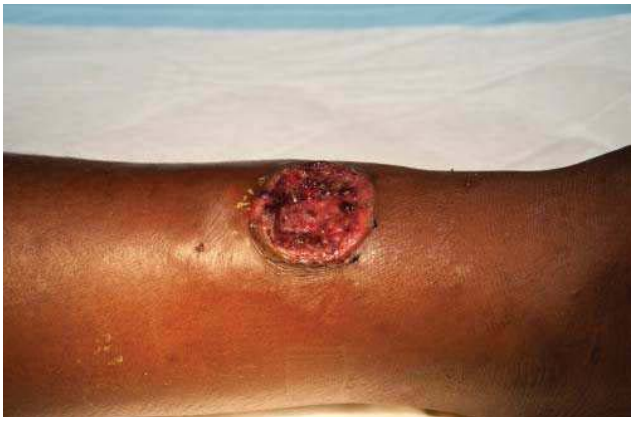

Figure 1. Painless ulcer with raised edges corresponding to a primary yaws skin lesion on an infant case-patient's leg, Papua New Guinea, 2009. Source of photograph: Lihir Medical Centre, Dr Oriol Mitjá.

required 1 or 2 additional doses before initial symptoms disappeared. According to the estimated minimum incidence, in 9 villages the disease was classified as highly endemic, and in 15 villages, the disease was considered of low endemicity (Figure 2). Of the 138 analyzed case-patients, 90 (65.2%) persons came from a high minimum incidence village (HMIV) and 48 (34.8%) came from a low minimum incidence village (LMIV). Secondary stage lesions were found in 47 (52.2%) of 90 case-patients among the HMIV group and only in 16 (33.3%) of 40 case-patients in the LMIV group ($p = 0.035$). VDRL titers were significantly lower in case-patients in the HMIV group than in those in the LMIV group; 70% of case-patients in the HMIV group had a titer ≤32 ($p = 0.026$), as did 50% of those in the LMIV group. A positive association between a low initial VDRL titer and secondary stage disease was also found (79% of case-patients with secondary yaws had a low initial titer, compared with 51% who had primary yaws [$p<0.01$]). Overall, 24 (17.4%) case-patients experienced serologically defined treatment failure during follow-up, including 21 (23.3%) and 3 (6.3%) from the HMIV and LMIV groups, respectively. Multivariate analysis (Table 2) showed that only residence in a high incidence village (odds ratio 3.75, 95% confidence interval 1.02–13.76) and an initial VDRL titer ≤32 (odds ratio 4.05, 95% confidence interval 1.06–15.38) proved to be independent predictors for treatment failure.

Conclusions

Serologically defined treatment failures occurred in ≈17% of case-patients in our series. Treatment failure could have been influenced by the capacity of the infecting agent to develop resistance to the antimicrobial drug used, or the failure could have been caused by other factors related to the human host. Our findings show that in Lihir, the factors predicting treatment failure after 12 months of drug therapy were the following: residence in a village where incidence of infection was high and initial VDRL titer was low. False-positive VDRL reactions, classically associated with viral and autoimmune diseases (*12*), are unlikely to be the cause of failure in our series, because no chronic underlying disease or concurrent febrile illnesses were registered in 23 (96%) of the case-patients who did not achieve a cure. Moreover, the strict epidemiologic criteria required (obtained through patient history) for inclusion in the study aimed to reduce the likelihood of false-positive results for syphilis. A VDRL titer of <32 dilutions proved to be a robust predictor of failure.

In our experience, this low titer is also associated with longer lasting infections and is more commonly found in high incidence villages (as are longer lasting infections). Even after multivariate analysis, clarifying the role of these confounding factors is difficult. We suspect that the true factor at work here rests upon the assumption that a chronic infection is more difficult to resolve. The tissue-to-plasma ratios for bone penetration are usually between 0.1 and 0.3 for penicillins and are even lower for cortical bone than for cancellous bone (*13*). On the basis of these ratios, treponemes that invade the bone would encounter subtherapeutic levels of penicillin, which could simply lead to persistent infection or even provide selective pressure for mutations for penicillin resistance. On the other hand, the risk for reinfection caused by repeated contact with infected children seems to be a pivotal factor in predicting

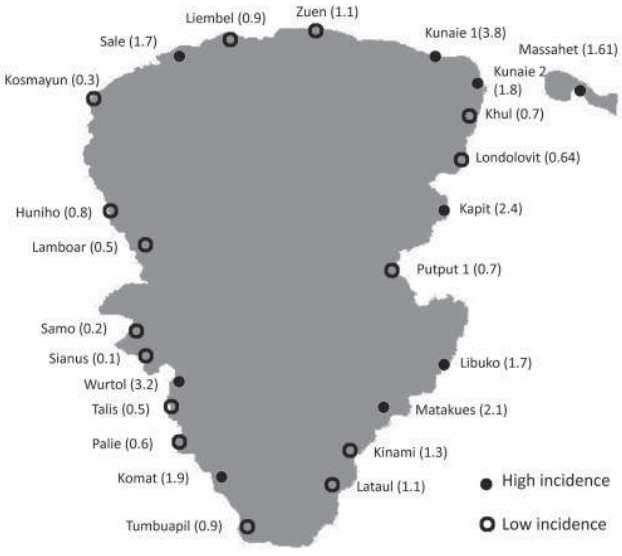

Figure 2. Map of Lihir Island, Papua New Guinea, showing incidence of infection in the 24 villages where cases of yaws were diagnosed, 2009. Lihir Medical Center is located in Londolovit village. Incidence proportions are shown within parentheses.

Table 2. Association between characteristics of case-patients and *Treponema pertenue* infection treatment failure, Papua New Guinea, January–September 2009*

Characteristic	No. (%) patients treated		Univariate analysis		Multivariate analysis	
	Success, n = 114	Failure, n = 24	OR (95% CI)	p value	OR (95% CI)	p value
Mean age, y (SD)	9.54 (4.69)	10.13 (2.96)	0.58 (–1.39 to 2.56)	0.56	NA	NA
Male sex	69 (60.5)	12 (50.0)	0.65 (0.27–1.58)	0.34	NA	NA
Lived in a high-incidence village	69 (60.5)	21 (87.5)	4.57 (1.29–16.20)	0.02	3.75 (1.02–13.76)	0.04
Secondary yaws	49 (43.0)	14 (58.3)	1.86 (0.76–4.53)	0.17	1.01 (0.37–2.75)	0.99
Clinical healing	108 (94.7)	24 (100.0)	NA	0.59	NA	NA
Positive family history	27 (23.7)	9 (37.5)	1.93 (0.76–4.91)	0.17	1.91 (0.70–5.28)	0.20
VDRL titer ≤32	67 (58.8)	21 (87.5)	4.91 (1.39–17.41)	0.01	4.05 (1.06–15.38)	0.04

*p<0.05 was considered significant. OR, odds ratio; CI, confidence interval; NA, not applicable; VDRL, Venereal Disease Research Laboratory test.

treatment failure. The high number of asymptomatic persons or persons with few symptoms in high prevalence areas is the main reservoir of the infection and a known obstacle to achieving the eradication of yaws. A limitation of our study is the use of incidence rates derived from hospital-based detected cases, which likely underestimated the real incidence of infection. Also, the calculation of this proportion might be less precise because we did not take into account factors such as the distance of the village from the health center or the proportion of children to adults in a particular village.

On the basis of our findings, we anticipate that a community-based strategy will be required to effectively control yaws on Lihir Island. The current strategy for eradication of yaws in areas where the disease is moderately endemic (prevalence <5%) is to treat patients with active cases and their contacts. In our experience, most children did not have a family history of yaws. Thus, the disease likely is not clustered in households but, rather, transmission is more likely to occur among children in the community, in schools, and in other public places. Future eradication programs will need to take into account all epidemiologic, biological, and pharmacologic factors, along with the practical considerations of a mass campain to deliver and administer drugs in isolated and underresourced communities. In this context, the potential treating yaws with oral, single-dose therapy, for example, with azithromycin, should be explored.

Acknowledgments

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Osteoperiostitis in early yaws: case series and literature review.

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Osteoperiostitis in Early Yaws: Case Series and Literature Review

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We describe the clinical and radiological manifestations and outcome after treatment of 7 children who received a diagnosis of early yaws osteoperiostitis. Osteoperiostitis occurred some weeks after the primary infection, and the most common finding was hypertrophic periostitis of long bones. All treated patients had excellent responses to benzylpenicillin therapy.

Yaws is a contagious, nonvenereal, treponemal infection that mainly occurs in children <15 years of age. The disease is caused by infection with *Treponema pallidum pertenue* and occurs primarily in warm, humid, tropical regions among poor rural populations [1, 2]. Although a mass eradication campaign in the 1950s greatly reduced the incidence of yaws, a resurgence of the disease has recently occurred in West and Central Africa, Southeast Asia, and the Pacific Islands [3,4]. The most recent World Health Organization estimate (1997) suggested that the prevalence of yaws at that time was 3 million cases [5].

Direct personal skin-to-skin contact is the major route of transmission in yaws. The most common clinical manifestations in early yaws are the single papillomatous reddish primary lesion and multiple hyperkeratotic papules in the secondary stage [1]. Bone and joint involvement, including periostitis and osteitis, have been reported in the early stages and may result in severe bone pain and swelling [6–8]. Moreover, if untreated, the chronic osteoperiostitis may result in destructive lesions during the late yaws period [9–12].

In this series, we describe children treated at our institution who received a diagnosis of early yaws osteoperiostitis and review other cases of early yaws osteoperiostitis reported in the English-language literature.

PATIENTS AND METHODS

We evaluated all cases of yaws from January through December 2009 at Lihir Medical Center (Lihir Island; Papua New Guinea).

The diagnosis of yaws was based on clinical suspicion and serologic parameters. Patients <15 years of age whose mothers had negative treponemal test results at antenatal screening, with clinical evidence of early yaws (primary or secondary stage) and scoring positive in both the nontreponemal test (Venereal Disease Research Laboratory [VDRL]) and the Treponema pallidum hemagglutination test were eligible. A diagnosis of primary yaws was established by clinicians on the basis of chronic (>2 weeks), painless, atraumatic ulcers with raised margins and a soft, red, moist bed. Criteria for the diagnosis of secondary yaws included one of the following signs or symptoms: (1) multiple hyperkeratotic papules or (2) bone pain and swelling affecting the fingers or toes (dactylitis), forearm, tibia, or fibula.

Four experienced clinicians were responsible for screening the patients and ordering radiological studies based on the following criteria: visible bone changes or palpable thickening of the bone or surrounding soft tissue swelling or marked pain in the long bones of extremities. Arthralgias are well-recognized symptoms of secondary-stage yaws and usually affect the knees, ankles, elbows, and wrists. They do not in themselves constitute an indication for a radiological study. Radiological diagnostic criteria of early yaws osteoperiostitis were periosteal reaction or osteolysis affecting the fingers or toes, forearm, tibia, or fibula.

Patients were re-examined clinically and serologically 6 months and 9 months after treatment. A 4-fold decrease in VDRL titer after 9 months was considered to be necessary to demonstrate cure.

RESULTS

During the 12-month period, 222 patients received a diagnosis of yaws on the basis of epidemiological, clinical, and serological criteria. Of 194 patients for whom clinical data were available, 104 (53.6%) presented with skin lesions, 64 (33.0%) with joint or bone pain, and 26 (13.4%) with both. Radiological studies were performed at the time of diagnosis in 28 (43.7%) of 64 patients with bone and joint pain.

Seven children had cases that met the radiological diagnostic criteria of early yaws osteoperiostitis. Six patients underwent follow-up clinical, radiological, and laboratory evaluation at 6

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Table 1. Epidemiology and Clinical Presentation for Children with Early Yaws Osteoperiostitis

				Signs and symptoms						
Patient	Age	Sex	Village	Join Pain	Bone afection	Soft tissueswelling	PrimarySkin lesion status	Primary skin lesion localization	Duration, [a]weeks	Secondary skin lesions
1	6	M	Komat	Present	Monodactilitis	Present	Active	lower limb	6	Absent
2	8	M	Komat	Present	Periostitis	Present	DR	DR	DR	Absent
3	4	F	Kunaye1	Present	Poli-periosteitis	Present	Healed	lower limb	8	Present [b]
4	5	F	Kul	Present	Periostitis	Absent	Healed	lower limb	8	Present [b]
5	6	M	Latahul	Present	Periostitis	Present	Healed	lower limb	3	Absent
6	5	M	Latahul	Present	Periostitis	Present	Active	upper limb	4	Absent
7	9	M	Kul	Present	Poli-periosteitis	Present	Healed	lower limb	12	Absent

NOTE. DR, do not remember.

[a] Time since appearance of primary lesion.

[b] Skin biopsy specimen was taken.

and 9 months after diagnosis. One patient was evaluated at the time of infection and was subsequently lost to follow-up. Including the 7 cases that are described here for the first time, there are, to our knowledge, 25 cases documented in the literature of bone involvement in yaws and only 18 during the early period (primary or secondary stage) [7, 8, 10, 11]. The demographic characteristics, clinical presentation, diagnostic test results, radiological findings, treatment, and outcome for the 7 cases from Lihiri Medical Center are shown in tables 1 and 2.

The cases were all diagnosed 3 weeks to 3 months after the primary lesion appeared. Patients presented with bone pain (7 [100%] of 7), soft tissue swelling (6 [85.7%] of 7), multiple bones involved (3 [42.9%] of 7), hand lesions (3 [42.9%] of 7), and elevated alkaline phosphatase level (4 [100%] of 4 for whom data were available). Radial involvement was most common (5 cases [71.4%] of 7), followed in frequency by ulnar and phalanges, metacarpals, or metatarsals.

Spindle-shaped soft-tissue swelling was visible around the phalanges in the patients with dactylitis (Figure 1). The bony changes consisted of increased density and sclerosis involving the shaft of the phalanx (Figures 1 and 2). When long bone involvement was noted, the presence of a periosteal reaction was the predominant bone lesion (Figure 1). In 2 patients, there was also a loss of clarity of the cortex of the distal radius diaphysis, corresponding to areas of osteolysis (Figure 2).

Six patients (85.7%) recalled having recently had a large, single papule on the lower limbs; this papule had resolved spontaneously in 4 of these patients, leaving a tissue paper scar. The other 2 patients (28.7%) still presented with the active primary skin lesion, and another 2 presented with multiple hyperkeratotic skin papules at the time of diagnosis. The main findings on skin biopsy for these 2 cases were parakeratosis with prominent epidermal hyperplasia and intraepidermal microabcesses. The result of an immunoperoxidase stain for spirochaetes was negative, and *T. pallidum* DNA (NAA) was not detected in either of the 2 cases.

After the diagnosis was serologically confirmed, all treated patients had excellent responses to antibiotic therapy with 3 doses of intramuscular benzyl-penicillin. The mean duration of follow-up was 9 months to date and showed that the bone

Table 2. Laboratory and Radiological Findings for Children with Early Yaws Osteoperiostitis

Patient	Initial VDRL titer	VDRL titer at 9 months after treatment	TPHA	AlkPh level,[a] U/L	Type of bone affection	Number of bones affected	Hands or feet affected	Radius or ulna involvement	Tibia or Peronne involvement
1	1:16	Negative	Positive	Not available	Monodactilitis	1	Unilateral	Absent	Absent
2	1:64	1:8	Positive	201	Poli-periostitis	5	Absent	Bilateral	Unilateral
3	1:32	Negative	Positive	188	Poli-osteoperiostitis	7	Bilateral	Bilateral	Absent
4	1:32	1:2	Positive	Not available	Mono-periostitis	1	Absent	Absent	Unilateral
5	1:32	1:32	Positive	149	Poli-osteoperiostitis	2	Absent	Unilateral	Unilateral
6	1:32	Lost of follow up	Positive	Not available	Poli-osteoperiostitis	2	Absent	Unilateral	Unilateral
7	1:32	Negative	Positive	240	Poli-periosteitis	5	Bilateral	Bilateral	Absent

NOTE. AlkPh, alkaline phosphatase; TPHA, treponema pallidum hemagglutination; VDRL, Venereal Disease Research Laboratory test.

[a] Reference range in our laboratory is 36–126 U/L

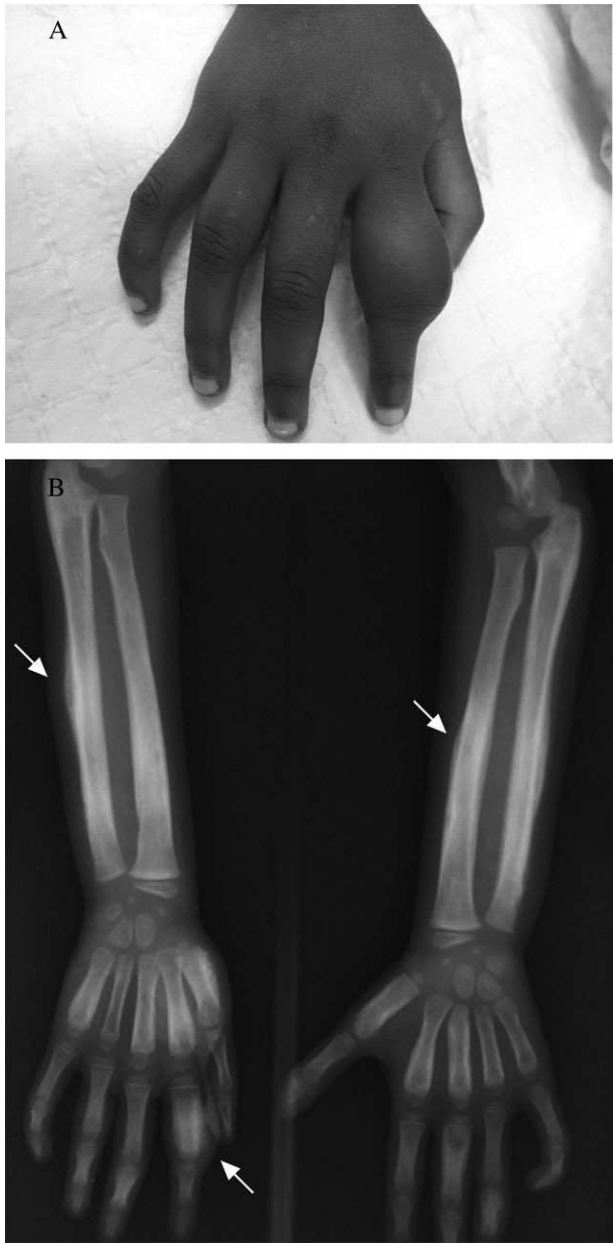

Figure 1. Fusiform swelling of the second digit in patient 3 *(A)* and radiograph of her forearms and hands *(B)*. Arrows show dactilitis with organized periosteal reaction, some thickening of the cortex, and increase in width of the phalanx and bilateral periosteal reaction of the ulna and radius with widespread ''onion layering'' deposition of periosteal bone.

lesions had resolved in all patients, complete healing of all cutaneous lesions occurred in most instances, and VDRL had decreased by >2 dilutions in 5 of 6 patients. No long-term sequelae were observed.

DISCUSSION

Yaws is an increasing public health concern in Papua New Guinea. The disease occurs primarily in populations living in

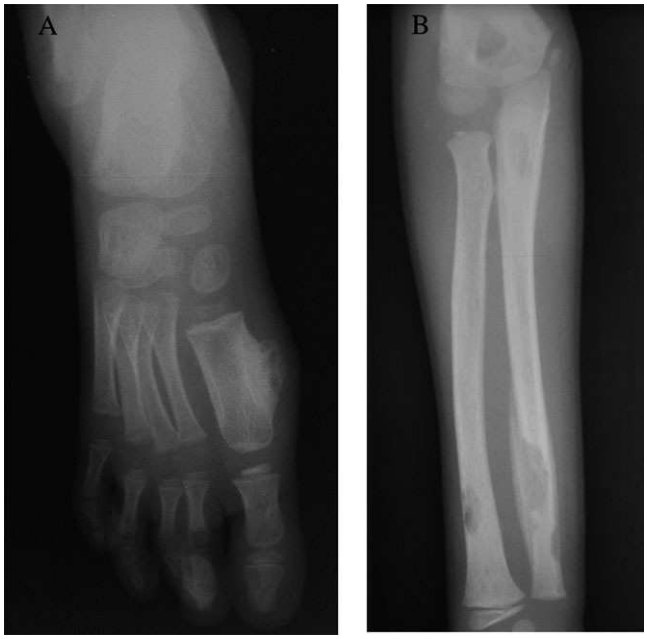

Figure 2. Radiograph of the right foot of patient 7, showing dactilitis of the proximal phalanx of the first digit *(A)* and radiograph of his arm with a loss of clarity of the cortex of the distal radius and ulna *(B)*.

rural areas where lack of sanitation and hygiene prevails and varies in severity from a self-limiting illness to irreversible, incapacitating bone lesions.

After the World Health Organization–sponsored mass eradication campaign in the 1950s, clinical and radiographical descriptions of bone abnormalities in yaws have rarely been published. Archaeological-based research has been the only source of information that has increased the understanding of osteoperiostitis in yaws. Examination of skeletons from populations with clinically diagnosed yaws revealed pathological changes distinctive to that disease, clearly separating it from changes caused by other bone diseases (eg, infantile cortical hyperostosis and hypertrophic osteoarthropathy) or from other treponemal infections, such as syphilis [13].

Yaws, as one form of pathologic treponematosis, alters the appearance of bones in a highly specific manner. According to our observations, yaws is a polyostotic disorder. The mean number of affected bones was 3.3 (range, 1–7), similar to that noted by Lin et al [7]. The radius, ulna, and phalanges were the bones most frequently implicated, and involvement was often bilateral. This contrasts with the pauciostotic presentation and rare involvement of hands and feet found in syphilis. An archaeological study in which skeletons from a 500-year-old site were examined found yaws-related periostitis in 19% of skeletons. Invariably, polyostotic involvement was present, and hand and foot lesions were frequent [14].

The radiological abnormalities demonstrated in early yaws consisted of dactylitis and osteoperiostitis. We did not observe any

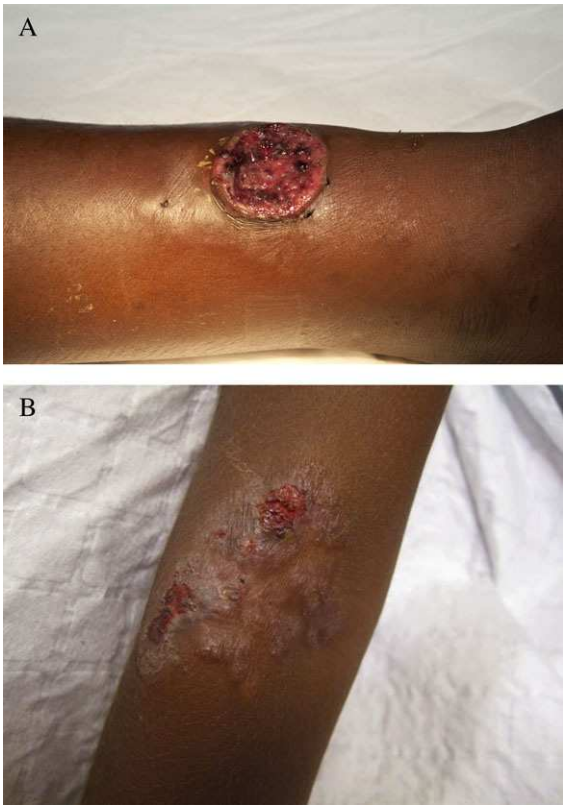

Figure 3. Primary yaws skin lesion (ulcer with raised edges) on the leg of patient 1 *(A)* and secondary skin lesion (crustopapillomatous) on the left arm of patient 4 *(B)*.

characteristic late-stage lesions, such as juxtaarticular nodules (gummas), bowing of the tibia (saber shins), nasal cartilage destruction (gangosa), or exostosis of the paranasal maxilla (gondou). In contrast with secondary yaws, tertiary yaws is a devastating and deforming process that occurs 5–10 years after inoculation. This article describes the findings of 3 cases of dactylitis that are very similar to those documented previously in 2 cases reported from Indonesia [6]. Of note, mild hyperphosphatasemia was found, probably resulting from elevations in the bone isoform of alkaline phosphatise caused by an accelerated skeletal turnover.

In our study, secondary skin lesions appeared somewhat less frequently (28.5%) than in a recent Chinese study of 9 patients with early yaws osteoperiostitis in which most of the patients were noted to present with them [7].

On the basis of the limited number of cases reported to date, early yaws osteoperiostitis appears to be a relatively mild disease if it is diagnosed and treated in a timely manner. The diagnosis should be considered in young children who present with bone pain in regions where yaws is endemic. In patients in whom the illness is suspected, attempts should be made to confirm the diagnosis serologically. Diagnosis of the specific treponema causing bone disease, however, is necessarily on the basis of epidemiological data (children without history of sexual relations and a VDRL-negative mother), because no histological, biochemical, immunologic, or microbiologic techniques are available for distinguishing between them. This series of cases suggests that the presence of supportive clinical and radiological findings may be useful in the clinical diagnosis.

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Potential conflicts of interest. All authors: no conflicts.

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Single-dose azithromycin versus benzathine benzylpenicillin for treatment of yaws in children in Papua New Guinea: an open-label, non-inferiority, randomised trial

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Summary

Background Yaws—an endemic treponematosis and, as such, a neglected tropical disease—is re-emerging in children in rural, tropical areas. Oral azithromycin is effective for syphilis. We assessed the efficacy of azithromycin compared with intramuscular long-acting penicillin to treat patients with yaws.

Methods We did an open-label, non-inferiority, randomised trial at Lihir Medical Centre, Papua New Guinea, between Sept 1, 2010, and Feb 1, 2011. Children aged 6 months to 15 years with a serologically confirmed diagnosis of yaws were randomly allocated, by a computer-generated randomisation sequence, to receive either one 30 mg/kg oral dose of azithromycin or an intramuscular injection of 50 000 units per kg benzathine benzylpenicillin. Investigators were masked to group assignment. The primary endpoint was treatment efficacy, with cure rate defined serologically as a decrease in rapid plasma reagin titre of at least two dilutions by 6 months after treatment, and, in participants with primary ulcers, also by epithelialisation of lesions within 2 weeks. Non-inferiority was shown if the upper limit of the two-sided 95% CI for the difference in rates was lower than 10%. The primary analysis was per protocol. This trial is registered with ClinicalTrials.gov, number NCT01382004.

Findings We allocated 124 patients to the azithromycin group and 126 to the benzathine benzylpenicillin group. In the per-protocol analysis, after 6 months of follow-up, 106 (96%) of 110 patients in the azithromycin group were cured, compared with 105 (93%) of 113 in the benzathine benzylpenicillin group (treatment difference –3·4%; 95% CI –9·3 to 2·4), thus meeting prespecified criteria for non-inferiority. The number of drug-related adverse events (all mild or moderate) was similar in both treatment groups (ten [8%] in the azithromycin group *vs* eight [7%] in the benzathine benzylpenicillin group).

Interpretation A single oral dose of azithromycin is non-inferior to benzathine benzylpenicillin and avoids the need for injection equipment and medically trained personnel. A change to the simpler azithromycin treatment regimen could enable yaws elimination through mass drug administration programmes.

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Introduction

Yaws—an endemic treponematosis and, as such, a neglected tropical disease—is re-emerging. 40 years after a worldwide control programme almost eradicated the disease, it has re-emerged in children in poor, rural, and marginalised populations in parts of Africa, Asia, and South America. Yaws is caused by *Treponema pallidum* subsp *pertenue*, and affects mainly skin, bones, and cartilage. The disease has a natural history in primary, secondary, and tertiary stages. Unless diagnosed and treated at an early stage, yaws can become a chronic, relapsing disease, and can lead to severe deforming bone lesions in the long term.[1]

Between 1952, and 1964, WHO and UNICEF led a worldwide campaign to control and eventually eradicate yaws and other endemic treponematoses.[2] Yaws became the second disease targeted for eradication, after smallpox. Control programmes were established in 46 countries and, by the end of 1964, the number of cases had reduced by 95%, from 50 million to 2·5 million. However, control efforts were gradually abandoned in most countries[3] and the disease re-emerged in the late 1970s, prompting the adoption of WHO's assembly resolution 38·58.[4] According to the last estimate by WHO in 1995, more than 500 000 children were still affected in Africa, Asia, and South America.[5]

Penicillin remains the drug of choice to treat endemic treponematoses.[6,7] WHO guidelines recommend one intramuscular injection of long-acting benzathine benzylpenicillin at a dose of 1·2 MU for adults and 0·6 MU for children;[8] however, other guidelines recommend higher doses.[9] This treatment is effective and has several advantages, as described for venereal syphilis.[10] Although this treatment is cheap and well tolerated, it has drawbacks, including the operational and logistical difficulties related to treatment with drug injection, the potential risk of transmission of blood-borne pathogens with unsafe injection practices, the pain related to deep intramuscular injection of a large volume (4 mL), and a high rate of self-reported allergy to penicillin.

Oral phenoxymethylpenicillin for 7–10 days (50 mg/kg daily in four doses; maximum dose 300 mg four times a

day) was effective in a yaws control programme.[11] Such a regimen overcomes the disadvantages of intramuscular drug administration, but poor adherence to a multiday treatment regimen is a risk. In pilot studies of the potential of oral, single-dose treatment against several infectious disorders, azithromycin—a macrolide antibiotic with a long half-life in tissue—seemed to be a valuable drug against *Chlamydia trachomatis*,[12] *Neisseria gonorrhoeae*,[13] and *Haemophilus ducreyi*[14] infections. Promising results were also reported from a large-scale study[10] done in Tanzania, with two regimens to treat early syphilis: one oral dose (2 g) of azithromycin and one intramuscular dose of benzathine benzylpenicillin 2·4 MU. A multicentre trial[15] in North America and Madagascar had similar findings.

The immediate-release formulation of azithromycin given in one oral dose of 30 mg per kg of bodyweight has been approved and widely used to treat acute otitis media in children since 2001.[16,17] The product is available as an oral tablet or as syrup, which is easier to administer to very young children.

We assessed the efficacy of a single oral dose of azithromycin compared with the standard single intramuscular dose of benzathine benzylpenicillin to treat yaws.

Methods

Study setting and patients

We undertook a prospective, open-label, non-inferiority, randomised controlled trial at Lihir Medical Centre in Papua New Guinea between Sept 1, 2010, and Feb 24, 2011. The Lihir islands are geographically remote, and despite being host to a major gold-mining operation since 1995, the living conditions and sanitation remain basic in most areas. Yaws is still a substantial cause of morbidity in Papua New Guinea.[18,19] Monthly reports for monitoring several indicators of infectious diseases and maternal and child health are being collected via forms from hospitals, health centres, and aid posts throughout the country. The national health department estimated the number of yaws cases to be 17 000 nationwide in 2003, and 23 000 in 2008, of which 5000 were in New Ireland province, where Lihir Island is located, and another 5000 in the neighbouring province of West New Britain (unpublished).

All patients examined in the outpatient medical department and suspected to have primary-stage or secondary-stage yaws were assessed for possible inclusion in the study. Eligible patients were children aged 6 months to 15 years with a rapid plasma reagin titre of at least 1 in 16 and a reactive *T pallidum* haemagglutination test. Exclusion criteria were known allergy to penicillin or macrolide antibiotics, use of antibiotics active against *T pallidum* during the preceding month, and known or suspected coexisting diseases for which additional antibiotic treatment with drugs effective against *T pallidum* would be needed (use of quinolones, sulphonamides, trimethoprim, and metronidazole was allowed).

A diagnosis of yaws chancre (primary stage) was established by dermatological examination on the basis of chronic (symptomatic for >2 weeks), painless, atraumatic ulcers with raised margins. Criteria for the diagnosis of secondary yaws included the presence of one or more of: multiple hyperkeratotic papules; polyarthralgia; or bone pain and swelling affecting the fingers or toes, forearm, tibia, or fibula. When an overlap between the stages occurred (ie, primary lesion persisting after the appearance of secondary yaws symptoms) we classified the case as secondary stage. The study was approved by the National Medical Research Advisory Committee of the Papua New Guinea Ministry of Health. All patients, or their parents, provided signed informed consent.

Randomisation and masking

Eligible participants were randomly assigned, by use of a computer-generated random-numbers list, to receive either 30 mg/kg (maximum 2 g) azithromycin orally or 50 000 units per kg (maximum 2·4 MU) benzathine benzylpenicillin by intramuscular injection. Randomisation was done in permuted blocks of four and in a 1:1 ratio. The allocation was concealed from investigators by use of opaque, sealed, and sequentially numbered envelopes that were opened after the study team had decided to enrol a patient. Laboratory technicians were unaware of participants' treatment allocation, treatment response, and previous rapid plasma reagin results at all times. All participants received directly observed treatment, but masking of patients was not possible for logistical reasons.

Procedures

The primary endpoint was serological cure, defined as a decrease in the rapid plasma reagin titre by at least two dilutions at the 6-month follow-up examination, compared with the titre at time of treatment. For ulcers, improvement of lesions in 2 weeks after treatment was also needed. Secondary endpoints were the individual components of the primary endpoint, cure rate 3 months after treatment, and cure rates according to stage of yaws, rapid plasma reagin titre at treatment, and history of household exposure.

To guarantee timely follow-up of participants, we implemented a community-based follow-up strategy. A field team, consisting of a physician, a laboratory technician, and a local health worker, located patients twice a week (for follow-up visit) at their residence by tracking detailed locator information. All participants were re-examined 2 weeks after treatment to assess clinical resolution. Photographic documentation of skin lesions was obtained at diagnosis and at the 14-day follow-up visit for comparison over time. Patients with worsening ulcers were retreated with benzathine benzylpenicillin (at the same dose). We assessed all participants at 3 months and 6 months after treatment. A

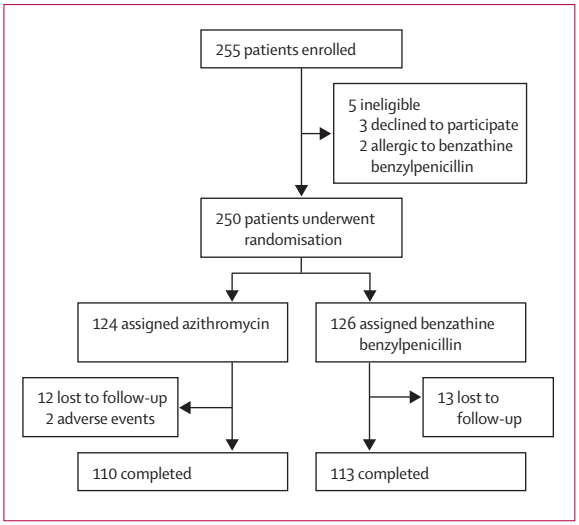

Figure 1: **Trial profile**

	Azithromycin (n=124)	Benzathine benzylpenicillin (n=126)
Age (years)	9·2 (3·7)	8·4 (3·3)
Male sex	54 (44%)	59 (47%)
Exposure*	26 (21%)	20 (16%)
Clinical presentation		
Primary stage	50 (40%)	56 (44%)
Secondary stage	74 (60%)	70 (56%)
Persisting ulcer	18 (15%)	15 (12%)
Secondary skin lesions	16 (13%)	11 (9%)
Arthralgias	68 (55%)	64 (51%)
Bone swelling or pain	12 (10%)	10 (8%)
RPR titre at treatment		
≤1 in 32	47 (38%)	60 (48%)
≥1 in 64	77 (62%)	66 (52%)

Data are mean (SD) or number (%). RPR=rapid plasma regain. *Household exposure to other children with open skin ulcers during the previous 3 months.

Table 1: **Baseline characteristics of the intention-to-treat population**

5 mL blood sample was obtained at each follow-up visit for serological analysis for *T pallidum*. All rapid plasma reagin tests were done in duplicate by two independent trained technicians at the Lihir Medical Centre microbiology department, and tests were done a third time in cases of discrepant results.

Safety assessments included documentation of immediate adverse events and patient-reported adverse events. So that immediate reactions could be recorded and treated, patients stayed at the health centre for 30 min after treatment. Patient-reported adverse events were assessed at the 2 week examination. Patients (or their parents or guardians) were explicitly asked about pain at site of injection, rash, fever, vomiting, diarrhoea, and stomach pain.

Statistical analysis

This study was based on the notion that azithromycin would be non-inferior to benzathine benzylpenicillin for the primary efficacy outcome, with use of a pre-specified non-inferiority margin; the upper limit of the 95% CI for the difference in cure rates between groups would not exceed 10%. We calculated that a sample size of 242 patients (121 per group) would give a power of 80% to test the hypothesis of non-inferiority. This sample size accounted for an expected efficacy of benzathine benzylpenicillin of 95%,[11,20] a non-inferiority margin of 10%, and a one-sided type 1 error rate of 0·05, with the assumption that 10% of participants would be lost to follow-up.

We selected the per-protocol population for the primary analysis. This population included all patients who underwent randomisation and who completed the study procedures to month 6. We also did a supporting analysis with the intention-to-treat (missing equals failure) population, which included all eligible patients, and in which patients with missing data were regarded as having treatment failure.

For analysis of the primary endpoint (cure rate at 6 months), we estimated two-sided 95% CIs for the difference in cure proportions between the benzathine benzylpenicillin group and the azithromycin group according to Altman and colleagues' method.[21] We used the same method to analyse secondary binary endpoints. We did additional post-hoc analyses to assess the consistency of treatment effects in subgroups defined according to disease stage, rapid plasma reagin titre, and household exposure, with Fisher's exact test. To compare baseline characteristics and adverse events between the treatment groups, we used two-sided *t* and Fisher's exact tests with a significance level of 0·05. We did all statistical analyses with Stata (version 11.1).

This study is registered with ClinicalTrials.gov, number NCT01382004.

Role of the funding source

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Figure 1 shows the trial profile. 250 patients with serologically confirmed yaws were randomly assigned to receive either azithromycin or benzathine benzylpenicillin. Baseline clinical and serological characteristics of the two treatment groups were similar (table 1). Mean age of the participants was 8·8 years (SD 3·6; range 8 months to 15 years). 42% of patients had primary yaws (table 1). The rapid plasma reagin titre was less than 1 in 32 in 107 (43%) participants and 1 in 64 or more in 143 (57%; table 1).

25 (10%) of the 250 participants could not be traced: ten (4%) of these children could not be located for any follow-up visit and 15 (6%) were lost after the first follow-up visit. We could not locate seven (3%) participants because they provided an invalid address, and 18 (7%) were originally from the study area but moved elsewhere during follow-up. Two patients did not complete follow up because of adverse events related to drug administration. The remaining 223 patients constituted the per-protocol population.

Adverse events in the first 14 days of treatment were reported by ten (8%) of 119 patients interviewed in the azithromycin group, and by eight (7%) of 121 in the benzathine benzylpenicillin group. Of participants given azithromycin, six (5%) reported nausea, two (2%) stomach pain, and two (2%) vomiting within 30 min of taking the drug. We classed the two patients who vomited as having had treatment failure in the intention-to-treat analyses, and they were retreated with benzathine benzylpenicillin. In patients given benzathine benzylpenicillin administration-related adverse effects were the most common. Six (5%) patients in the benzathine benzylpenicillin group reported persistent injection-site pain, despite use of lidocaine 1% as a diluent, and two (2%) had an injection-related abscess. No serious adverse events were reported during treatment or for the entire follow-up period.

129 participants with ulcers (in primary or secondary stage) were re-examined 2 weeks after treatment; the ulcers had resolved in 51 (40%) and were healing in 70 (54%; figure 2). The rates of healing did not differ significantly between the two treatment groups (data not shown). We classed the remaining eight (6%) patients (four in the azithromycin group and four in the benzathine benzylpenicillin group) as having clinical treatment failure.

In both the per-protocol and intention-to-treat analyses the criteria for non-inferiority were met for the composite primary endpoint of serological cure at 6 months and clinical healing of ulcers. In the per-protocol analysis, 106 of 110 patients assigned azithromycin were cured at 6 months compared with 105 of 113 patients in the benzathine benzylpenicillin group (risk difference –3·4%, 95% CI –9·3 to 2·4; table 2). Incidence of the individual components of the primary endpoint and intermediate cure rates did not differ significantly between groups (table 2). In the intention-to-treat population, 106 of 124 patients assigned azithromycin and 105 of 126 patients assigned benzathine benzylpenicillin met the criteria for the primary endpoint (–2·2%, –11·1 to 6·8; table 2).

In subgroup analyses, the cure rates at 6 months according to yaws stage, rapid plasma reagin titre at treatment, and household exposure did not differ significantly between treatments in the per-protocol population (table 3). No participant in either treatment group had recurrent clinical signs of yaws or serological

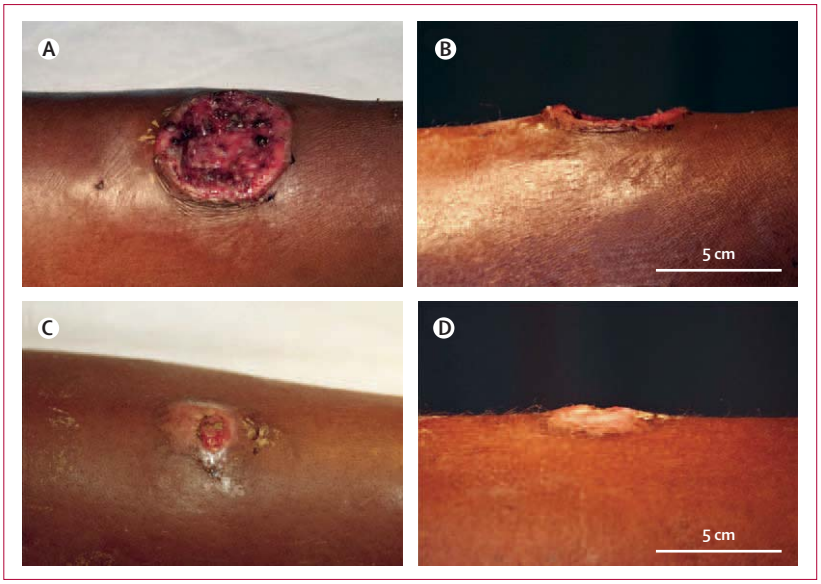

Figure 2: **Ulcers in patients with primary-stage or secondary-stage yaws who were re-examined 2 weeks after treatment**
(A, B) Red, moist, bedded, 5 cm ulcer on the left leg of a 9-year-old patient with primary yaws. (C, D) Partially epithelialised tumour 2 weeks after treatment with azithromycin.

	Azithromycin % (95% CI)	Benzathine benzylpenicillin % (95% CI)	Risk difference % (95% CI)
Primary population (PP) analysis (n=223)*			
Primary endpoint: cure at 6 months	96·4% (91·0–98·6)	92·9% (86·7–96·4)	–3·4% (–9·3 to 2·4)
Cure at 3 months	80·0% (71·6–86·4)	80·5% (72·3–86·8)	0·5% (9·9 to 10·9)
Serologically defined cure at 6 months	100% (96·5–100)	96·3% (90·3–98·8)	–3·7% (–7·2 to –0·1)
Clinical cure of ulcers 14 days after treatment	96·4% (91·3–98·6)	96·5% (91·0–98·6)	0·1% (–4·8 to 5·0)
Secondary population (ITT) analysis (n=250)†			
Primary endpoint: cure at 6 months	85·5% (78·2–90·6)	83·3% (75·9–88·8)	–2·2% (–11·1 to 6·8)
Cure at 3 months	71·0% (62·5–78·2)	72·2% (63·4–79·7)	1·3% (–9·9 to 12·4)
Serologically defined cure at 6 months	88·3% (81·4–92·9)	86·1% (78·8–91·1)	–2·3% (–10·7 to 6·1)
Clinical cure of ulcers 14 days after treatment	85·4% (78·2–90·6)	86·5% (79·5–91·4)	1·0% (–7·6 to 9·6)

PP=per protocol. ITT=intention to treat. *Including only patients with complete follow-up and study endpoint. †Including all randomised patients; we regarded patients with missing data as having treatment failure.

Table 2: **Incidence of clinical endpoints**

	Azithromycin % (95% CI)	Benzathine benzylpenicillin % (95% CI)	Risk difference % (95% CI)
Cure at 6 months by yaws stage			
Primary	90·9% (78·8–96·4)	89·1% (78·2–94·9)	–1·8% (–13·7 to 10·0)
Secondary	100% (94·5–100)	96·6% (88·3–99·1)	–3·4% (–8·1 to 1·2)
Cure at 6 months by RPR titre at treatment			
≤1 in 32	100% (90·8–100)	92·9% (83·0–97·2)	–7·1% (–13·9 to -0·4)
≥1 in 64	94·4% (86·6–97·8)	93·0% (83·3–97·2)	–1·4% (–9·9 to 7·0)
Cure at 6 months by household exposure			
Positive	100% (85·1–100)	100% (81·6–100)	..
Negative	95·5% (88·9–98·5)	92·0% (85·0–95·9)	–3·5% (–10·3 to 3·4)

Data are for the per-protocol analysis. RPR=rapid plasma reagin.

Table 3: **Subgroup analysis of the primary endpoint at 6 months**

evidence of recurrence during the 6-month follow-up period.

Discussion

Our findings show that azithromycin was non-inferior to benzathine benzylpenicillin for the primary composite endpoint of serological cure at 6 months and healing of ulcers. Furthermore, the two treatment groups had similar rates of cure at 3 month follow-up and in subgroups defined according to demographic and biological characteristics. These results add to previous evidence of the suitability of use of a single dose of a drug such as azithromycin to treat various infectious diseases (panel). Rates of serologically defined cure at 6 months were substantially higher than expected for both treatments, which validates our non-inferiority hypothesis for the estimated penicillin cure rate. All participants had a lower rapid plasmin reagin titre at 6 months than at 3 months, including 150 (67%) patients who seroconverted. Additionally, we did not identify any clinical or serological relapse after cure at 6 month follow-up. The azithromycin regimen did not resolve active primary lesions in four patients. However, in the three cases of failure that could be investigated, an immunoperoxidase stain from a skin biopsy specimen was negative for spirochaetes; therefore, we could not confirm the biological treatment failure.

Azithromycin was well tolerated and no major adverse effects occurred. Of participants who were treated with azithromycin and interviewed, 8% reported mild to moderate side-effects that were mainly gastrointestinal. Only two children vomited within 30 min of oral azithromycin administration, thus negligible drug absorption would have occurred. These children were then re-treated with benzathine benzylpenicillin. The small number of participants vomiting after administration emphasises the suitability of azithromycin for mass treatment programmes.

Our study had several limitations. First, diagnostic criteria for inclusion in the study of primary lesions did not include a microbiological test (eg, darkfield microscopy); therefore, the non-healing ulcers could have had post-treatment infection by other pathogens. However, darkfield microscopy is rarely used to diagnose treponemal infections because rapid serological tests are available. Second, the imprecise definition of serological cure, which could lead to overestimations in true rates of cure, is a major issue affecting all research on the treatment of treponematoses. Because laboratory technicians in this study were unaware of participants' treatment assignments, this drawback should not have biased the comparison of cure rates between the groups. Third, 6 months of follow-up might not be sufficient to assess the results after antibiotic treatment for yaws. Four participants in the benzathine benzylpenicillin group did not achieve serological cure. This finding could represent a slower than usual decline in non-treponemal test titres after treatment, rather than a true penicillin-resistant infection. Finally, because our trial design required patients to meet certain prespecified criteria, and because the study was done in one centre, our findings might not be generalisable to all children with yaws.

Two important reasons for caution with use of azithromycin are the sustained success of benzathine benzylpenicillin treatment for yaws, and the emergence of azithromycin-resistant *T pallidum*. Clinical treatment failure with penicillin has been reported for yaws,[20] although, because in-vitro culture for *T pallidum* has not been achieved,[22] penicillin resistance has not been proven by microbiological methods. Moreover, in countries such as Papua New Guinea, cases of reinfection are occurring, which suggests increased tolerance of some *T pallidum* subsp *pertenue* strains to penicillin treatment.[23] Azithromycin resistance in the non-venereal treponemes has not been investigated, but resistance in the syphilis treponeme is geographically clustered—eg, more than 95% resistance in Shanghai versus 0% in Madagascar.[24,25] In areas where mutations have been found (eg, Seattle, USA) the frequency of resistance has increased substantially in the past 10 years.[26] Use of azithromycin in the Lihir Island community to treat other infections has been scarce, which might explain why we did not encounter a substantial problem with resistance in our study since there had been very little selective pressure. Nonetheless, *T pallidum* subsp *pertenue*, seems to have two of the genes encoding 23S ribosomal RNA where the mutation that confers high-level resistance to macrolides is located, as does *T pallidum* subsp *pallidum*.[27] Thus, close monitoring for potential treatment failure should be considered in future studies of azithromycin.

With yaws re-emerging, treatment with an effective drug that can be easily administered on a large scale is the

***Panel:* Research in context**

Systematic review

We searched PubMed from Jan 1, 1952, to Aug 1, 2010, with the terms "yaws", "*Treponema pallidum*", "penicillin", and "azithromycin". We searched for trials that assessed the efficacy and safety of single-dose oral azithromycin to treat infectious diseases in adults and children. We identified two randomised controlled trials,[10,12] which showed the efficacy of oral azithromycin for the treatment of treponemal disease (syphilis) in adults. However, we did not identify any study that explored yaws treatment with azithromycin. We searched only publications written in English.

Interpretation

Our results provide substantial evidence of the non-inferiority of a single oral-dose of azithromycin compared with the standard recommended therapy—benzathine benzylpenicillin—for treatment of yaws. This finding represents a potentially useful advance in yaws control.

preferred method for treatment, prevention, and, eventually, elimination worldwide. Elimination programmes need to take account of all epidemiological, biological, and pharmacological factors, and the practical considerations of a mass campaign to deliver and administer drugs in isolated and under-resourced communities. The potential for treatment of yaws with an oral, single-dose drug has been explored in this context. Azithromycin overcomes the major logistical and medical disadvantages of the present regimen: it avoids the need for injection equipment and medically trained personnel, which can be scarce in countries with few health resources; it prevents all the injection-related risks and side-effects; and it can be safely administered to individuals with penicillin allergy (1% in our trial population). Although we did not formally assess the relative costs related to drug acquisition and administration, low-cost generic preparations of azithromycin are widely available and the treatment could therefore be highly cost effective.

Our findings provide clear evidence that one high dose of azithromycin is non-inferior to benzathine benzylpenicillin for treatment of yaws. If further studies confirm our findings (a similar trial is in progress in Ghana, West Africa (Kwakye-Maclean C, Ga West Municipal Heath Directorate, personal communication), the next step is to attempt elimination and possibly eradication of the disease in the remaining endemic countries with mass drug administration programmes under WHO's leadership.

Contributors

OM conceived and designed the study. OM, RH, AI, MP, and RP contributed to the recruitment, clinical care, and follow-up of patients. OM, EdL, and QB analysed and managed the data. DF did all laboratory tests. OM, RH, and QB wrote the article.

Conflicts of interest

We declare that we have no conflicts of interest.

Acknowledgments

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New treatment schemes for yaws: the path toward eradication

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REVIEW ARTICLE

New Treatment Schemes for Yaws: The Path Toward Eradication

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Yaws—an infectious disease caused by *Treponema pallidum* subsp. *pertenue*—is a paradigmatic example of the neglected tropical disease and is reemerging as a public health concern in many countries, causing suffering particularly in children aged <15 years of age in poor rural communities. However, its global eradication, a goal since 1950, may now be closer than ever as a result of the recent expansion and simplification of treatment options to include oral azithromycin. Indeed, the results of a trial published last January [1] allow certain optimism about the treatment and eradication of this ancient disease because a simple single-dose oral treatment targeting whole populations could be sufficient to adequately cure the infection in its early stages and interrupt transmission to others. A new eradication policy around the azithromycin pillar was sketched at a World Health Organization (WHO) consultation meeting held in Morges, Switzerland, in March 2011. It was envisaged that a last global mass campaign in the remaining endemic countries should permit worldwide eradication by 2020 in accordance with the WHO Neglected Tropical Diseases Roadmap [2].

Yaws was one of the first diseases to be targeted for eradication on a global scale. After a WHO-coordinated worldwide control program reduced the number of infections from 50 million in 1952 to 2.5 million in 1964, the disease reemerged in the 1970s when control efforts lagged [3]. According to the most recent estimates reported by the WHO in 1995, >500 000 people, mostly children in poor rural areas, were affected by the disease [4]. Some of the most important endemic foci today are located in Africa (Ghana, Congo, Cameroon) [5], Southeast Asia (Indonesia, Timor-Leste), and the Pacific islands (Papua New Guinea, Solomon Islands, Vanuatu) [6], but figures are imprecise due to patchy surveying, especially in isolated districts and islands [7].

STANDARD ANTIBIOTIC TREATMENT

The WHO yaws treatment guidelines date to the 1950s, and since then, no alternatives to penicillin for first-line treatment have been introduced. Penicillin was proven to be highly effective against yaws and other treponemal diseases in 1948, and it revolutionized the therapy of these infections. Tests on experimentally infected animals and infected patients showed that benzylpenicillin levels $\geq$0.03 units/mL of serum maintained for at least 7 days were treponemicidal [8]. These levels can be achieved either by giving repeated doses of short-acting benzylpenicillin preparations (ie, aqueous benzylpenicillin) or a single intramuscular injection of slowly absorbed, repository benzylpenicillin preparations such as benzathine benzylpenicillin or penicillin aluminium monostearate [9]. Intramuscular benzathine benzylpenicillin was chosen as the preferred treatment for yaws because of its convenient pharmacokinetics and manufacturing advantages. The WHO guidelines still recommend 1 intramuscular injection of long-acting benzathine benzylpenicillin at a dose of 1.2 MU for adults and 0.6 MU for children [7].

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Although it is generally recognized that treponematoses have remained exquisitely sensitive to penicillin, there are some reports of possible penicillin treatment failures in yaws. In Papua New Guinea, apparent treatment failures were reported in 11 of 39 (28%) cases on Karkar Island [10], and a few penicillin treatment failures have also been observed in Ecuador [11]. It can be difficult to distinguish between reinfection and relapse, and even if penicillin resistance may be a true, albeit rare, event, these clinical failures have had minimal impact on the elimination of the disease in different countries. The development of penicillin resistance often involves the acquisition of new genetic information and a multistep mutational process with a probability of occurrence that is much rarer than those of the single-point mutations that are responsible for macrolide resistance [12].

On the other hand, the large-scale use of benzathine benzylpeniciilin for the eradication of yaws presents several operational obstacles. Experienced medical personnel and the equipment needed to administer intramuscular injections are often lacking in the areas most in need of treatment, and a risk of transmitting bloodborne infections exists if sterile protocols are not followed. Furthermore, benzathine benzylpenicillin requires refrigeration [13], and this is difficult, if not impossible, to achieve in many remote tropical areas [14]. Despite these constraints, efforts to develop new strategies to make eradication easier have been scarce in the last 50 years. In 2007, the International Task Force for Disease Eradication articulated the obvious potential advantages of a single-dose oral drug for yaws and highlighted the need for investigation [15].

REVIEW OF PAST ORAL TREATMENTS

Oral penicillin V for 10 days was used in rural Guyana and successfully cured yaws in individual children and decreased the prevalence in a community [16]; however, such a regimen requiring the administration of multiple oral doses over a number of days has a potential compliance problem and is not suitable as an epidemiological treatment to be employed in eradication campaigns targeting vast areas. There is little information on the use of drugs other than penicillin to treat yaws (see Table 1). Oral tetracycline, doxycycline, or erythromycin for 15 days are also likely to be effective [17–20]. These recommendations, however, are based solely upon known clinical efficacy in small series of patients and not upon the results of any clinical trials. The dosing schedule and duration of tetracyclines and erythromycin again raise the possibility of missed doses and unfinished courses of therapy. Furthermore, the use of tetracyclines in children aged <8 years (in whom many cases of yaws occur) is currently not recommended because of their association with dental staining and interference with bone growth [21].

NEW ORAL TREATMENT

The azalide structure of azithromycin confers a much improved pharmacokinetic profile in comparison with erythromycin. Its unique features—including in vivo activity against *T. pallidum* and high concentrations in tissues relative to serum, resulting in prolonged tissue half-lives—make it an excellent candidate for an oral shortened course therapy for yaws. The oral bioavailability of azithromycin is high (approximately 37%), and tissue concentrations exceed serum concentrations by as much as 100-fold following a single oral dose [22], with high concentrations found in skin and bones, the principal target tissues for yaws. Pharmacokinetic data from clinical studies show that a single 30-mg/kg dose of azithromycin provides drug exposure that is equivalent to at least a 5-day regimen [22]. Both regimens maintain azithromycin

Table 1. Review of Past Oral Treatments and the New Oral Treatment for Yaws Q16

Oral Treatments (year)	Dosage	Usual Indication of Treatment	Scientific Evidence of Efficacy
Phenoxymethylpenicillin (2003)	7–10 d; 12.5 mg/kg q6h (maximum dose, 300 mg q6h)	Tested for oral delivery in mass campaign	Prevalence of clinical yaws lesions fell from 5.1% to 1.6% 1 year after a treatment campaign in rural Guyana [16] Q13
Tetracyclines (1951)	15 d; tetracycline 500 mg q6h or doxycycline 100 mg q12h	Alternative agents for the treatment of yaws in nonpregnant adults [3]	Efficacy is not well documented. Their use is based upon small series of yaws patients treated with tetracycline derivatives (aureomycin, terramycin, or oxytetracycline) in Africa [17], Haiti [18], and Jamaica [19]
Erythromycin (1963)	15 d; 8–10 mg/kg q6h	Alternative for treating yaws in penicillin-allergic children aged <12 y [3]	Based upon the known clinical efficacy of erythromycin for patients with venereal syphilis [20]
Azithromycin (2012)	Single-dose; 30 mg/kg (maximum dose 2 g)	New first-line oral treatment for yaws	It has been shown to be noninferior to benzathine benzylpenicillin for the treatment of yaws in children in Papua New Guinea [1]

levels in tissue sites of infection above the minimum inhibitory concentration of treponemes for several days after administration has ceased.

In January 2012, an open-label, noninferiority, randomized trial conducted on Lihir Island in Papua New Guinea involving 250 children aged 6 months–15 years with yaws showed that patients treated with oral azithromycin were cured as well as those receiving an intramuscular injection of benzathine benzylpenicillin (96% vs 93%). Oral azithromycin thus met the prespecified criteria for noninferiority. A similar trial is in progress in Ghana, and preliminary observations show results in line with those found in Papua New Guinea (C. Kwakye-Maclean, Ga West Municipal Health Directorate, personal communication). In a review published by Meheus and colleagues in 2010 [23], azithromycin was hinted at as a potential treatment for sporadic cases, but more important, it may represent a suitable tool for deployment in mass treatment campaigns aimed at the global eradication of this disease.

A NEW ERADICATION STRATEGY BASED ON LESSONS LEARNED FROM THE PAST

The biological features of yaws and the diagnostic and treatment tools currently available to combat it make yaws a potentially eradicable disease. First, humans are the sole reservoir, and infection spreads only through close body contact, which would allow some mitigation of the disease incidence simply through public health education. In addition, there are practical diagnostic tools (ie, rapid serological tests) with high sensitivity and specificity to detect levels of infection that can lead to transmission. Finally, the new simple pharmacological intervention based on azithromycin can facilitate mass treatment.

Simply moving from penicillin to azithromycin as a therapeutic tool, however, is unlikely to be sufficient to interrupt transmission of yaws. For each case of yaws detected, there might be 5–10 subclinical cases (seropositive patients without clinical manifestations) [3] that may give rise to infectious relapses for some years. These must also be treated in order to eliminate the reservoir of infection. Problems and systematic failures, which compromised the completion of eradication programs in the 1950s, must be acknowledged and addressed if future campaigns are to be successful [24].

The treatment policies of the 1950s (see Table 2) were based on the prevalence of clinically active yaws in the community, which required purposeful and costly surveys and often focused on the treatment of active cases and contacts. In addition to the logistical problems of administering injectable antibiotics in mass treatment, the imprecise definition of "contacts" [24] and the limitations of the juvenile and selective mass treatment strategies in dealing with latent cases required multiple visits to endemic communities to identify and treat new cases. Most of the active cases found at resurveys were in persons who were in the latent stage originally [25]. This placed a burden upon health services, which were often in areas poorly resourced and under stress in the first place. Understandably, once the prevalence of yaws fell to a low level, active surveillance was discontinued because it was no longer considered cost effective, thus allowing subclinical infections to spread the disease again.

Table 2. Old World Health Organization Treatment Policies for Yaws Based on Benzathine Penicillin (1950s)

Prevalence of Clinically Active Yaws in the Community	Recommended Treatment
High: >10% (hyperendemic)	Benzathine penicillin to the entire population (total mass treatment)
Medium: 5%–10% (mesoendemic)	Treat all active cases, all children aged <15 y and obvious contacts of the infectious cases (juvenile mass treatment)
Low: <5% (hypoendemic)	Treat all active cases and all household and other obvious contacts (selective mass treatment)

The new strategy based on azithromycin, which was outlined at the WHO consultation in Morges in March 2012, aims to be more proactive in order to deal with all potential contacts and latent cases. In view of the ease of administering oral treatment, the new policy employs an initial total community treatment (TCT) in endemic communities, irrespective of the prevalence of yaws (Table 3). Also, to make sure all cases are tracked down and treated, village volunteers (community drug distributors) could play a role in achieving greater coverage (follow-up with missed cases during TCT), and strict follow-up measures, with resurveys/retreatment conducted every 3–6 months, are recommended until 0 case prevalence is reached [26]. By this approach, if the coverage of mass treatment is excellent (>90%) and local health services remain robust and engaged in dealing with cases and contacts in-between services, a few cycles of treatment should interrupt transmission [26].

Once criteria for stopping mass treatment (ie, 0 cases reported) have been met, young children (aged <5 years) should be tested annually for serology. Elimination in an endemic country would be certified in the absence of any report of the disease for 3 consecutive years and continuous negative serological tests in children aged <5 years, confirming no further exposure to the infection in the community.

Community-based mass administration of azithromycin has been widely used in many locations for the control of trachoma [27], which, like yaws, is a disease common in poor rural communities in developing countries, and has been used in a more limited way to control granuloma inguinale

Table 3. New World Health Organization Treatment Policies for Yaws Based on Azithromycin (2012) Q14

Component 1: mapping	Review of existing information and implementation of mapping surveys in districts with limited information (ie, baseline population screening for clinical lesions with confirmatory serology)	
Component 2: treatment policies	First round	Total community treatment (TCT): Initially treat the entire endemic community irrespective of the prevalence of active clinical cases (at least 1 case).
	Subsequent rounds	Resurvey/retreatment every 3–6 mo until clinical 0 case prevalence Total targeted treatment: treat all active clinical cases, and their contacts (household, classmates, and playmates) Repeated TCT if coverage in the initial TCT was <90% or access to the endemic communities is difficult
Component 3: health system	Diagnosis and treatment of patients presenting to healthcare (passive case finding) Also active case finding (eg, by village volunteers) Tracing and treatment of contacts	
Component 4	Health promotion and community mobilization	

(donovanosis) [28] and outbreaks of venereal syphilis [29]. The use of azithromycin has generally been found to be safe, and there have even been unexpected health benefits reported in some trachoma control programs, such as reduction of all-cause mortality by 50% in children aged 1–5 years in a study in Ethiopia [30] and a significant reduction in prevalence of impetigo and diarrhea among treated children in Nepal [31]. We could find no studies that looked at the impact of trachoma control programs using azithromycin on the incidence of yaws or positive treponemal serology. This may partly reflect the fact that the 2 diseases are most prevalent in different climatic or geographical regions.

Biological evidence that selective pressure can engender resistant strains, as has occurred with the causative agent of syphilis, *T. p. pallidum*, in a number of sexual networks in developed countries, serves as a note of caution about the use of azithromycin. Background macrolide use for unrelated infections (mainly respiratory) is thought to have contributed significantly to the rise of *T. pallidum* strains with increased resistance. Interestingly, clinical treatment failure with macrolides appeared to be uncommon in trials in Uganda [32] and Tanzania [33], and no laboratory evidence of resistance to azithromycin in specimens from 141 patients with syphilitic lesions was found in Madagascar [34]. There is little likelihood therefore that resistance will emerge in resource-poor communities where azithromycin has not been used in the past and where yaws typically occurs [35]. However, the recognition of this possibility dictates that measures be taken to ensure the sustainability of the strategy, including tracking misuse or diversion of the antibiotic for other purposes. Emergence of resistance in *T. p. pertenue* should ideally be prospectively evaluated in the communities where azithromycin is deployed. This will represent a challenge in itself because molecular typing techniques (ie, 23S ribosomal RNA amplification) needed to identify mutations in patients who fail therapy are not readily available in most developing countries. Finally, treatment failure should be monitored, and in cases of treatment failure, patients should be switched to a different antibiotic.

The potential effect of mass treatment with azithromycin on resistance in *Streptococcus pneumoniae* may impact the management of acute respiratory infections in children. This phenomenon has been extensively evaluated after mass treatment campaigns to control trachoma, and the results have been reassuring. Some surveillance studies have demonstrated short-term and not persistent changes in susceptibility patterns in the nasopharyngeal carriage of children [36–38], and the largest surveillance study done to date in a hyperendemic trachoma region did not show an effect of mass treatment with azithromycin on the prevalence of antibiotic-resistant *S. pneumoniae* [39].

PROOF OF PRINCIPLE OF MASS TREATMENT WITH AZITHROMYCIN

A way to secure that the new eradication strategy is both doable and effective is to have a proof of principle that would provide accurate information for introducing necessary corrective measures. To this end, the WHO is developing standard operating guidelines for pilot studies to assess the impact of mass treatment of yaws using azithromycin in limited geographical areas.

This later phase 3 clinical development should involve larger numbers of patients—including adults, for whom efficacy has not yet been proven—to show convincing, statistically significant evidence of effectiveness in eradicating yaws. The minimum set of essential indicators required for assessing trends in yaws eradication includes clinical signs of the disease, serological prevalence in children, and mass treatment coverage, which are all recommended to be measured in sentinel sites randomly chosen from high endemic areas.

Serological prevalence surveys of young children aged <5 years will exclude ongoing transmission (risking that, if tested in the first years, some may have had a period of exposure to transmission). Alternatively, negative nontreponemal tests in those aged <15 years would detect falling serology in treated cases.

COADMINISTRATION WITH OTHER MDAs FOR NEGLECTED TROPICAL DISEASES

As a future possibility, national yaws programs may explore synergistic collaboration with other neglected tropical diseases control programs to enhance efficiency and allow better use of limited resources. Available evidence already exists supporting the safety and efficacy of the combination of the commonly used antihelminthic drugs and azithromycin, with no significant pharmacokinetic interactions [40]. However, at this stage, integration of azithromycin for yaws eradication with other MDAs in areas of geographical overlap is not recommended until enough experience has been gathered.

The suitability of coadministering azithromycin with ivermectin and albendazole was evaluated in a crossover study in 18 healthy volunteers. The authors concluded that the magnitude of interactions were minimal (modest increases in ivermectin parameters) and unlikely to be clinically relevant [41]. A further pharmacokinetic model analysis showed that the maximum ivermectin exposures that might be observed during coadministration with azithromycin were below those previously shown to be safe and well tolerated [42]. These analyses called for further pharmacovigilance studies, which are currently in progress.

Regarding the interaction between diethylcarbamazine and azithromycin or other macrolides, there have been no pharmacokinetic studies published so far; however, available information on the kinetics of each drug suggests that interactions may be minimal and have little clinical relevance. Diethylcarbamazine is only minimally metabolized and is eliminated largely unchanged in the urine [43], whereas azithromycin is eliminated to a major extent through the biliary tract and intestinal lumen [44]. Additionally, azithromycin binds little to plasma proteins (7%–52%), making a possible interaction at this level unlikely.

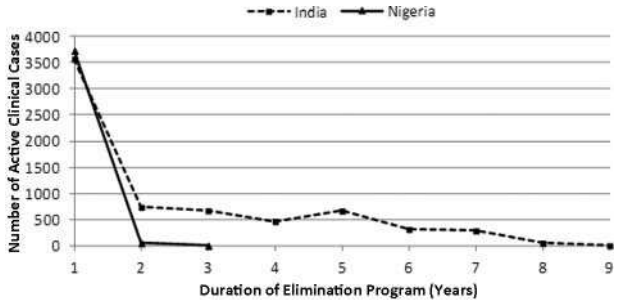

Figure 1. Outcome of yaws elimination programs in India and Nigeria. The India campaign (started 1996) employed the strategy of selective mass treatment with injected penicillin in an at-risk population of 7 million. The campaign in Enugu Ezike, Nigeria (started 1954) employed the strategy of total mass treatment in an at-risk population of 57 000.

THE POSSIBILITY OF GLOBAL ERADICATION

The real prospect of yaws eradication is highlighted by recent experiences in India [45]. Between 1996 and 2003, India undertook a successful campaign employing the conventional strategy of selective treatment with injected penicillin (Figure 1). Since 2004, no infectious cases have been reported. The success in India was clearly due to an excellent and tenacious system for clinical and serological surveillance during and after completion of the program. However, all countries may not have the political commitment and efficient social mobilization of India to deal with only a few yaws cases over a period of 7 years. The high-coverage (95%) treatment of the entire population, as was witnessed in a yaws eradication campaign in Nsukka, Nigeria,

Table 4. Assessment of Cost of Treatment for Yaws at a Peripheral Center in Papua New Guinea

	Aged <5 y		Aged >14 y	
	Injection Penicillin[a]	Azithromycin	Injection Penicillin[a]	Azithromycin
Drug	0.18 (0.6 MU)[b]	0.27 (500 mg)	0.73 (2.4 MU)	1.10 (2 g)
Water for injection	0.12	…	0.12	…
Syringe and needle	0.30	…	0.30	…
Alcohol swab	0.05	…	0.05	…
TOTAL	0.65	0.27	1.20	1.10

All costs are given in US dollars. Source: Papua New Guinea Medical/Dental Catalogue 2012, Department of Health.

[a] Costs can not be calculated for proper system for disposing needles, time required to prepare and give the injection, pain on the part of the patient, risk of injection abscess, and volume and weight of drug and all the accompanying materials.

[b] Calculation based on the use of a single drug vial (2.4 MUI) for multiple patients.

in the 1950s, resulted in a fast geometric reduction of prevalence within 6–12 months [26]. An initial TCT, even in low-prevalence-level communities, seems to be the most rapid and economic way to achieve yaws eradication.

Needless to say, issues related to political commitment and costs will be critical. Azithromycin, like benzathine benzylpenicillin, is included in the WHO essential drugs list and is available internationally in generic forms. In Papua New Guinea, for example, there is no drug price regulatory system; therefore price variability across different pharmaceutical suppliers is considerable. However, the costs related to drug acquisition and administration of low-cost generic preparations of azithromycin are highly competitive and may be lower than those of the classic treatment for yaws (see Table 4). On the other hand, given the large number of people to be treated, a donation program would be an essential ingredient of the new eradication effort.

CONCLUSIONS

The strategy for yaws eradication in 1952 called for the screening of patients for clinical disease and their treatment with penicillin. Despite its undisputable success in greatly reducing the number of cases worldwide, the program had 2 glaring deficiencies. First, the strategy had not been validated in pilot studies. Second, for the first 10 years of its history, there was no surveillance, so it was not clear what was actually happening beneath the visible surface [24, 25]. When sample serological surveys were eventually conducted, it was discovered that subclinical infections were far more prevalent than had been recognized. The campaign had largely failed in identifying contacts of those infected and those with latent infections, and surveillance had been discontinued prematurely, allowing subclinical infections to spread the disease again.

Eradication of yaws is now considered biologically feasible, programmatically attainable, and economically affordable. The strategy currently suggested to rid the world of yaws once and forever is total community treatment with oral azithromycin followed by resurveys and repeated total or targeted treatments as required. The new strategy should be validated first in proof-of-principle studies, including appropriate clinical and serological surveys, so we can determine the impact on both clinical and subclinical infections in the treated population, and *T. pertenue* macrolide resistance monitoring should be conducted to ensure sustainability of the strategy. If successful, this strategy will be an effective, logistically feasible, safe, and acceptable protocol for global eradication of this neglected disease.

Notes

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The Impact of a Filariasis Control Program on Lihir Island, Papua New Guinea

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Abstract

Background: Annual mass drug administration (MDA) over five years is the WHO's recommended strategy to eliminate lymphatic filariasis (LF). Some experts, however, consider that longer periods of treatment might be necessary in certain high prevalence and transmission environments based upon past unsuccessful field experience and modelling.

Methodology/Principal Findings: To evaluate predictors of success in a LF control program we conducted an ecological study during a pre-existing MDA program. We studied 27 villages in Lihir Island, Papua New Guinea, from two areas with different infection rates before MDA. We undertook surveys to collect information on variables potentially having an influence on the outcome of the program, including epidemiological (baseline prevalence of infection, immigration rate), entomological (vector density) and operational (treatment coverage, vector control strategies) variables. The success in a village was defined using variables related to the infection (circulating filarial antigenemia prevalence $<1\%$) and transmission (antigenemia prevalence <1 in 1000 children born since start of MDA). 8709 people were involved in the MDA program and average coverage rates were around 70%. The overall prevalence of filariasis fell from an initial 17.91% to 3.76% at round 5 ($p<0.001$). Viewed on a village by village basis, 12/27 (44%) villages achieved success. In multivariate analysis, low baseline prevalence was the only factor predicting both success in reducing infection rates (OR 19,26; CI 95% 1,12 to 331,82) and success in preventing new infections (OR 27,44; CI 95% 1,05 to 719,6). Low vector density and the use of an optimal vector control strategy were also associated with success in reducing infection rates, but this did not reach statistical significance.

Conclusions/Significance: Our results provide the data that supports the recommendation that high endemic areas may require longer duration MDA programs, or alternative control strategies.

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Introduction

Lymphatic filariasis (LF), caused by the mosquito-borne nematode Wuchereria Bancrofti, is a major public-health problem in many tropical and subtropical regions. Papua New Guinea represents the biggest remaining challenge for elimination of the disease. The Global Program to Eliminate Lymphatic Filariasis (GPELF) was launched in 1997. In the Pacific, the World Health Organization (WHO) has implemented from 1999, the Pacific Program to Eliminate Lymphatic Filariasis (PacELF) bringing together 22 countries and territories, in a common effort to eliminate the disease [1,2]. The PacELF strategy is based on five rounds of mass drug administration (MDA), monitored by a prevalence survey to assess the impact at completion of the last round [3,4]. Therefore, the assessment is designed to conclude whether to stop or to continue MDA after round 5. The rationale of this approach is to suppress microfilaremia (mf) in infected populations and bring the infection level down below a threshold that will prevent resurgence of infection and ultimately lead to interruption of transmission [5].

The exact infection level to achieve LF elimination in different endemic regions remains unknown, such that it is difficult to predict or decide when to stop ongoing MDA programs. Previous reports have suggested that residual filarial infections disappear when prevalence rates fall to less than 1% but it may vary depending on specific ecological conditions [6,7]. Moreover, some programs which have achieved this threshold have reported evidence of ongoing transmission, as measured by antibody or antigen prevalence in children aged 2–4 years and mosquito infection rates [8,9]. The current recommendation of the PacELF is that programs should reach an antigenemia level below 1% and that less than 1 in 1000 children born since start of MDA should

Author Summary

Large-scale intervention programmes to control filariasis are currently underway worldwide. However, a major unresolved question remains: what is the appropriate duration for these programmes? Recent theoretical work and clinical field experience has highlighted how the ecological diversity between different endemic regions hinders decision making processes of when to stop ongoing MDA programs. The goal of our study was to identify the factors determining success for a five year LF elimination program. We undertook different types of surveys together with a pre-existing MDA program in villages from two regions that had different infection prevalence rates. Our study shows that the five yearly cycles of MDA could neither eliminate the disease nor stop transmission in the high prevalence villages, such that low baseline lymphatic filariasis prevalence has a positive influence on the outcome of a program. Thus, the study provides data supporting the recommendation that in certain high prevalence and transmission environments more sustained efforts may be necessary.

become newly infected [1,2]. End-points for the GPELF have recently been changed to a level below 2% in areas where the main vector is an anopheline [4].The optimal duration of MDA programs has also not been established. Mathematical models suggest that 4 to 6 years of treatment should be sufficient [10]. However, several programs have reported evidence of failure to control the infection, as indicated by mf and circulating filarial antigenemia prevalence rates after completing five annual rounds of MDA [11–14].

Numerous attempts have been made to establish which variables may influence the outcome of a program. Some variables, such as the coverage of the target population [9,15,16], the drug regimen employed [5,17–20], and the integration of vector control measures [21–23], are controllable. Other biological and epidemiological variables, such as the initial prevalence of mf in an area and the vectorial abundance of the mosquito, are less amenable to modification. All the above mentioned factors need to be taken into consideration when developing an elimination strategy [24].

The aim of this study was to estimate success rates of the program to eliminate lymphatic filariasis (PELF) in villages from different areas and to identify determinants of success affecting a PELF's outcome.

Methods

Data for this ecological study were collected at a community-level during the delivery of an MDA program in villages of Lihir Island, Papua New Guinea. The program was closely monitored epidemiologically, entomologically, and through laboratory studies as outlined below. Together with drug administration we undertook different types of surveys including village surveys to collect information about variables potentially having an influence on the outcome of the program; circulating filarial antigenemia (CFA) prevalence surveys to assess the infection status and new infections since start of MDA; and mosquito surveys to determine mosquito abundance. CFA prevalence of the entire population was reassessed once after round 5.

The surveys were administered to the entire population of 27 villages in two regions of Lihir Island that had different infection prevalence rates before MDA was initiated. The study villages are only separated by between 1 and 3 kilometres from each other, however they constitute independent transmission zones as the vector species, *Anopheles farauti*, is generally considered incapable of flying more than 700 metres [25]. Many residents had been previously treated with diethylcarbamazine citrate (DEC) alone in 1995 during a campaign started by the New Ireland provincial government which continued for a short time [25]. However, ten out of twelve villages located in the swampy regions of the west coast recorded prevalence levels of filariasis as high as 20–60% in 2003. The other study villages on the dry savannah grassland of the north-east had rates 3–7 times lower than those in the west. In addition, the eastern area of the island in the vicinity of Londolovit has been host to a mining operation by LGL Australia since 1996. This has seen the influx of approximately 2000 workers from other areas of PNG and internationally, and a considerable unofficial migrant population from surrounding regions. There has been a degree of local development in the mine affected area.

Field teams consisting of a physician, a technician, and a local health worker visited the villages at spot check sites, annually. Prior to each visit, efforts were made to educate the public to the program's aims through health educators who disseminated information about LF at community meetings and through public notices, in cooperation with church and village leaders. MDA comprised the WHO-recommended regimen of a single oral dose of DEC (6 mg/kg body weight) and albendazole (400 mg regardless of weight) under direct observation. Simultaneously the teams collected the blood samples and recorded on a register epidemiological data and coverage information. Some people agreed to receive MDA but refused to provide blood samples. The observed coverage rates were based on the number of subjects seen to ingest the tablets and calculated on the basis of the total eligible population. However, a coverage survey was not carried out to verify the coverage achieved. The global programme uses coverage data reported by surveys, while PacELF uses data from registers [1]. The source of data chosen to calculate the total population was the local census carried out among all island villagers annually. We classified as high drug coverage rate all villages where the percentage of treated population was estimated at more than 70%. Migration from other areas was considered to be low when it involved less than 5% of the village population.

Circulating filarial antigenemia (CFA) was assessed with a rapid-format antigen card test (Filariasis Now, Binax Inc., Portland, Maine, USA) together with the first and after fifth round of MDA. While microfilaremia is the gold standard for monitoring filarial infection, PacELF guidelines are based on the use of the antigen test in a community-wide survey [1], as this is a simple card test with a high reported sensitivity (98.5%) and specificity (100%) [26,27], and provides the additional advantage of allowing daytime blood sampling. We defined the prevalence rate of CFA as the number of people with a positive antigen test divided by the number of people tested. A low endemicity was defined as a CFA positivity rate in the population of less than 10%.

Mosquitoes were collected to assess the vector biting activity before the first round of MDA (January 2003). Indoor human landing catches of the vector mosquito, *Anopheles farauti* [25], were conducted from sunset to sunrise (18:30–06:30 h). With the help of a simple aspirator mosquitoes were caught when they landed on a human volunteer for taking a blood meal. A monthly biting rate (MBR) was computed by multiplying the number of mosquitoes contacting a man per 24 hours with the number of days in the month. Vector density was considered to be low when the MBR was under 100 bites/person/month.

A supplementary vector control strategy involving anti-mosquito measures was put in place. Source reduction of potential

breeding sites in the vicinity of villages, and community-wide distribution of long-lasting insecticide-treated netting materials (LLITNs) were promoted in the entire island. However, indoor spraying of residual pyrethroids was used only in certain villages located in the vicinity of the Lihir Gold mine. We defined an optimal vector control strategy as one where all of these anti-mosquito tools were employed. Our study did not assess compliance in the use of bed nets, nor assess the effectiveness of local mosquito control measures.

The success of the program in a village was defined using variables related to the infection (reaching antigenemia level below 1%) and transmission (less than 1 in 1000 children born in the community since start of MDA having infection measured by antigenemia).

Statistical analysis

Data entry was undertaken with EpiInfo software (version 6), with field limits and double data entry. We analysed demographic data (age and sex), migration from other areas, the initial endemicity of infection (prevalence rate), the vector abundance, treatment coverage (number of tablets distributed), the use of adjuvant vector control strategies and the outcome of the elimination program. Univariate analyses of data from the villages were performed using the χ^2 test for categorical data, and the *t*-test or Mann–Whitney *U*-test for continuous data. Predictors for success of PELF in controlling the infection prevalence were analysed by multivariate logistic regression, which included the following variables: low baseline prevalence, low migration, low vector density, high treatment coverage, and optimal vector control strategy. Predictors of success in stopping the transmission were also analysed by logistic regression analysis, which included the variables: average age <20 years, low endemicity of infection, low vector density and high treatment coverage. Odds ratios and 95% confidence intervals are presented. All multivariate logistic analyses were done using Firth's method to overcome problems of separation in small samples [28]. Data were analysed using SAS 9.1.3 (SAS Institute Inc., Cary, NC, USA) and SPSS 14.0 (SPSS Inc., Chicago, IL, USA).

Reporting of the study has been verified in accordance with the STROBE checklist (provided as Checklist S1).

Ethical clearance

Ethics approval for this study, including the oral consent process, was obtained from the Papua New Guinea Ministry of Health Medical Research Advisory Committee. The consent sought was verbal because of the high illiteracy rate in rural population, and it was documented on case report forms. Study personnel informed prospective study participants about the study by reading them a consent document in the local language. All subjects provided informed consent at every stage of the study including for collection of samples, interviews, and individuals involved in calculating monthly bite rates. Participation by children required consent from at least one parent and the child's assent.

Results

The annual census in the year 2003 estimated that 8709 people lived in the 27 villages which were part of the study and that were visited and treated annually over a period of 5 years. At the baseline survey, a total of 6037 individuals were registered corresponding to 70.0% of the entire population (as determined by the 2003 census). 50% of the villagers were male, and the mean age was 20.6 years. Reported coverage in 2004–2007 for MDAs 2–5 was 69.8%, 73.0%, 74.1% and 71.5% respectively. Drug coverage remained stable over time and it was similar in all the territories, with an average of 72,9% in eastern coast villages and 67,4% in western coast villages ($p = 0.35$). The reason why 26% to 30% of the target population were not treated is that they were not available at the time of the medical team visit (i.e. working, visiting relatives) or that they were ineligible persons (3.0% to 6.0% of the de facto population), including pregnant women and children younger than 2 years old or of weight less than 10 kg.

The demographic and epidemiological data and program operational details of the 27 villages are shown in Figure 1. Almost half (44,4%) of the villages had migration rate over 5% of the total population, 12 (80.0%) of them were villages from the eastern coast. The migrants mainly came from low endemic areas for filariasis such as the PNG mainland, and from the small islands surrounding Lihir. The details of treatment coverage were recorded during all the five rounds of treatment and the average calculated. Individually, 55.6% of the villages had a high drug coverage, including 60,0% (9/15) in the eastern coast group and 50,0% (6/12) in the western coast group.

Mosquito transmission indices varied significantly in different villages. The highest indices of transmission were observed in villages located in the swampier regions of the west coast with a MBR median (interquartile range) of 460.8 (1812.6) bites/person/month, compared to 57.6 (180.0) in the east coast. These data indicate that there is regional micro-variation in the intensity and temporal pattern of filariasis transmission. It is noteworthy that only nine villages (33.0%) used indoor residual spraying and therefore achieved an optimal vector control strategy.

Table 1 shows data for filarial infection rates before and after the PELF. Overall, all variables showed significant decreases from pre-MDA to round 5 ($p<0.001$). The analysis of data from all villages shows a significant decrease in circulating filarial antigenemia (CFA) over this period from a mean prevalence of 17.9% to 3.8% ($p<0.001$). Pre-MDA CFA prevalence rates were much higher in the Western than in the Eastern territories. The mean prevalence of infection was 7.7% and 0.8% in eastern villages, and 30.7% and 7,5% in western villages in the pre-MDA and at completion of round 5, respectively (table 1). Pre-MDA antigenemia prevalence rates in children under 5 years were not significantly different in the western village schools and in the eastern village schools (60.1 vs 31.0 in 1000; $p = 0.10$). Rates of circulating filarial antigenemia in under 5 y.o. children fell more rapidly in the less heavily infected eastern villages than in the western villages (30.0 vs 0.95 in 1000; $p<0.01$). Twenty-one children with a positive result out of 700 tested were identified in the Western villages after round 5.

As shown in figure 2, the CFA prevalence in individual villages ranged from 1.1% to 58% and 0 to 17%, in the pre-MDA and post-MDA surveys respectively. PELF had a successful outcome on infection prevalence control in 12 of the 27 villages (44.4%), whereas it failed in the remaining 15 (55.5%). Transmission, assessed on the incidence of new infections, was successfully controlled in 19 (70,3%) villages. On univariate analysis (table 2), numerous factors were found to be significantly associated with PELF success on the control of infection status including low baseline prevalence, low vector abundance, and implementation of an optimal vectorial control. A low percentage of migration, unexpectedly, was found to be a risk factor. On multivariate analysis (table 2), the only independent factor predicting PELF infection control success was low endemicity of infection (OR 19.26; CI 95% 1.12–331.82). Table 3 shows the univariate and multivariate predictors associated with transmission control success. Low endemicity of infection (OR 27.44; CI 95% 1.05–

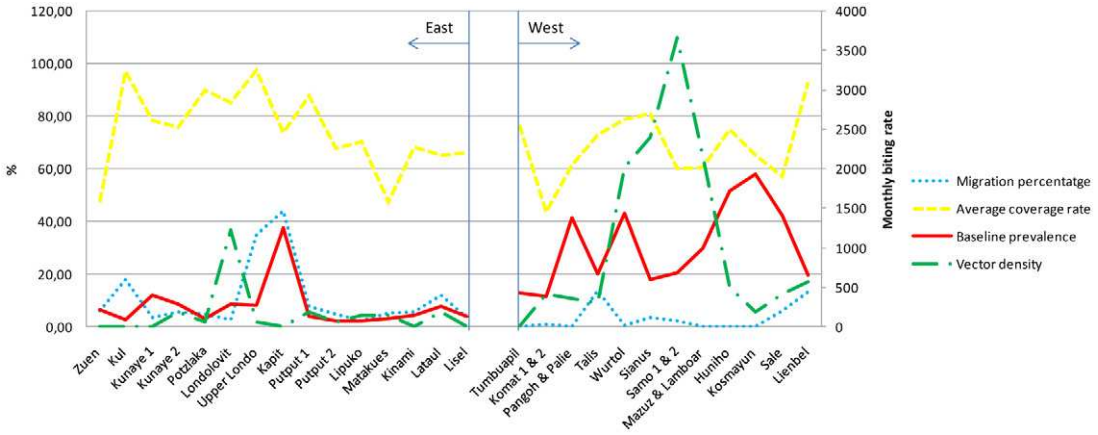

Figure 1. Baseline epidemiological, infection status and entomological data and program coverage details of 27 villages, Lihir Island.
doi:10.1371/journal.pntd.0001286.g001

719.6) was again the only factor independently associated with transmission control success.

Discussion

In the present study the overall prevalence of circulating filarial antigenemia was reduced by 79.0%. Despite undeniable success, the program did not achieve its very ambitious goals based on the PacELF recommendations, with post treatment prevalence remaining at 3.8% and 14 new infections per 1000 children born since start of MDA. This overall failure was the result of the intervention specifically failing in some villages. Understanding what factors lead to success or failure when the intervention is applied to a specific setting may help improve the MDA program. Our findings reveal that in Lihir, the baseline infection status was an important factor influencing on the outcome of the PELF. Our discussion will focus on possible explanations for this observation and the influence of other factors on the outcome.

The first objective of our study was to test the hypothesis that bancroftian filariasis can be eliminated from communities by yearly cycles of MDA with diethylcarbamazine and albendazole. Over all, success in controlling the infection and in stopping transmission was confirmed in 45% and 70% of the villages, respectively, most of them located in the eastern coast. The eastern coast villages had low baseline levels of filariasis endemicity, whereas the western coast villages had very high baseline rates that were more typical of filariasis endemic islands in the Western Pacific Region [2]. Our data suggest that five rounds of MDA will not have eliminated filariasis in the western study area. However the observed post-treatment antigen prevalence rates are unlikely to sustain transmission as the vector-parasite relationship in Lihir is extremely fragile involving the *An. Farauti* which is one of the least efficient vectors in the world. The cut-off point for interruption of transmission in the PacELF region was based on the fact that transmission in most of the Pacific island countries is carried out by the highly efficient Culex and Aedes mosquitoes. The second major objective of our study was to evaluate the factors having a positive influence on the markers of success. In our study the most prominent determinant of success was low baseline prevalence of infection. Low vector density appeared to have an association but did not reach statistical significance. The sample size, as it is based on the number of villages, is unfortunately low and may have caused the study to be underpowered when trying to determine the significance of this

Table 1. Effect of MDA on circulating filarial antigenemia prevalence rates on Lihir Island.

	Infection prevalence		Ongoing transmission (new infections detected)	
	Number of people tested	Antigenemia prevalence rate[a] (%[SD])	Number of children tested	Positive Antigenemia in 1000 children[b] (%[SD])
East coast study area				
Pre-MDA	3009	7.67 (8.77)	537	30.98 (49.19)
MDA round 5	3799	0.76 (0.92)	1006	0.96 (3.68)
West coast study area				
Pre-MDA	1969	30.71 (15.87)	462	60.14 (37.36)
MDA round 5	2464	7.51 (3.77)	700	30.00 (29.96)
Total				
Pre-MDA	4978	17.91 (16.86)	999	43.94 (45.95)
MDA round 5	6263	3.76 (4.26)	1706	13.86 (24.57)

[a]Antigenemia prevalence rate in a large size sample from the whole treated population. Some people agreed to receive MDA but refused to provide blood samples.
[b]Antigenemia prevalence rate in children under 5 years old which represents new infections since start of MDA.
doi:10.1371/journal.pntd.0001286.t001

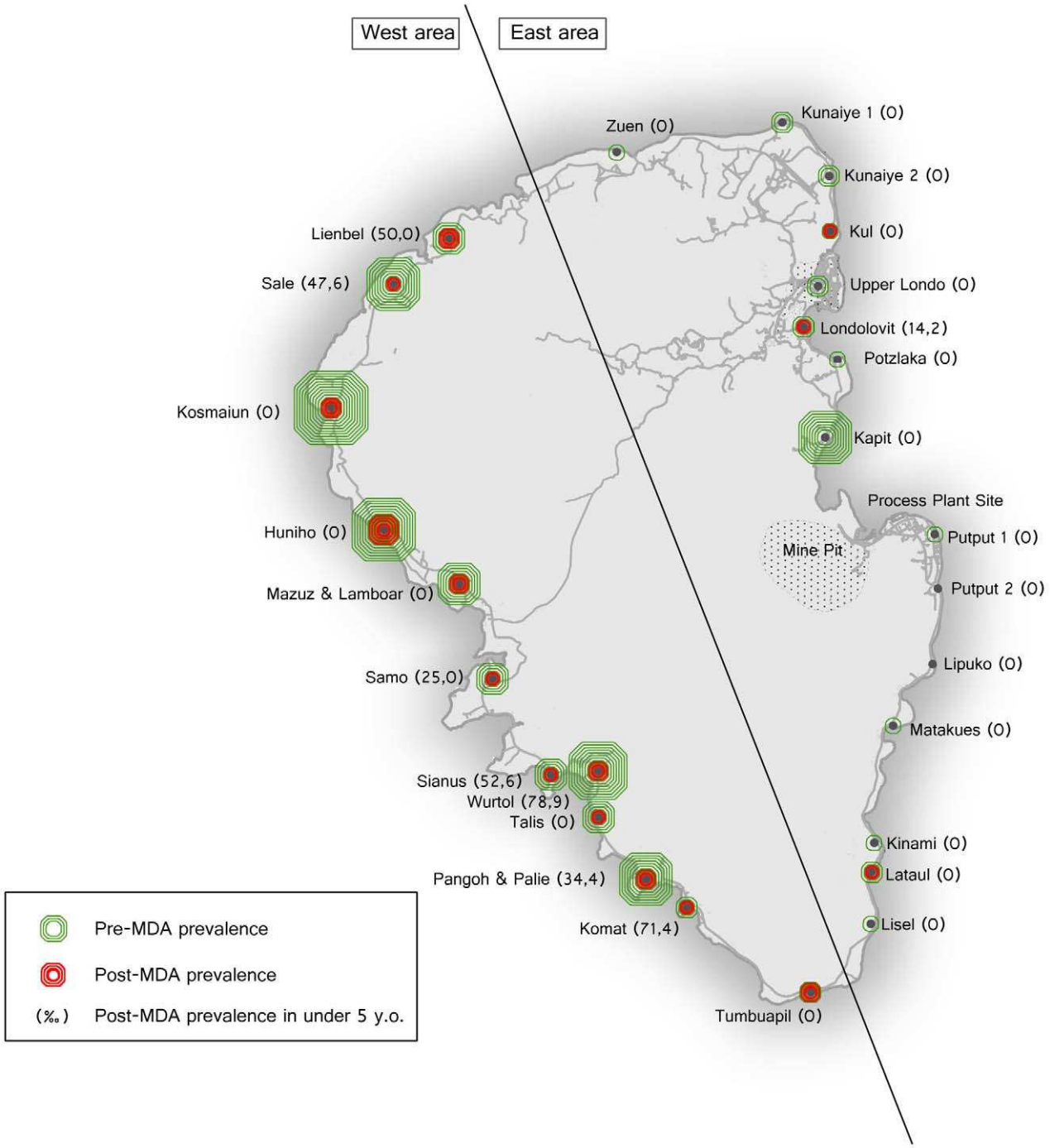

Figure 2. Percentage of Infected people, in Lihir Island Villages, in the pre-MDA and post-MDA surveys. NOTE. The diameter of the circles is proportional to the estimated prevalence of Lymphatic filariasis, implying that every line corresponds to an increase in prevalence of 5%.
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trend. Other specific factors have previously been described as having a positive influence in the outcome of a PELF. These include high coverage of the targeted population [9,15,16], low levels of migration from other areas and integration of the different available control strategies into the program [21,22]. In the current study however, these variables did not show an association.

Prior to the current study there has been little reliable clinical evidence comparing low prevalence communities with high prevalence populations. Our study followed a large cohort, contained detailed information about risk factors and outcomes and established comparisons among several independent areas of transmission. The current study also had the advantage of being conducted in an area of Papua New Guinea with a relatively high rate of infection and transmission, and a pronounced inter-area variation in prevalence. Moreover, an island population such as Lihir presents more ideal conditions for epidemiological studies and evaluation of control programs than large land areas. This study has the limitations of an observational ecological study, and

Table 2. Association between characteristics of villages and program related factors and PELF success to control infection prevalence.

Factor	Villages where PELF succeeded (N = 12)	Villages where PELF failed (N = 15)	Univariate Analysis		Multivariate Analysis	
			OR (95% CI)	P value*	OR (95% CI)	P value*
Demographic data						
average age <20 yr old	3 (25.0)	6 (40.0)	0.5 (0.09–2.64)	0.41		
sex, male-female rate >0.50	7 (58.3)	7 (46.7)	1.60 (0,34–7.40)	0.54		
Epidemiologic data						
Low endemicity of infection	10 (83.3)	3 (20.0)	20.0 (2.77–144.31)	0.003	19.26 (1.12–331.82)	0.04
Low migration from other endemic areas	2 (16.7)	10 (66.7)	0.1 (0.02–0.64)	0.015	0.57 (0.03–11.46)	0.72
Low vector density	8 (66.7)	2 (13.3)	13.0 (1.92–87.99)	0.009	11.58 (0.68–197.0)	0.09
Operational data						
High treatment coverage	7 (58.3)	8 (53.3)	1.22 (0,27–5.67)	0.79	0.23 (0.01–11.28)	0.46
Optimal vectorial control	7 (58.3)	1 (6.7)	19.60 (1.91–201.62)	0.01	18.00 (0.36–894.6)	0.14

OR, odds ratio. PELF, Program for Elimination of Lymphatic Filariasis.
*A P value ,0.05 was considered to be statistically significant.
doi:10.1371/journal.pntd.0001286.t002

obviously causality cannot be inferred from it. The observed risk factors need to be considered with caution. Also, data for some factors which may influence success rates (e.g. number of persons per household, use of bednets) were not collected. However, the analyses performed controlling for the widely recognized prime predictors, the strong and similar results obtained in the multivariate analyses for two different markers of success, and the use of specific techniques to obtain unbiased risk estimates with small samples allow us to have confidence in the results obtained.

The percentage of the population covered is an important factor in determining the success of a PELF that has been previously analysed [9,15,16]. We developed a timely and coordinated drug delivery strategy that included elements of community information and education in an attempt to achieve widespread acceptance of drug treatment and the DOT (Directly Observed Therapy) distribution method. We made an effort to reach those groups of individuals who are recognized to be at risk of systematic non-compliance during MDAs including children, the upper socioeconomic classes, young men and the elderly. We achieved an overall 70% reported population treatment coverage which was probably underestimated, since it was calculated using the number of people in the local census. In the multivariate analysis the coverage was not associated with any of the markers of success. This is likely due to the similar levels of coverage achieved in all the villages in the current program.

The lack of influence of population migration in this study may be explained by the demographics of the migrant population. The presence of the gold mining operation at Lihir has attracted a large

Table 3. Association between characteristics of villages and program related factors and PELF success to stop transmission.

Factor	Villages where PELF succeeded (N = 19)	Villages where PELF failed (N = 8)	Univariate Analysis		Multivariate Analysis	
			OR (95% CI)	P value*	OR (95% CI)	P value*
Demographic data						
average age <20 yr old	6 (31.6)	3 (37.5)	0.76 (0.13–4.32)	0.76	3.19 (0.21–46.86)	0.40
sex, male-female rate >0.50	9 (47.4)	5 (62.5)	0.54 (0.1–2.93)	0.47		
Epidemiologic data						
Low endemicity of infection	12 (63.2)	8 (12.5)	12.00 (1.21–118.89)	0.03	27.44 (1.05–719.6)	0.04
Low migration from other endemic areas	7 (36.8)	5 (62.5)	0.35 (0.06–1.93)	0.23		
Low vector density	9 (47.4)	1 (12.5)	6.30 (0.64–61.63)	0.11	21.85 (0.61–786.3)	0.09
Operational data						
High treatment coverage	9 (47.4)	6 (75.0)	0.30 (0.05–1.88)	0.20	0.08 (0.01–1.41)	0.08
Optimal vectorial control	7 (36.8)	1 (12.5)	4.08 (0.41–40.45)	0.23		

OR, odds ratio. PELF, Program for Elimination of Lymphatic Filariasis.
*A P value ,0.05 was considered to be statistically significant.
doi:10.1371/journal.pntd.0001286.t003

number of relatively skilled and affluent workers, often from areas such as Port Moresby and other regional centres where LF endemicity is low. Thus migration did not contribute to the reservoir of filariasis in Lihir.

The long term impact of MDA is determined by the drugs' effects on microfilaria, and particularly on adult worms [29]. A single dose of DEC and Albendazole rapidly reduces the number of circulating microfilaria, but also has a temporary effect in reducing the production of microfilaria by adult worms, probably due to sterilization. After some months renewed production occurs but at a reduced intensity [20,29]. In the absence of macrofilaricidal activity, current programs rely on the interruption of transmission through sustained suppression of microfilaremia over the 5 years of a program. Experimental studies have documented the median fecund lifespan of *W. Bancrofti* worms to be more than the 5 years typical of an MDA [30]. In addition, single doses of DEC and Albendazole have been shown to have a limited capacity to kill the adult worm. A Brazilian study found a significant proportion of adult worms were insensitive to DEC at doses of 6 mg/kg, with ultrasound studies showing only a 56% mortality for adult worms after 5 years [29]. This has led some physicians to suggest that MDA programs should be of at least the same duration as the lifespan of adult worms. Moreover, it has been demonstrated that individuals in areas of high endemicity will have a higher average adult worm burden, and therefore a higher chance of a fecund worm pair surviving after MDA is complete [14]. A theoretical analysis with field data from 9 villages, in distinct endemic areas, identified the degree of infection aggregation as one of the main factors related to failure of a PELF. Through a simulation procedure, the author estimated that following the current approach, only 50% of programs would achieve parasite elimination [6]. Dunyo et al. in their study showed a higher level of microfilarial resurgence than in other programs, and suggested that this may have been due to a high pre-treatment worm burden [31].

The fact that successful elimination of disease in high prevalence areas may require longer duration of MDA programmes has already been recognized by experts [1–4,24,32–34]. This paper provides the data that support such recommendations. It is clear that local data needs to be taken into account when designing MDA programs. Alternative strategies may be needed, including modified drug regimens (e.g., biannual MDA), vector control measures, or perhaps antibiotic treatment.

Supporting Information

Checklist S1 STROBE checklist.
(DOC)

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Author Contributions

Conceived and designed the experiments: OM RP MS. Performed the experiments: RP LG NL. Analyzed the data: OM QB. Wrote the paper: OM RH QB.

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9. Summary of results and conclusions

Study 1

Challenges in Recognition and Diagnosis of Yaws in Children in Papua New Guinea

Results

Demographic data, clinical presentation and laboratory results of patients with yaws

- Out of 233 patients with clinically suspected yaws evaluated, 138 (59%) received a diagnosis confirmation of yaws on the basis of positive serologic results and epidemiologic history.
- Mean age of patients with confirmed yaws was 9.6 years
- Among patients with confirmed yaws, 81 (59%) yaws displayed active primary cutaneous yaws lesions
- Among patients with confirmed yaws, 63 (46%) exhibited signs of secondary stage yaws, including 58 (92%) with osteoarticular involvement.
- Arthralgias were the most common presentation of secondary stage yaws (48 [76.2%] of 63)

Association between stage of infection and demographic data, and laboratory results

- There was a positive association between primary stage disease and a high initial VDRL titre (OR 0.34, CI 0.16-0.70)
- Secondary stage cases were more likely to live in a high prevalence village as compared to primary stage cases (OR 2.51, CI 1.20–5.26)

Conclusions

- Only 60% of the cases with a clinical suspicion of yaws were confirmed by serologic tests.
- The diagnosis of yaws is complicated because its clinical manifestations are diverse or may be totally unspecific.
- Manifestations of secondary yaws, particularly bone and joint involvement, are now more frequent

- A factor that could have contributed to the change on clinical presentation is the widespread use of oral antibiotics
- Longer-term infections, as secondary stage, were more commonly associated with a lower VDRL test titre - < 1:32.

Study 2

Outcome Predictors in Treatment of Yaws

Results

- 138 patients were identified during enrolment with clear documentation of baseline characteristics and at least 1 follow-up titre 12–15 months after treatment
- Overall, 24 (17.4%) case-patients experienced serologically defined treatment failure during follow-up.
- According to the estimated minimum incidence, in 9 villages the disease was classified as highly endemic, and in 15 villages, the disease was considered of low endemicity
- Among patients with yaws, 65% persons came from a high incidence village and 35% came from a low incidence village

Association between characteristics of patients and yaws treatment failure

- Multivariate analysis showed that residence in a high incidence village (OR 3.75, CI 1.02–13.76) was a risk factor for treatment failure.
- An initial VDRL titre <32 (OR 4.05, CI 1.06–15.38) proved to be also an independent predictor for treatment failure.
- A positive association between a low initial VDRL titre and secondary stage disease was found.

Conclusions

- Serologically defined treatment failures occurred in ≈17% of case-patients in our series.
- In Lihir, the factors predicting treatment failure after 12 months of drug therapy were the following: residence in a village where incidence of infection was high and a low initial VDRL titre.
- The risk for reinfection caused by repeated contact with infected children in high endemic areas seems to be a pivotal factor in predicting treatment failure.
- We also hypothesise that a chronic infection, usually accompanied of lower VDRL titres, is more difficult to resolve.

Study 3

Osteoperiostitis in Early Yaws: Case Series and Literature Review

Results

- Out of 222 patients with confirmed yaws, seven children met the radiological diagnosis criteria of early yaws osteoperiostitis.
- All patients (7 [100%] of 7) presented with bone pain and soft tissue swelling.
- Almost half of the patients (43%) had multiple bones involvement.
- Radial involvement was most common (71%) followed in frequency by ulnar and phalanges.
- We did not observe any characteristic late-stage lesions
- Most patients (86%) recalled having had recently a yaws chancre.
- All patients had excellent responses to benzathine benzylpenicillin.

Conclusions

- Since the 1950s, archaeological-based research has been the only source of information that has increased the understanding of osteoperiostitis in yaws.
- Yaws, as one form of pathologic treponematoses, alters the appearance of bones in a highly specific manner. It is a polyostotic disorder and involvement of hands and arms is most common. This contrasts with the bone involvement in syphilis.
- Early yaws osteoperiostitis appears to be a relatively mild disease if it is diagnosed and treated in a timely manner.
- This series of cases suggests that the presence of supportive clinical and radiological findings may be useful in the clinical diagnosis

Study 4

Single-dose azithromycin versus benzathine benzylpenicillin for treatment of yaws in children in Papua New Guinea: an open-label, non-inferiority, randomised trial

Results

Recruitment and compliance

- 250 children aged 6 months to 15 years were recruited and randomly assigned in a 1:1 ratio to receive either 30 mg/kg (maximum 2 g) azithromycin orally or 50,000 units per kg (maximum 2·4 MU) benzathine benzylpenicillin by intramuscular injection.
- 110 of 124 assigned azithromycin and 113 of 126 in the benzathine benzylpenicillin group completed follow-up and constituted the per-protocol population.
- Randomization generated two treatment groups that were similar in terms of baseline clinical and serological characteristics

Safety and tolerability

- The number of drug related adverse events (all mild or moderate) was similar in both treatment groups (ten [8%] in the azithromycin group vs eight [7%] in the benzylpenicillin group).
- Of participants given azithromycin with adverse events, all were related to mild gastrointestinal intolerance – nausea, stomach ache and only 2 vomiting within 30 minutes of taking the drug.
- In patients given benzathine benzylpenicillin administration-related adverse effects were the most common – persistent injection-site pain and injection-related abscess.
- No serious adverse events were reported during treatment or for the entire follow-up period.

Efficacy

- Primary endpoint estimates (PP population, cure rate at 6 months) were similarly high in both treatment arms: 96% in the azithromycin group compared to 93% in the benzathine benzylpenicillin group.

- Risk difference in cure proportions between groups was –3·4; 95% CI 9·3–2·4
- The upper limit of the 95%CI for the difference in cure rates between groups was 2.4 (PP), and thus within the pre-specified non-inferiority margin. In the ITT population the upper limit bound was 6.8.
- Incidence of the individual components of the primary endpoint and intermediate cure rates did not differ significantly between groups.
- In subgroup analyses, the cure rates at 6 months according to yaws stage, rapid plasma reagin titre at treatment, and household exposure did not differ significantly between treatments in the per-protocol population.
- No participant in either treatment group had recurrent clinical signs of yaws or serological evidence of recurrence during the 6-month follow-up period.

Conclusions

- Azithromycin was non-inferior to benzathine benzylpenicillin for the primary composite endpoint of serological cure at 6 months and healing of ulcers.
- The two treatment groups had similar rates of cure at 3 month follow-up and in subgroups defined according to demographic and biological characteristics
- Azithromycin was well tolerated and no major adverse effects occurred what emphasises the suitability of azithromycin for mass treatment programmes.
- Our study was done in only in one centre; therefore our findings might not be generalisable to all children with yaws.
- A reason for caution is the sustained success of benzathine benzylpenicillin treatment for yaws, despite treatment failure has been occasionally reported.
- The emergence of azithromycin-resistant *T. pallidum* in American syphilis patients suggests that careful follow up will be needed to ensure that clinically significant resistance to azithromycin does not develop in *T. pallidum subspecies pertenue.*
- Oral azithromycin is safe and easy to administer and it overcomes the major disadvantages of the present regimen: it avoids the need for injection administration and medical trained personnel.
- Community based mass treatment programmes using this antibiotic, as for the control of trachoma, should be explored to attempt yaws elimination.

Study 5

Review article. New treatment schemes for yaws: the path towards eradication

Key points

Past and future treatment schemes for yaws disease

- The mainstay for the treatment of yaws is benzylpenicillin which demonstrated to be treponemicidal when concentrations were greater than 0.03 units / mL of serum and maintained for at least 7 days.
- Since 1948, no reasonable alternatives to injectable penicillin for the treatment of yaws had been proposed.
- Benzathine benzylpenicillin has the operational drawbacks of a treatment that requires injected administration in rural, remote areas.
- The oral delivery of phenoxymethylpenicillin, tetracyclines and erythromycin have been shown effective to cure yaws, but the three regimens require the administration of multiple doses over a number of days.
- A single-dose of oral azithromycin has been shown to be non-inferior to benzathine benzylpenicillin for the treatment of yaws.

New strategies for a global and sustainable elimination of yaws

- Policies to eliminate yaws developed years ago, which generally targeted only a selected part of the affected population, demonstrated to be insufficient.
- With oral treatment the mass drug administration should be massive (i.e. to the entire population) and followed by frequent re-surveys.
- Community-based mass administration of azithromycin has been widely used in many locations for the control of trachoma and it has demonstrated to be safe.
- It is recommended to incorporate azithromycin into other MDAs against parasitic diseases to enhance efficiency. Pharmacokinetic and safety data, about the co-administration with anti-helminthic needs to be confirmed under field conditions.
- Antibiotic susceptibility in *T. p. pertenue* and *S. pneumoniae* needs to be monitored throughout the elimination campaigns.

Study 6

The Impact of a Filariasis Control Program on Lihir Island, Papua New Guinea

Results

Effect of MDA on circulating filarial antigenaemia prevalence rates on Lihir Island.

- 8709 people were involved in the MDA program and average coverage rates were around 70%
- 50% of the villagers were male, and the mean age was 21 years
- The highest indices of transmission were observed in villages located in the swampier regions of the west coast with a MBR median of 461 bites/person/ month, compared to 58 in the east coast.
- Pre-MDA CFA prevalence rates were much higher in the Western (average 31%) than in the Eastern territories (average 8%)
- Almost half (44%) of the villages had migration rate over 5% of the total population
- The overall prevalence of filariasis fell from an initial 17.91% to 3.76% at round 5 (p,0.001)
- Viewed on a village by village basis, 12/27 (44%) villages achieved success

Association between characteristics of villages and program related factors and PELF success to control infection prevalence and stop transmission

- In multivariate analysis, low baseline prevalence was the only factor predicting success in reducing infection rates (OR 19,26; CI 95% 1,12 to 331,82)
- In multivariate analysis, low baseline prevalence was the only factor predicting success in preventing new infections (OR 27,44; CI 95% 1,05 to 719,6)
- Low vector density and the use of an optimal vector control strategy were also associated with success in reducing infection rates, but this did not reach statistical significance

Conclusions

- Prior to the current study there has been little reliable clinical evidence comparing Filariasis MDA in low prevalence communities with high prevalence populations.

- Despite a reduction of CFA by 79%, the program did not achieve the goal of CFA prevalence < 2% as a result of specific failure in some villages. However it is unlikely that transmission is sustained with the least efficient vector, An. farauti.
- In our study the most prominent determinant of success was low baseline prevalence of infection.
- In the absence of macrofilaricidal activity, current programs rely on the interruption of transmission through sustained suppression of microfilaraemia over the 5 years of a program.
- Our study provides data supporting the recommendation that in certain high prevalence and transmission environments more sustained efforts may be necessary.

10. General conclusions

Study 1

1. Clinical diagnosis of yaws is challenging and may require the support of specific laboratory techniques.
2. Yaws in Papua New Guinea has changed its pattern of presentation by showing an increased number of secondary stage forms.

Study 2

3. Cases of penicillin treatment failure are occurring in yaws in Papua New Guinea.
4. Re-infection caused by repeated contact with infected children seems a pivotal factor related to treatment failure, which indirectly suggests increased tolerance of some *T. pallidum subsp. pertenue* strains to penicillin treatment.

Study 3

5. Yaws alters the appearance of bones in a highly specific manner and the presence of supportive clinical and radiological findings may be useful in the clinical diagnosis.

Study 4

6. A single oral dose of azithromycin is non-inferior to benzathine benzylpenicillin and avoids the need for injection equipment and medically trained personnel.
7. A change to the simpler azithromycin treatment regimen could enable yaws elimination through mass drug administration programmes.

Study 5

8. Elimination of yaws in endemic areas is now considered biologically feasible and programmatically attainable with the use of total community treatment of azithromycin

9. Yaws mass treatment should be monitored by prevalence surveys to assess the impact of the intervention and antibiotic resistance surveys might need to be carried out to ensure sustainability.
10. The yaws and the Lymphatic Filariasis elimination programs might be linked in the South Pacific Islands.

Study 6

11. The most prominent factor having a positive influence on the programme for elimination of lymphatic filariasis in Lihir Island was a low baseline prevalence of infection. Low vector density was also associated with success.
12. The successful elimination of lymphatic filariasis in high prevalence areas may require longer duration of MDA programmes or alternative strategies.

11. Overall discussion. The way forward

11.1 Translating research findings into policy

In January 2012, the Director General of the World Health Organization launched the roadmap for neglected tropical diseases at a partners meeting in London. In this roadmap, yaws has been targeted for eradication by 2020. This will be the second attempt at yaws eradication after the uncompleted mission in the 1950s and 1960s to achieve that goal.

Our finding that a single-dose of oral azithromycin was as efficacious as the standard injection of benzathine penicillin in treating yaws prompted the WHO to convene a meeting of experts in Morges, Switzerland to develop a new strategy towards the eradication of yaws. WHO now plans to wrap its renovated effort to eradicate yaws by 2020. With this new therapeutic tool in one hand and a better understanding of the epidemiology in the other, we may be closer to eradication of yaws now than we have been in decades.

Moving away from penicillin to azithromycin

Substituting a painful injection of penicillin with a single dose of an oral antibiotic could really be a significant advantage, as no trained staff would be needed to treat cases in remote areas, infection and anaphylactic shock control measures and other logistical problems linked to penicillin use would be overcome, and acceptability of treatment by those who receive it would certainly improve. Azithromycin could be employed in the treatment of sporadic cases, but more importantly may represent a suitable tool for deployment in mass drug campaigns. Notably, community based mass treatment programmes using this antibiotic for the control of trachoma have been well accepted by rural communities in many parts of Africa (65). On the political side, switching to the new elimination/eradication strategy should similarly stimulate commitment and willingness to cooperate, signalling national governments that this will be not just a new attempt to complete the unfinished job using the same means

Prevention and elimination of yaws: lessons from the past

Given that there is no vaccine, the principles of prevention in yaws, are based on the interruption of transmission by mass or targeted treatment of affected population. The strategy of the yaws program in 1952 called only for a selective mass treatment of active cases and contacts; however it failed in identifying contacts of those infected and left subclinical infections to spread the disease again. A mass treatment to the entire

population in endemic areas to treat the population manifesting the disease, the population infected but not manifesting the disease (latent carriers) and the population exposed to risk (contacts) is now deemed necessary. Other glaring deficiencies at that time were the fact that the strategy had not been validated in pilot studies and that there was no monitoring of the impact and so it was not clear what was actually occurring (66). When sample serological surveys were eventually conducted, subclinical infections were found to be far more prevalent than had been recognized, making the eradication goal become utopia.

New strategies for elimination of yaws

The use of oral therapy should affect the treatment policies developed years ago. If we want to embark on a new elimination programme with oral treatment the mass drug administration should be massive (i.e. to the entire population). A new policy sketched at a WHO consultation in Morges (March, 2012), moves away from penicillin to azithromycin and enforces an initial total mass treatment of the entire population in known endemic communities irrespective of the prevalence. Also, to make sure all cases are tracked down and treated, WHO will require strict follow-up measures, with re-surveys conducted every six months and either total or selective mass treatments, depending on prevalence, plus active case finding, until zero case prevalence is reached. A high coverage (>90%) of mass treatment is essential. Experience from past yaws MDA campaigns using benzathine benzylpenicillin suggests that at least 90% coverage would be needed for each round in order to achieve success (67). For example, experience from yaws eradication programme in Nsukka division South-Eastern, Nigeria in the 1950s using injection penicillin showed that if the coverage during mass treatment is high (>95%), one or two rounds of treatment would interrupt transmission.

In addition to mass treatment campaign, there should be the possibility to rapidly detect and treat any new infections and close contacts through the static health facilities. Given the peculiarities of yaws, the strategy must be robust to prevent that one case leads to other new cases.

11.2 Uncertainties in the path to eradication

Nevertheless, some operational unresolved questions and technical uncertainties still exist, including the identification of endemic foci and their measurement and strategies for impact assessment. Also a way to secure that the new strategy is both doable and

effective would be to have a 'Proof-of-principle' (PoP) that includes intensive and careful monitoring.

Review of epidemiological situation

At this stage it is of tremendous importance to get a better understanding of the current epidemiological situation through a strong and systematic assessment of yaws in the World and Pacific in general and in PNG, Vanuatu and Solomon in particular. Only then, sound strategies towards elimination of yaws can be developed and the work started more than half a century ago, can be completed.

Assessment of the impact after mass treatment

Next point is how to assess prevalence and ongoing transmission in the community after mass treatment is completed. It seems that the failure to eradicate yaws last time round was due to a breakdown in surveillance. The success in India was clearly due to an excellent system for serological surveillance to certify interruption of transmission and to look for resurgence.

Once criteria for stopping mass treatment (i.e., zero cases reported) have been met, surveillance should continue for a minimum of 3 years, until yaws is declared eradicated. No community or even country can afford to stop surveillance for yaws until eradication. Also, whether at community or country level, will all likely going to be at different stages of reaching zero cases so an area cannot stop surveillance when the neighbour is still on fire.

Post-zero case surveillance should include monthly reporting of cases (zero cases should be reported) and yearly serological surveys of randomly selected children 1 – 5 years. If transmission is interrupted, continuous negative serological tests in children under five will confirm no further exposure to the infection. Rapid treponemal syphilis tests, can be easily performed in the field and available information on sensitivity and specificity in syphilis, suggests that test performance should be good for yaws.

Assessment of treatment failure

It will also be important to identify cases of treatment failure in case resistance develops to azithromycin. The working case definition of treatment failure would be a person with clinically active yaws who has been treated with a single-dose oral azithromycin (or injection benzathine penicillin) and the lesion(s) has not healed or not healing satisfactorily at 4 weeks after treatment. Swab samples must be obtained from these cases' ulcer lesions and transported, in medium for DNA preservation, to a

laboratory capable of performing the test to detect the genetic mutation that confers resistance to macrolides in treponemes.

The next step: 'Proof of Principle' of the new strategy

The next step to eradicate yaws is pilot implementation of azithromycin mass treatment and appropriate monitoring to test the principle of interrupting transmission. This later clinical development, Phase III, involves larger numbers of patients to show convincing, statistically significant evidence of efficacy to eliminate yaws in limited endemic regions. The minimum set of essential indicators required for assessing trends in yaws elimination includes clinical signs of the disease, serological prevalence in children and mass treatment coverage, which are all recommended to be measured in sentinel sites randomly chosen from high endemic areas. The minimum frequency for collecting these data should be before the initial mass treatment and then annually to the end.

On Lihir Island, Papua New Guinea, we are planning to compare the effectiveness of two strategies of mass distribution of oral azithromycin to completely eliminate yaws infection. The primary aim of the new research project would be to determine whether four biannual mass treatments with azithromycin are more likely to eliminate yaws from endemic communities than a single mass treatment followed by targeted treatments. This would be confirmed by zero cases, and no evidence of transmission among children under 15 years, after 3 years post-MDA surveillance. This would potentially be the world's first trial of yaws elimination in a defined population using oral treatment. If successful, it will demonstrate an effective, logistically feasible, safe, and acceptable protocol for global elimination/eradication of this neglected, but highly debilitating and preventable tropical disease.

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I was born in a developed country in a family devoted for their relatives and generous with others, a family with an extraordinary capacity for love. A sequence of challenges led me to study medicine, to specialize in infectious diseases and eventually to do research about Neglected Tropical Infections. These infections affect people who, unlike me, have not been able to choose their destiny.

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In a special way I thank the support and love of my parents, Jordi and Tere, my brother and sister-in-law, Jordi and Carol, and also Tati and Abuela. To them I dedicate this thesis. Their unconditional love is what allowed me to be all that I am now.

Finally, I thank the person who is closer to me, and with whom I will continue the journey to Itaca[1] for making me happy and for teaching me that it is not important to reach the destination but to enjoy the journey.

[1] *Viatge a Itaca* (1975), Lluís Llach, based on texts by Kavafis (Alexandria, 1863 – 1933)

Agraïments

Escriure aquesta tesi doctoral ha estat un 'llarg viatge, ple d'aventures i de coneixences', una feina de grans dimensions per la realització de la qual ha estat imprescindible l'ajut i comprensió de les persones que tinc a prop. És per això que vull expressar a continuació el meu sincer agraïment a tots els que directa o indirectament han participat en l' elaboració d'aquest projecte.

Vaig néixer a un país desenvolupat al si d'una família gran, entregada als seus i generosa amb els altres; una família amb una capacitat extraordinària per estimar. Ells em van ensenyar què és la naturalesa, la cultura i la humanitat. La resta d' esdeveniments que em van portar a completar una tesi dirigida a combatre la pobresa van ser fruit de la imprudència "assenyada" heretada del meu pare i que enorgulleix a la meva mare. Una seqüència de reptes em van conduir a l'estudi de la medicina, l'especialització en malalties infeccioses i finalment la recerca en infeccions tropicals oblidades. Aquestes infeccions afecten a persones que, a diferència de mi, no han gaudit de la sort d'escollir el seu destí.

De manera molt especial agraeixo el seu amor i suport als meus pares, Jordi i Tere, al meu germà i cunyada, Jordi i Carol, i també a la Tati i la Abuela. A tots ells dedico aquesta tesi. Els meus primers records, o potser els més dolços, son dels estius a Arenys de Munt. L'olor fresca a gespa tallada, els dies llargs i assolellats, les excursions i baralles amb el meu germà, la cuina amb la Tati, els vespres de lectura amb la Abuela. Sempre vaig ser un nen tímid i reflexiu. La meva família em va donar la seguretat en mi mateix i l'ànim per perseguir els meus somnis. El seu amor incondicional es el que m'ha permès ser tot el que ara sóc.

A la doctora Maria Villar li dono les gràcies perquè em va atreure a l'estudi de la medicina, i juntament amb la resta de les meves ties, sempre m´ han fet costat. Elles comparteixen el do de la cordialitat i seva sola presència crea el gaudir i la concòrdia dels presents.

Agraeixo al doctor Carles Pigrau per haver-me iniciat a descobrir l' apassionant món de les malalties infeccioses. Amb ell vaig mantenir llargues i intenses converses científiques. El Dr. Pigrau ho llegeix tot, té un coneixement que m'enlluerna, malgrat que per humilitat parla com si no donés importància a res del que diu.

Al doctor Quique Bassat, guia d'aquest treball, dono el meu agraïment profund per la seva direcció propera i constant, i la seva dedicació al meu aprenentatge en

investigació i epidemiologia que han estat un pilar essencial per aquesta tesi. El Dr. Bassat, passional, compromès, lúcid; el seu raonament provoca una reflexió sobre cada tema a totes les nostres xerrades. A ell dec haver arribat fins aquí.

Al doctor Russell Hays, sobretot, he d'agrair l'oportunitat de treballar a una illa del Pacífic, on he crescut i madurat com a persona i com a professional. Als 30 anys, jo prenia consciència de la realitat laboral al món de la medicina i la investigació, que de vegades s'impregna de colors grisos entristits. Era més senzill trobar arguments per superar el dia a dia que saber com influirien en la meva vida els esforços que feia. A Lihir, una illa de 22 Km de llarg, on hi viuen 20,000 persones amb difícil accés a aigua potable, m'han donat una lliçó de vitalitat. L'hospital es alegre, ple de llum. Tots, treballadors i pacients, anhelen un progrés i lluiten junts per aconseguir alguna cosa millor. És fàcil contagiar-se de l'entusiasme i sentir-se còmode entre una població de tracte amable i proper.

Finalment, li agraeixo a la persona que tinc més a prop, i amb qui continuaré el meu 'viatge cap a Itaca', l'amor i la felicitat que em dóna. De la seva saviesa he après que l'important no és on s'ha d'arribar ni els ports fondejats ni les ciutats conegudes, sinó gaudir del 'bell viatge ple d'aventures, ple de coneixences'. La seva senzillesa i tranquil·litat en qualsevol instant de la vida s'ha forjat en mi com un símbol de la felicitat. Coses així d'elementals poden donar resposta a la gran pregunta de - Perquè hi ha vida a un món enmig de l' immensitat de les estrelles? -

Oriol Mitjà, Illa de Lihir, Gener 2012


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